I. Catalysis of Intra- and Intermolecular Schmidt Reactions.

II. Copper-Catalyzed Oxaziridine-Mediated C–H Bond Oxidation.

III. Synthesis and Cytotoxic Evaluation of Withalongolide A Analogues.

By

Hashim F. Motiwala
M.S. (Med. Chem.), NIPER, 2006

Submitted to the graduate degree program in Department of Medicinal Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Dissertation Committee

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Dr. Jeffrey Aubé (Chairperson)

_____
Dr. Barbara N. Timmermann

_____
Dr. Blake R. Peterson

_____
Dr. Jon A. Tunge

_____
Dr. Helena C. Malinakova

Date Defended: January 22, 2014

The Dissertation Committee for Hashim F. Motiwala
certifies that this is the approved version of the following dissertation:

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Dr. Helena C. Malinakova

Date approved: April 8, 2014

Abstract

The research presented herein describes four separate projects, focusing on synthetic methodology development, discovery of novel cytotoxic agents, and natural product isolation.

Catalysis of Intra- and Intermolecular Schmidt Reactions. A method for carrying out the intramolecular Schmidt reaction of alkyl azides and ketones using a substoichiometric amount of catalyst is described. Following extensive screening, the use of the strong hydrogen-bond-donating solvent hexafluoro-2-propanol (HFIP) was found to be consistent with low catalyst loadings, which ranged from 2.5 mol % for favorable substrates to 25 mol % for more difficult cases. Reaction optimization, broad substrate scope, and preliminary mechanistic studies of this improved version of the reaction are discussed. The use of HFIP as the solvent also allowed for the extension of this methodology to intermolecular variants of Schmidt reaction favoring the development of mild, operationally simple, and more efficient protocols, requiring considerably less amounts of acid catalysts for these variants.

Copper-Catalyzed Oxaziridine-Mediated C–H Bond Oxidation. The highly regio- and chemoselective oxidation of an activated C−H bond via a copper-catalyzed reaction of oxaziridine is described. The oxidation proceeded with a variety of substrates, primarily comprising of allylic and benzylic examples, as well as one example of an otherwise unactivated tertiary C−H bond. The mechanism of the reaction is proposed to involve single-electron transfer (SET) to the oxaziridines to generate a copper-bound radical anion, followed by hydrogen atom abstraction and collapse to products, with regeneration of the catalyst by a final SET event. The involvement of allylic radical intermediates en route to the product was supported by a radical-trapping experiment with TEMPO.

Synthesis and Cytotoxic Evaluation of Withalongolide A Analogues. The natural product withaferin A exhibits potent antitumor activity and other diverse pharmacological activities. The recently discovered withalongolide A, a C-19 hydroxylated congener of withaferin A, was reported to possess cytotoxic activity against head and neck squamous cell carcinoma (HNSCC). Interestingly, semisynthetic acetylated analogues of withalongolide A were shown to be considerably more cytotoxic than the parent compound. To further explore the structure–activity relationship (SAR), 20 new semisynthetic analogues of this highly oxygenated withalongolide A were designed, synthesized, and evaluated for cytotoxic activity against four different cancer cell lines. A number of derivatives were found to be more potent than the parent compound and withaferin A.

Isolation of Withalongolide O from *Physalis longifolia*. The SAR analysis of reported bioactive withanolides revealed certain crucial structural requisites for possessing a potent cytotoxic activity. The semisynthesis of a putative unnatural withanolide incorporating all the basic and essential structural features to boost the antiproliferative activity was contemplated. Withaferin A was considered as an appropriate starting material for this purpose. Although the semisynthetic efforts met with failure, it was during the isolation of withaferin A from the crude plant extract that we discovered a novel withanolide, withalongolide O. The structure of withalongolide O was determined using various spectroscopic techniques and subsequently confirmed by X-ray crystallographic analysis. Both withalongolide O and its diacetate exhibited potent cytotoxicity against four different cancer cell lines.

Acknowledgments

بسم الله الرحمن الرحيم

First and above all, I praise and pay obeisance to Allah, the almighty for His showers of blessings and the strength He granted me throughout the life.

I also express my shukur (gratitude) to his Holiness Aqamoula Syedna Mohammed Burhanuddin (RA) and Syedna Aliqadr Mufaddal Saifuddin (TUS) for their blessings and dua mubarak.

I would like to express my sincere and heartfelt appreciation to my graduate advisor, Professor Jeffrey Aubé for his exceptional mentorship, continual guidance, seemingly infinite patience, unwavering support, encouragement, and constructive criticism, which have helped me grow, both professionally and personally, and has left me gratified as a graduate student. I am truly grateful for the opportunity I had to work in his laboratory. His research and scholarly excellence, erudite scientific writing, and scientific creativity had a direct influence in fostering my academic excellence, which will continue to do so in my future career.

I would like to thank Professors Barbara N. Timmermann, Blake R. Peterson, Thomas E. Prisinzano, Jon A. Tunge, Helena C. Malinakova, and Paul R. Hanson for their instrumental classroom instruction and the knowledge they shared, and their time and input as committee members. I would also like to thank other faculty members in the Departments of Chemistry and Medicinal Chemistry for their teachings.

I would like to express my gratitude towards all those who have lent a helping hand over these years. A special thanks to Dr. Thomas Coombs for being a wonderful friend and an amazing co-mentor, and the integral role he played in my graduate career. I am also grateful to all my friends (especially Gurpreet Singh, Drs. Ruzhang Liu, Jennifer Poole, and

Stephen Slauson) and colleagues in the Aubé group for their stimulating scientific discussions, constant motivation, and support. I also thank Gurpreet Singh, Drs. Sarah Scarry, Digamber Rane, and Robert Smith for proofreading my dissertation. I also acknowledge all the co-authors of the published manuscripts for their help and research contributions. I am grateful to my classmates, especially Tamara Vasiljevik and David Hymel for their friendship and support.

I would like to acknowledge David Hill, Shelley Sandberg, and Cady Bush for the technical and administrative assistance. I also thank the staff of Department of Medicinal Chemistry and Higuchi Biosciences Center for various administrative assistance. I am sincerely grateful to Dr. Victor W. Day, Dr. Justin Douglas, Sarah Neuenswander, and Patrick Porubsky for their timely assistance with the spectroscopic analysis.

I would like to thank Dr. Barbara N. Timmermann and her group members for providing with withalongolide A and crude withaferin A, and Dr. Mark S. Cohen and Joseph Bazzill at the University of Michigan Hospital and Health Systems and Abbas Samadi for carrying out the cytotoxicity evaluation of withalongolide A analogues.

I also express my appreciation to Drs. Blake R. Peterson and Justin Douglas for assistance with NMR titration experiments, and David Hymel for helpful discussions.

I thank Dr. Ruzhang Liu for providing 1-phenylhex-5-en-1-one **44a**, Dr. James N. Plampin III for 3-azidopropanol **24b**, Dr. Michael C. McLeod for 2-(3-azidopropyl)cyclohex-2-en-1-one **9**, and Manwika Charaschanya for *trans*-androsterone **12r**.

I would like to express my sincere gratitude to Professor Aubé for the nomination and the respective committee members for nominating me for the Les and Betty Mitscher Prize and the Irsay–Dahle Award.

I am also very grateful to the National Institute of General Medical Sciences (GM-049093) and the Office of Research and Graduate Studies from the University of Kansas for financial support.

Words have no power to express my deepest sense of gratitude to my mother Sakina and father Fakhruddin for their loving encouragement, endless support, and unwavering faith. Whatever good I have achieved in life, I owe it all to them. I also thank my brother Mohammed for his love and support over the years.

Finally, I would like to give my deepest thanks to my wife Alifya for her endless love, support, and understanding towards me.

My motto is more, "If you want to find something new, look for something new!" There is a certain amount of risk in this attitude, as even the slightest failure tends to be resounding, but you are so happy when you succeed that it is worth taking the risk.

–Yves Chauvin

<http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2005/chauvin-bio.html>

Table of Contents

List of Abbreviations

Abbreviation	Keyword
$[\propto]_{D}^{25}$	Specific Rotation [Measured at 589 nm (D-Line) and 25 °C]
Ac	Acetyl
acac	acetylacetonate
AcBr	Acetyl Bromide
AcCl	Acetyl Chloride
ACN	Acetonitrile
APT	Attached Proton Test
AUC	Area Under the Curve
BINOL	(±)-1,1′-Binaphthalene-2,2′-diol (2,2′-Dinaphthol)
$BMIMBF_4$	1-Butyl-3-methylimidazolium Tetrafluoroborate
BNDHP	1,1′-Binaphthyl-2,2′-diyl Hydrogenphosphate
bp	Boiling Point
brsm	Based on Recovered Starting Material
Bs	*p*-Bromobenzenesulfonyl (Brosyl)
Bu	Butyl
compd	Compound
Concn	Concentration
COSY	Correlation Spectroscopy (^1H–^1H)
***m*-CPBA**	*meta*-Chloroperoxybenzoic Acid
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur Trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	*N,N*-Dimethylacetamide
DMAP	4-(*N,N*-Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
dr	Diastereomeric Ratio

DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ee	Enantiomeric Excess
Et	Ethyl
EtOAc	Ethyl Acetate
equiv	Equivalent
FTIR	Fourier Transform Infrared
GC	Gas Chromatography
GHS	Growth Hormone Secretagogue
Hz	Hertz
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMBC	Heteronuclear Multiple-Bond Correlation
HMPA	Hexamethylphosphoramide
HNSCC	Head and Neck Squamous Cell Carcinoma
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
17β-HSD	17β-Hydroxysteroid Dehydrogenase
HSQC	Heteronuclear Single-Quantum Correlation Spectroscopy
IR	Infrared
IS	Internal Standard
LDA	Lithium Diisopropylamide
Me	Methyl
MeOH	Methanol
mp	Melting Point
NOESY	Nuclear Overhauser Effect Spectroscopy
NMR	Nuclear Magnetic Resonance
Ns	*p*-Nitrobenzenesulfonyl (Nosyl)
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
Pd/C	Palladium on Carbon
Piv	Pivalate
Pr	Propyl
PTSA/*p*-TsOH	*para*-Toluenesulfonic Acid
rac	*racemic*
rel*	*relative*

rt	room temperature
SET	Single-Electron Transfer
SPE	Solid Phase Extraction
SAR	Structure–Activity Relationship
TBAH	Tetrabutylammonium Hydroxide
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxyl
TFA	Trifluoroacetic Acid
TFE	2,2,2-Trifluoroethanol
TfOH	Triflic Acid
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMANO	Trimethylamine *N*-Oxide
TMS	Trimethylsilyl/Tetramethylsilane
$TMSN_3$	Trimethylsilyl Azide/Azidotrimethylsilane
***p*-TsCl**	*para*-Toluenesulfonyl Chloride
UPLC	Ultra Performance Liquid Chromatography
UV	Ultraviolet

*The term *rel* is used to denote that the entire stereochemistry of a structure is relative only. The terms *R* and *S* are employed for chiral elements possessing either absolute or relative stereochemistry. The term *rel* is used in conjunction with *R* and *S* for structures with only relative stereochemistry.

List of Figures*

*Figures S1–S5 are parts of Experimental Sections

List of Schemes

Chapter 2

List of Tables*

Chapter 1

Catalysis of Intra- and Intermolecular Schmidt Reactions

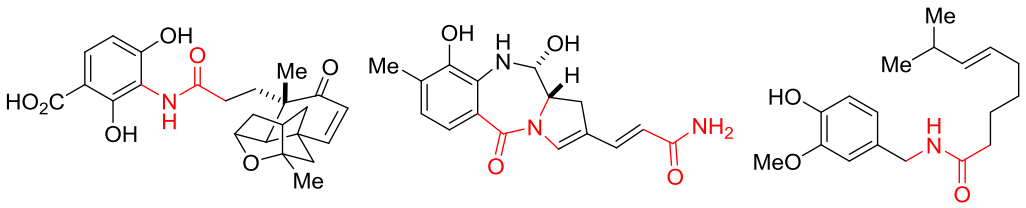
1.1 Introduction

Amide and Lactam

The amide bond is one of the most important functional groups in chemistry and biology.[1] The hydrogen bonding of amide groups defines the structural features of proteins, the key building blocks of life.[2] Apart from the prevalence of amide functionality in biological systems, the vast majority of molecules including natural products and major marketed drugs contain amide and lactam functionalities (Figure 1).[3] The ubiquity of amide and lactam skeletons in nature, pharmaceuticals, and technology as structural materials has continued to inspire the discovery of new reaction methodologies for their synthesis.

Amides are traditionally synthesized by the condensation of amine and carboxylic acids via an activated ester. Many new approaches have been developed over the past few decades including catalytic methods for amide formation.[4] Nitrogen-insertion reactions offer alternative routes to the formation of amides and lactams. The Beckmann rearrangement of ketoximes[5] and the Schmidt reaction of ketones[6] are the two most common rearrangement approaches to form amides or lactams (Scheme 1). The Beckmann rearrangement is a two-step transformation, where a ketone is first converted to an oxime, followed by an acid-catalyzed rearrangement to an amide or a lactam. The Beckmann rearrangement of cyclohexanone is commonly applied for the large-scale production of caprolactam, which is used in the manufacturing of Nylon-6, a synthetic polymer.[7] In contrast, the Schmidt reaction of a ketone with hydrazoic acid (HN_3) in the presence of an acid catalyst can lead to an amide or a lactam in a single step.

(a) Natural-products containing amide functional groups

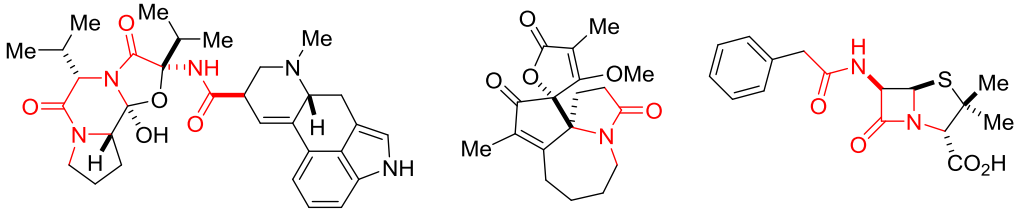


Platensimycin
(antibiotic)

(+)-Anthramycin
(antitumor)

Capsaicin
(analgesic)

(b) Natural-products containing lactams

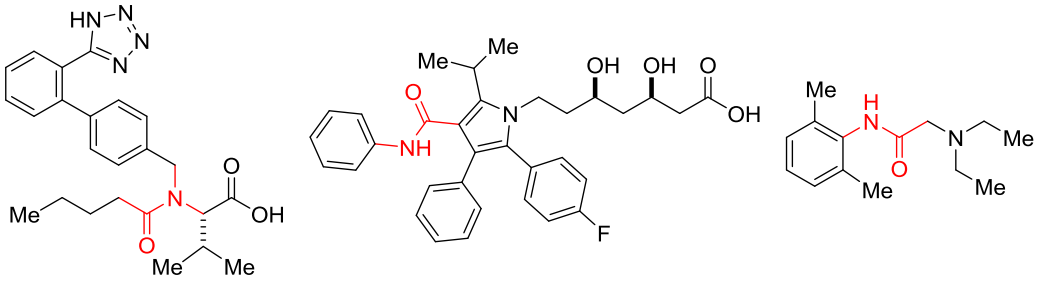


Ergocornine
(dopamine receptor agonist)

Stemonamide
(antitussive)

Penicillin G
(antibiotic)

(c) Drugs containing amides

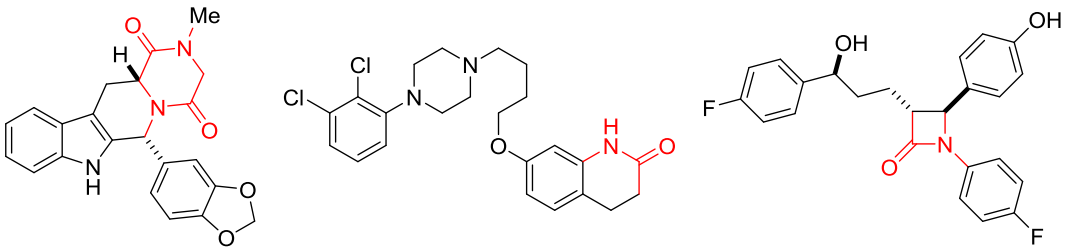


Valsartan
(antihypertensive)

Atorvastatin
(lipid-lowering agent)

Lidocaine
(local anesthetic)

(d) Drugs containing lactams



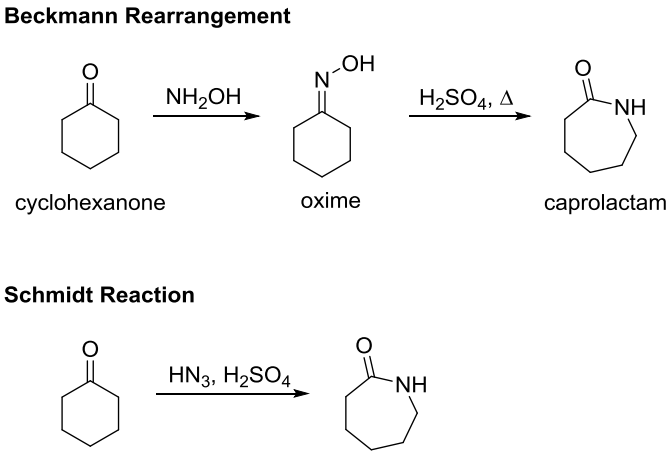
Tadalafil
(PDE5 inhibitor)

Aripiprazole
(antipsychotic)

Ezetimibe
(cholesterol-lowering agent)

Figure 1. Natural products and drugs with amide and lactam functionalities.

Scheme 1. Beckmann and Schmidt Reactions

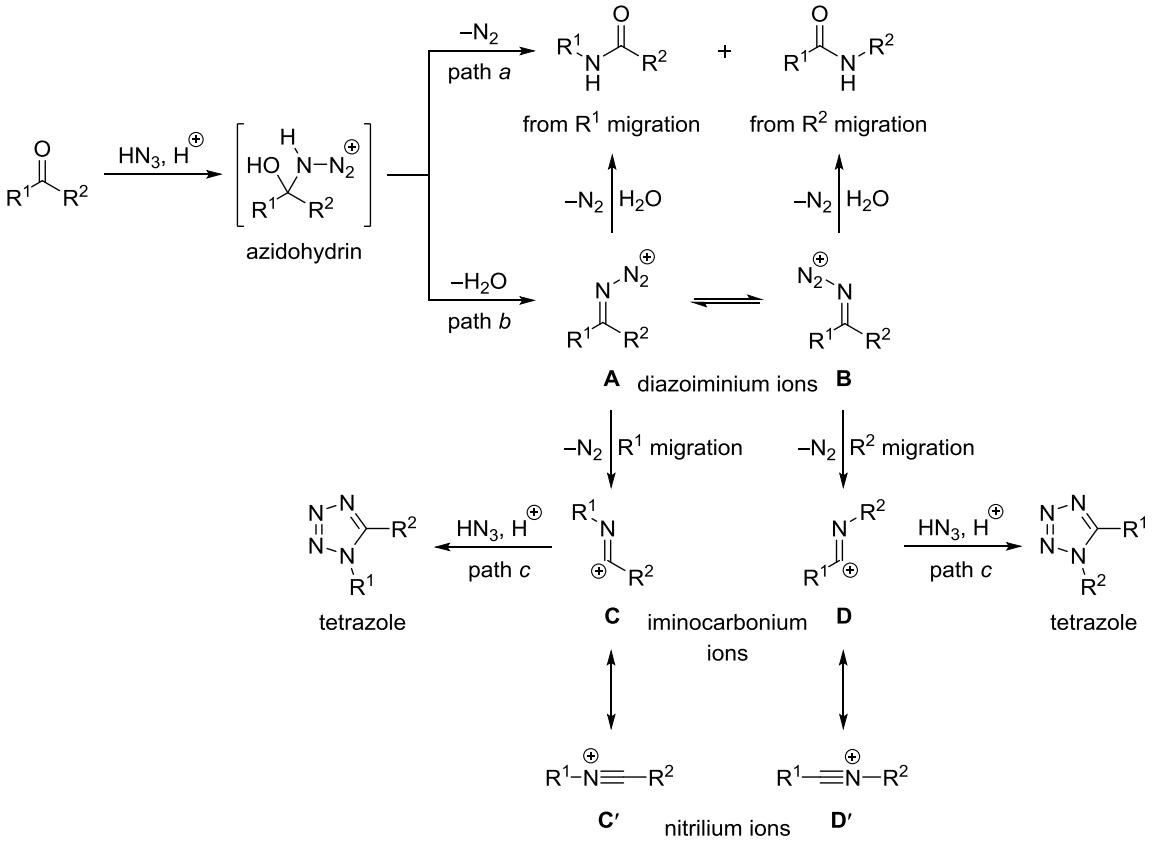


Schmidt Reaction

The Schmidt family comprises related reactions of carbonyl compounds with HN_3 (normally generated in situ from sodium azide, NaN_3) or alkyl azides to give a variety of nitrogen-insertion products.[6c] The mechanism for the Schmidt reaction of a ketone with HN_3 is shown in Scheme 2. Acid-catalyzed activation of the carbonyl followed by addition of the azide leads to the formation of an azidohydrin. This intermediate can directly collapse through concomitant migration of the R group and the loss of nitrogen, which is a powerful driving force through an entropic gain, to provide amide regioisomers (path *a*). Alternate pathway (path *b*) involves the initial dehydration step to form diazoiminium ions (**A** and **B**) followed by rearrangement to give iminocarbonium ions (**C** and **D**) or nitrilium ions (**C'** and **D'**). The iminocarbonium ions can either undergo hydration to provide same amide regioisomers or excess HN_3 can add to iminocarbonium ions via path *c* to form tetrazole isomers. Similar to the Beckmann reaction mechanism, the substituents (mostly alkyl groups) antiperiplanar to the nitrogen leaving group migrates from carbon to nitrogen leading to iminocarbonium or nitrilium ion intermediates. The group migrates with the

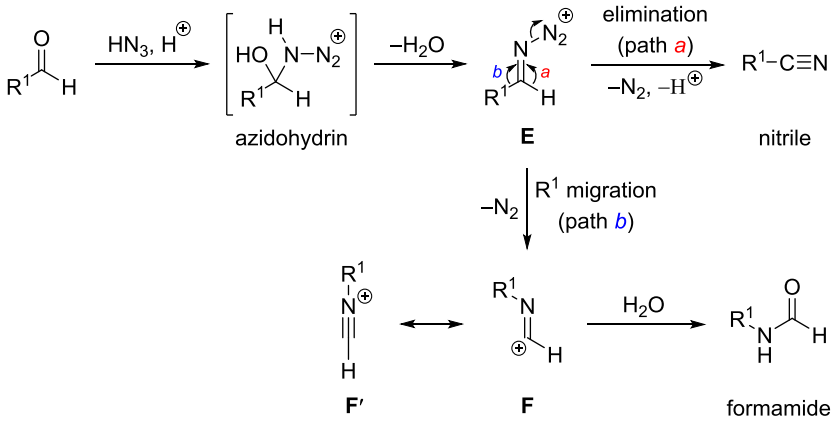
retention of configuration about the migrating carbon and generally the bulkier of the two carbonyl substituents migrates preferentially.[8]

Scheme 2. Mechanism for the Schmidt Reaction of a Ketone with HN_3



In the case of an aldehyde, the diazoiminium ion **E** formed after dehydration of an azidohydrin intermediate can undergo two pathways (Scheme 3). The elimination pathway (path *a*) via proton loss provides a nitrile and the rearrangement pathway (path *b*) through R^1 group migration generates a iminocarbonium ion **F** or nitrilium ion **F'**, which upon hydration affords a formamide.

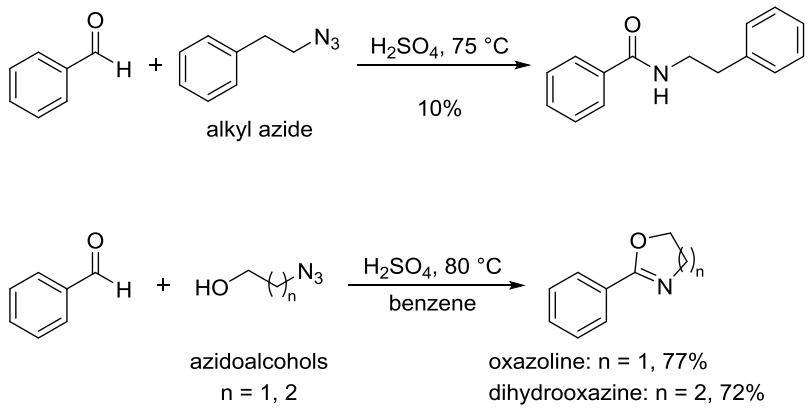
Scheme 3. Mechanism for the Schmidt Reaction of an Aldehyde with HN_3



Boyer Reaction

The use of alkyl azides in place of hydrazoic acid would provide a direct access to *N*-substituted lactams, which would further extend the scope of the Schmidt reaction. During its initial explorations, Briggs[9] and Smith[10] found that alkyl azides did not react with ketones to yield any Schmidt products under standard conditions such as the use of concentrated sulfuric acid (H_2SO_4). In the 1950's, Boyer reported a limited success for the Schmidt reaction of aromatic aldehydes with alkyl azides in the presence of concentrated H_2SO_4.[11] Though the reaction with alkyl azides afforded poor yields (10–25%) of corresponding amides, the reaction of aromatic aldehydes with hydroxyalkyl azides proceeded with much greater efficiency affording oxazolines and dihydrooxazines, respectively (Scheme 4). Unfortunately, this Boyer reaction was severely limited in scope and the reactions failed with aliphatic or electron-rich aromatic aldehydes and ketones.

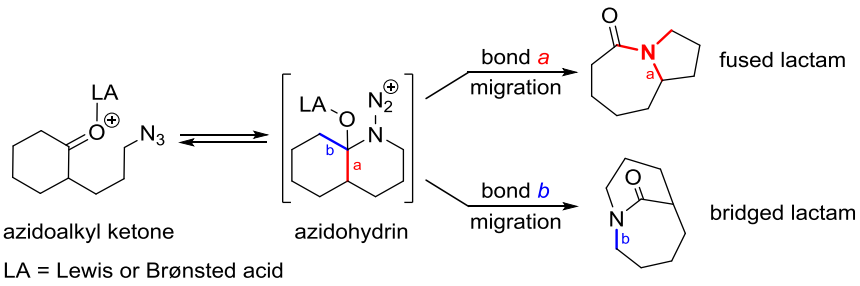
Scheme 4. Reaction of Aromatic Aldehydes with Alkyl Azides and Hydroxyalkyl Azides



Intramolecular Schmidt Reaction

In 1991, Aubé and Milligan discovered an intramolecular variant of the Schmidt reaction.[12] The tethered alkyl azide reacts with the ketone under Lewis or Brønsted acid activation in an intramolecular fashion to provide an amide or a lactam in high yield and in one step under straightforward reaction conditions (Scheme 5).[12-13] Formal insertion of the azide into the activated carbonyl provides an azidohydrin intermediate, which in theory could lead to two regiochemical outcomes. A fused lactam would arise from bond *a* migration whereas the migration of bond *b* would give a bridged system.[13-14] The reaction proceeds with retention of configuration at the migrating carbon.[13]

Scheme 5. Typical Example of an Intramolecular Schmidt Reaction



The intramolecular Schmidt reaction (also known as the Schmidt–Aubé reaction[15]) is an effective and useful method for generating fused lactams with varied ring sizes and substitution patterns.[6c,12-13,16] The typical fused lactam product with the nitrogen atom at a ring fusion (highlighted in red, Scheme 5) is a prominent structural motif found in a wide variety of alkaloids. This strategy has thus been applied to the syntheses of many biologically important alkaloids as well as natural product-inspired libraries (Figure 2).[17]

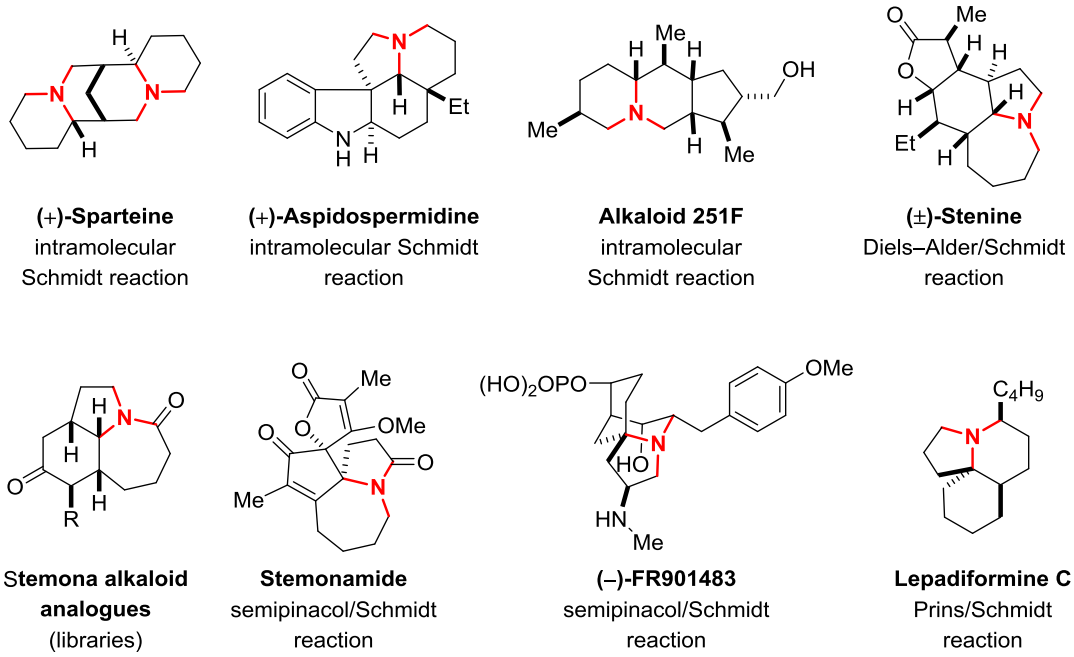


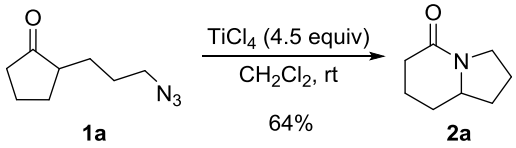
Figure 2. Applications of the intramolecular Schmidt reaction (ref. 17).

1.2 Catalysis of the Intramolecular Schmidt Reaction

Despite the broad utility, the main limitation of the intramolecular Schmidt reaction has been the requirement of excess Lewis or Brønsted acid[6c,13,18] in order to achieve complete conversion, which often renders it unsuitable for strongly acid-sensitive substrates and limits scalability. Two representative examples are shown in Schemes 6a,b. Indeed, we are unaware of any examples that proceed to high conversion with less than a full equiv of acid promoter. This can be attributed to strong product inhibition, which is intrinsic to any reaction that converts a ketone to an amide.

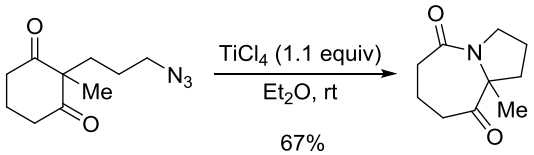
Scheme 6. Examples of Intramolecular Schmidt Reactions Requiring >1 Equiv Catalyst

(a) Intramolecular Schmidt reaction of an azido ketone (Aubé; ref. 13)



1a **2a**

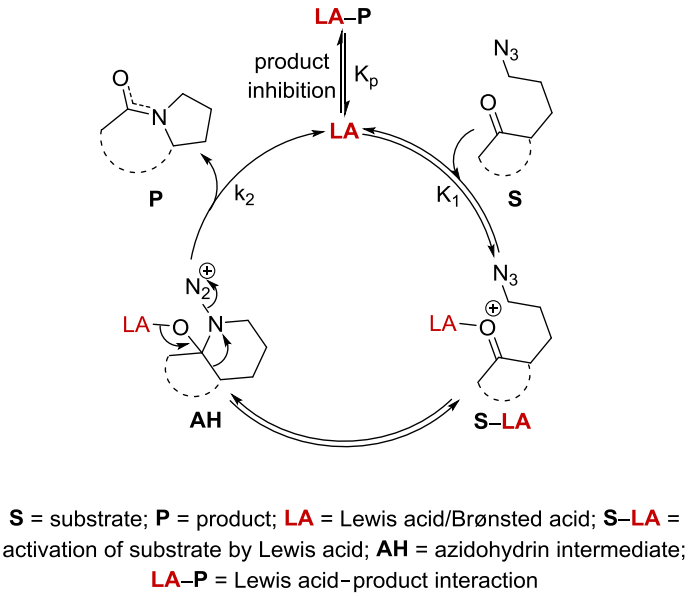
(b) Intramolecular Schmidt reaction of an azido 1,3-diketone (Marsden; ref. 18a)



1b **2b**

The first step in a hypothetical catalytic cycle for the intramolecular Schmidt reaction is the activation of a substrate **S** with a Lewis or Brønsted acid **LA** to form complex **S–LA** (Figure 3).[14] The tethered azide then attacks the activated carbonyl, forming the azidohydrin intermediate **AH**, which upon antiperiplanar bond migration and nitrogen extrusion results in the formation of a product **P**. The lactam produced is strongly Lewis

basic and sequesters the catalyst in an unproductive manner. We propose that this unfavorable catalyst–product interaction results in product inhibition deterring the progress of reaction and necessitating the use of superstoichiometric amounts of catalyst.[13,18a,19]



S = substrate; **P** = product; **LA** = Lewis acid/Brønsted acid; **S**–**LA** = activation of substrate by Lewis acid; **AH** = azidohydrin intermediate; **LA**–**P** = Lewis acid–product interaction

Figure 3. Hypothetical catalytic cycle showing product inhibition through catalyst sequestration by the product.

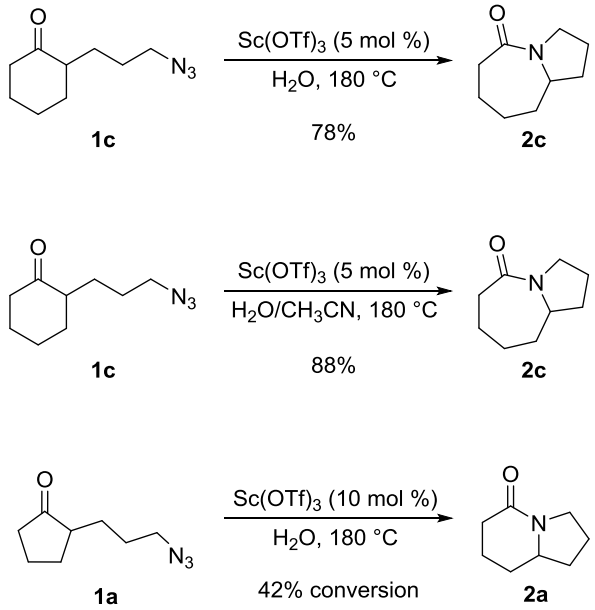
Catalytic reaction development could be considered as an effective strategy for streamlining many challenges that still lie in organic synthesis. In addition, a version of this reaction that employs vastly smaller amounts of metal may well be cleaner and more efficient, even as it minimizes the generation of metal waste.[20] Hard Lewis acids such as titanium(IV) chloride ($TiCl_4$) and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) and strong Brønsted acids such as triflic acid (TfOH, CF_3SO_3H) and trifluroacetic acid (TFA, CF_3CO_2H) are typically required to promote this reaction. A fundamental challenge in designing a catalytic variant for this reaction lies in the inherent strength of the complex formed between the catalyst and the product, which is a hard acid-hard base interaction. Related reactions that generate amide or lactam products, such as the Beckmann

rearrangement and Ritter reaction, have also suffered in the past from the requirement of a stoichiometric amount of strong acids and harsh reaction conditions.[21-22] The role of the lactam in product inhibition has been showcased for Beckmann rearrangement using a microchemical system.[23] However, recent catalytic developments for these reactions have allowed for the use of substoichiometric amounts of Lewis or Brønsted acid, improving efficiency and expanding scope of those processes.[21-22] The use of ionic liquids[24] and extensive screening of catalysts and solvents led to the realization of these catalytic reactions. We envisioned that catalysis in the intramolecular Schmidt reaction might be more efficient if conditions were identified wherein a ligand, solvent, or additive is capable of competing with the catalyst in forming a complex with the Lewis basic lactam, thus allowing catalyst turnover. Our long standing efforts in this direction led us to the development of a catalytic intramolecular Schmidt reaction[25] that is superior in essentially every way to the version that we and others have been exploring since 1991.[6c,12-13,18]

Screening and Optimization of Reaction Conditions

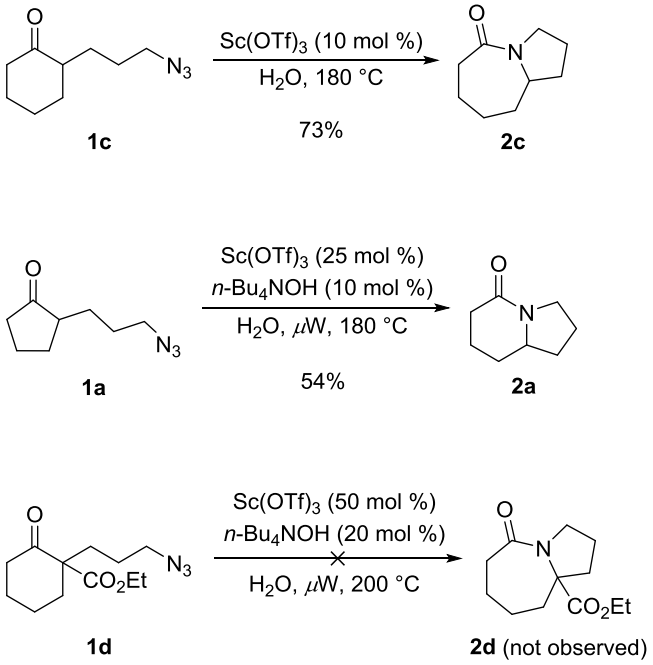
A long-standing goal of this laboratory has been to replace the stoichiometric Schmidt reaction by identifying conditions that would (1) require low, substoichiometric amounts of catalyst, (2) be mild, efficient, and proceed at room temperature, and (3) would have broad substrate scope. We initially focused on catalyst and additive screening. An initial survey of Lewis acids for the conversion of **1c** to **2c** was carried out by Sze-Wan Li (this laboratory; unpublished). After examining several conditions, she found that 5 mol % of scandium(III) triflate ($Sc(OTf)_3$) could efficiently promote the reaction of **1c** to **2c**, but only at high temperatures (Scheme 7; see Table S1 in the Experimental Section for details). However, for a more demanding five-membered cyclic azido ketone **1a**, only 42% conversion to lactam **2a** was observed, even when 10 mol % $Sc(OTf)_3$ was used.

Scheme 7. Preliminary Screening by Sze-Wan Li



Erin Hirt followed up on the results obtained by Sze-Wan Li and she found that 10 mol % of $Sc(OTf)_3$ was required for the similar transformation of **1c** to **2c** (Scheme 8; see Table S2 in the Experimental Section for details).[26] She further investigated various lanthanide triflates as Lewis acids to promote the reaction, however, all lanthanide Lewis acids examined were found to be less effective than $Sc(OTf)_3$ (see Table S2). Upon screening of additives, she found that the use of a phase-transfer catalyst, tetrabutylammonium hydroxide (TBAH, *n*-Bu_4NOH) under microwave irradiation conditions along with 25 mol % $Sc(OTf)_3$ helped achieve complete conversion of **1a** to **2a**. Unfortunately, these reaction conditions were plagued with extremely limited substrate scope (cf. **1c** and **1d** in Scheme 8). Furthermore, the use of a phase-transfer catalyst made the aqueous work-up and purification more cumbersome and less efficient resulting in lower yields of desired lactams.

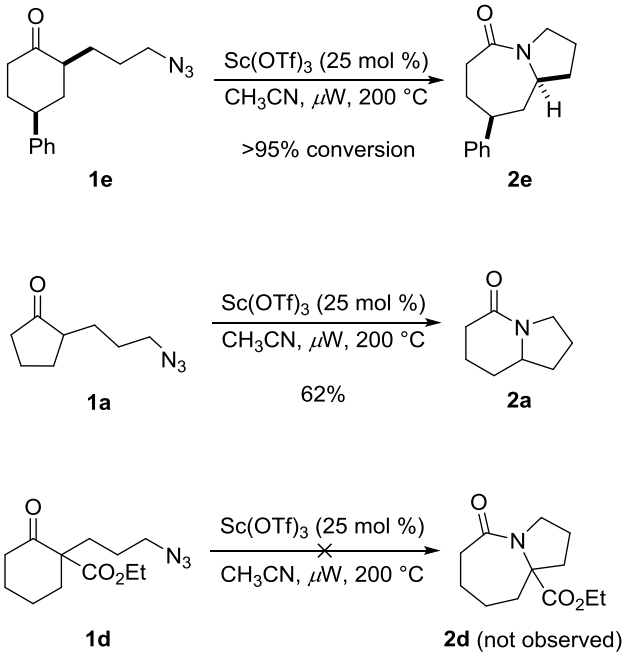
Scheme 8. Preliminary Screening by Erin Hirt



After Erin Hirt, Charlie Fehl further advanced the development by identifying acetonitrile (ACN, CH_3CN) as a better solvent than H_2O for this reaction, either alone or with a phase-transfer catalyst; albeit on a different substrate **1e** (unpublished; Scheme 9, see Table S3 in the Experimental Section for details). A short screening of different Lewis and Brønsted acids in ACN once again revealed $Sc(OTf)_3$ as an optimal catalyst. However, higher catalyst loadings up to 25 mol % and unacceptably high temperature of 200 °C were generally necessary (Scheme 9). Although the reaction of cyclopentanone **1a** in ACN gave slightly better yield of lactam **2a**, the reaction of **1d** under the same conditions failed as before (cf. Schemes 8 and 9). Reactions of substrates like **1a** or **1d** require longer reaction times than **1c** in the stoichiometric reaction and are often poorer yielding as well.[13,27] Several additives were also screened with or without $Sc(OTf)_3$ in ACN, H_2O, or DCE at different temperatures, but all of them delivered either similar or inferior conversion

compared to $Sc(OTf)_3$ alone (see Table S3, entry 4 in the Experimental Section; for the list of additives, see below Table S3).

Scheme 9. Preliminary Screening by Charlie Fehl



On the basis of these preliminary results, we decided to expand our search by focusing on three screening parameters: solvent, catalyst, and temperature. *trans*-4-Phenyl-2-(3-azidopropyl)cyclohexanone **1f** was chosen as a test example to probe several issues known to arise in the intramolecular Schmidt reaction (Scheme 10). The trans isomer was primarily chosen to probe for epimerization (known to be a problem in some applications),[28] which could lead to the thermodynamically more stable cis ketone **1e**; the read-out for this process would be the detection of lactam **2e** following ring expansion. In addition, the trans ketone **1f** is capable of generating either a fused lactam **2f** or a bridged isomer **3f** by migration of one α-carbon over the other (bond *a* vs bond *b* migration).[13] Finally, the phenyl chromophore in **1f** allowed faster analyses and quantification of reaction mixtures by UPLC (see the Experimental Section).

Scheme 10. Model Reaction

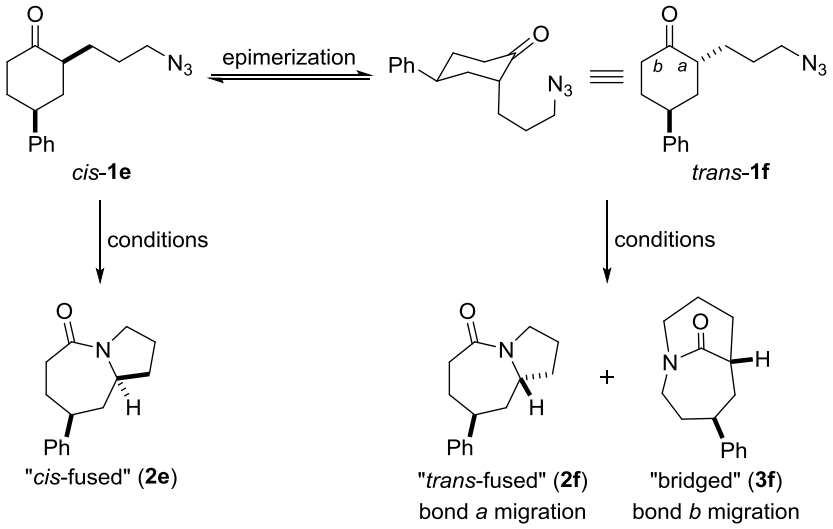


Figure 4 depicts the results of more detailed screening of reaction conditions (see the Experimental Section for details). Examination of 23 different solvents was first carried out using 20 mol % $Sc(OTf)_3$ at 150 °C. Only five solvents [nitromethane, benzonitrile, acetic acid, trifluoroethanol (TFE, CF_3CH_2OH), and the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIMBF_4$)] gave the product in high yield. When the $Sc(OTf)_3$ loading was reduced to 10 mol %, only TFE resulted in complete conversion. We then focused our attention on catalyst screening using 10 mol % catalyst with TFE as the solvent at 80 °C. In total, 51 catalysts were screened, including 44 Lewis acids representing 31 different elements and 7 Brønsted acids. Of these, a number of transition metal salts such as $TiCl_4$, $ZrCl_4$, and $Fe(OTf)_3$, some post-transition metal salts such as $In(OTf)_3$ and $Bi(OTf)_3$, and metalloid-containing compounds such as $SiCl_4$ and $SbCl_5$ gave results that were good enough for further screening. Further evaluation of these selected catalysts at 10 mol % loading in TFE at lower temperatures (50 and 25 °C) revealed $TiCl_4$ and $SiCl_4$ to be most effective. The identification of $TiCl_4$ was notable as it has been a catalyst of choice for many stoichiometric intramolecular Schmidt reactions.[13,18a,29]

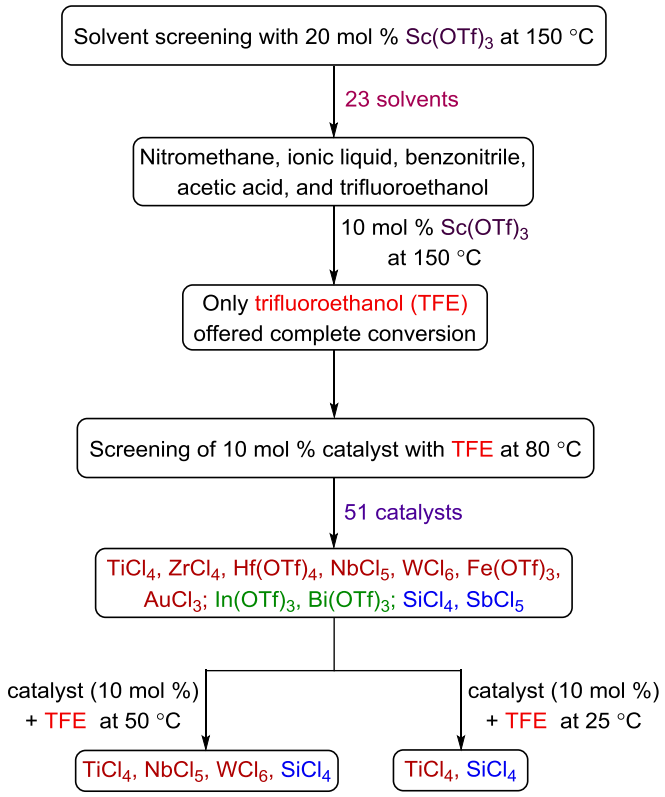
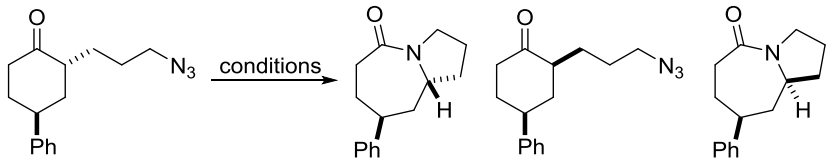


Figure 4. Screening flow chart. Transition metals are depicted in deep red, post-transition metals in green, and metalloids in blue.

Identification of TFE as nearly unique in permitting catalyst turnover prompted us to more rigorously examine the effect of solvents using **1f** as the substrate and 10 mol % $TiCl_4$ as the catalyst (Table 1). Again, TFE was observed to give the best results with respect to both conversion and stereochemical retention (cf. entry 7 with entries 1–6). The results with TFE prompted us to consider other fluorinated alcohols, specifically hexafluoro-2-propanol (HFIP, $(CF_3)_2CHOH$). Compared to their non-fluorinated alcohol analogues, TFE and HFIP have low nucleophilicity, low p*K*a, high ionizing power, high polarity, ability to solvate anions, and are strong hydrogen-bond donors (Table 2).[30] Accordingly, they are often used as a solvent, co-solvent, or a Lewis acid substitute[30j,31] in oxidations[32] and in ring-opening reactions of oxiranes, cycloadditions, and deprotection reactions.[30g,i,k] Their utility has been attributed to the strong hydrogen-bond donor ability of these solvents.[30g,h,32b,33] Moreover,

the use of these solvents to denature proteins and induce α-helical secondary structures provided some ancillary expectation that they might prove useful in modifying the ability of our product lactams to coordinate with acid promoters.[34] Because of the stronger hydrogen-bond donor ability and higher ionizing power of HFIP compared to TFE, HFIP often provides superior results both in reaction rate enhancement[30g,j,31,35] and as a helix-inducing co-solvent.[34a]

Table 1. Optimization of Conditions for Intramolecular Schmidt Reaction of 1f[a,b]



entry	catalyst	catalyst (mol %)	solvent	additive	temp (°C)	time (h)	% yield (**2f**:**2e**)[c]	% recovery (**1f**:**1e**)[d]
1	$TiCl_4$	10	CH_2Cl_2	–	25	18	6% (40:60)	84% (10:90)
2	$TiCl_4$	10	CH_3NO_2	–	25	18	35% (37:63)	61% (3:97)
3	$TiCl_4$	10	$BMIMBF_4$	–	25	18	12% (30:70)	80% (12:88)
4	$TiCl_4$	10	C_6F_5CN	–	25	18	30% (32:68)	58% (10:90)
5	$TiCl_4$	10	*i*-PrOH	–	37	18	trace	86% (3:97)
6	$TiCl_4$	10	CH_3CN	–	37	18	41% (15:85)	47% (1:99)
7	$TiCl_4$	10	CF_3CH_2OH	–	25	18	79% (82:18)[d]	trace
8	none	–	$(CF_3)_2CHOH$	–	37	18	ND	93% (98:2)
9	$TiCl_4$	10	CH_3CN	$(CF_3)_2CHOH$[e]	25	18	34% (10:90)	61% (5:95)
10	$TiCl_4$[g]	10	$(CF_3)_2CHOH$	–	25	12	88% (90:10)[f]	ND
11	$TiCl_4$	10	$(CF_3)_2CHOH$	–	25	12	91% (98:2)[f]	ND
12	$TiCl_4$	7	$(CF_3)_2CHOH$	–	25	24	88% (98:2)[f]	ND
13	**$TiCl_4$**	**5**	**$(CF_3)_2CHOH$**	–	**25**	**38**	**89% (99:1)[f]**	**trace**
14	$TiCl_4$[h]	5	$(CF_3)_2CHOH$	–	25	38	86% (98:2)	trace
15	$TiCl_4$[i]	5	$(CF_3)_2CHOH$	–	25	38	89% (98:2)	ND
16	$TiCl_4$	5	$(CF_3)_2CHOH$	DTBMP[j]	25	38	52% (98:2)	19% (98:2)
17	$TiCl_4$	5	$(CF_3)_2CHOH$	DTBMP[k]	25	38	21% (99:1)	50% (96:4)[c]

entry	catalyst	catalyst (mol %)	solvent	additive	temp (°C)	time (h)	% yield (**2f**:**2e**)[c]	% recovery (**1f**:**1e**)[d]
18	$TiCl_4$	5	$(CF_3)_2CHOH$	MS (4Å)	25	38	11% (97:3)	86% (98:2)
19	$SiCl_4$	5	$(CF_3)_2CHOH$	–	25	38	86% (98:2)[f]	ND
20	$SbCl_5$	5	$(CF_3)_2CHOH$	–	25	38	86% (98:2)[f]	ND
21	$NbCl_5$	5	$(CF_3)_2CHOH$	–	25	38	82% (98:2)	ND
22	WCl_6	5	$(CF_3)_2CHOH$	–	25	38	86% (98:2)[f]	ND
23	$HfCl_4$	5	$(CF_3)_2CHOH$	–	25	38	77% (99:1)[f]	15% (98:2)
24	$Hf(OTf)_4$ hydrate	5	$(CF_3)_2CHOH$	–	25	38	76% (98:2)	14% (98:2)
25	$Bi(OTf)_3$	5	$(CF_3)_2CHOH$	–	25	38	60% (98:2)	25% (98:2)
26	$Fe(OTf)_3$	5	$(CF_3)_2CHOH$	–	25	38	83% (98:2)[f]	trace
27	$Sc(OTf)_3$	5	$(CF_3)_2CHOH$	–	25	38	28% (97:3)	61% (98:2)
28	HCl	10	$(CF_3)_2CHOH$	–	25	38	40% (96:4)[f]	46% (98:2)
29	HCl	20	$(CF_3)_2CHOH$	–	25	38	78% (97:3)[f]	trace
30	CF_3CO_2H	10	$(CF_3)_2CHOH$	–	25	38	62% (97:3)	34% (98:2)
31	Armstrong's acid	5	$(CF_3)_2CHOH$	–	25	38	65% (98:2)	13% (98:2)
32	$ClSO_3H$	10	$(CF_3)_2CHOH$	–	25	20	80% (98:2)[f]	ND
33	(*S*)-BNDHP	5	$(CF_3)_2CHOH$	–	25	38	32% (96:4)[l]	62% (98:2)
34	$Ti(O^iPr)_4$	10	$(CF_3)_2CHOH$	–	25	38	trace	93% (95:5)

[a]To a solution of substrate **1f** (0.10 mmol) in solvent (0.50 mL) at rt was added a catalyst under nitrogen or argon atmosphere, unless otherwise mentioned. For $TiCl_4$, $SiCl_4$, or $SbCl_5$, a 1.0 M solution in CH_2Cl_2 was used. A 2.0 M solution of hydrogen chloride (HCl) in diethyl ether was used. ND = Not detected. [b]Concn of substrate was ca. 0.20 M, unless otherwise mentioned. [c]Isolated yield after preparative TLC purification; ratios were determined by ^{1}H NMR analysis. [d]Isolated yield after preparative TLC purification; ratios were determined by UPLC of the crude reaction mixtures. [e]1 equiv of $(CF_3)_2CHOH$ was added. [f]Bridged lactam **3f** was also isolated in 1–4% yield. [g]A 1.0 M solution of $TiCl_4$ in CH_2Cl_2 was added to substrate **1f** followed by the addition of $(CF_3)_2CHOH$. [h]Concn of substrate was ca. 0.40 M. [i]Concn of substrate was ca. 0.10 M. [j]10 mol % DTBMP was used as a Brønsted acid scavenger. [k]20 mol % DTBMP was used. [l]No kinetic resolution was observed. MS (4Å) = Molecular sieves activated (4Å). Armstrong's acid = 1,5-Naphthalenedisulfonic acid tetrahydrate. (*S*)-BNDHP = (*S*)-(+)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate.

Table 2. Properties of Fluorinated and their Corresponding Non-Fluorinated Alcohols

properties	CH_3CH_2OH (EtOH)	CF_3CH_2OH (TFE)	$(CH_3)_2CHOH$ (*i*-PrOH)	$(CF_3)_2CHOH$ (HFIP)
bp (°C)	78	73.8	82.5	58.6
mp (°C)	–114	–43.5	–89.5	–4
Density (ρ)	0.789	1.373	0.781	1.605
pK_a	15.9	12.4	17.1	9.3
Dielectric constant (ε)	24.5	26.7	19.4	16.7
Polarity (P_s)	–	10.20	–	11.08
Polarity (E_T^N)	0.654	0.898	0.546	1.068
Nucleophilicity (N)	0.09	–2.78	0.09	–3.93
Ionizing power (Y)	–2.03	1.045	–2.73	2.46
Polarizability (π*)	0.54	0.73	0.48	0.65
Dipole moment (μ)	1.69	2.03	1.68	2.05
Hydrogen-bond donor acidity (α)[30c]	0.83	1.51	0.76	1.96
Hydrogen-bond acidity (α_2^H)[30d]	0.328	0.567	0.324	0.771
Hydrogen-bond acceptor basicity (β)	0.77	0.00	0.95	0.00
Self-association constant (dm^3/mol)	0.89	0.65	–	0.13

Using HFIP as a substitute for $TiCl_4$ in a control experiment did not afford any product and substrate **1f** was recovered almost quantitatively (Table 1, entry 8). Using 1 equiv of HFIP as an additive with ACN as a solvent did not improve the yield (entry 9). However, when HFIP was used as solvent in combination with 10 mol % $TiCl_4$, complete conversion was observed with increased catalyst turnover compared to TFE (cf. entries 10 and 11 with 7). It was noted that the sequence of addition for the $TiCl_4$ was important. Slight epimerization was observed when $TiCl_4$ was added to substrate **1f** before the addition of HFIP (entry 10). However, when $TiCl_4$ was added to a solution of **1f** in HFIP, negligible epimerization was observed suggesting a buffering action of HFIP (entry 11; vide infra). Lowering the catalyst loading to 7 and 5 mol % $TiCl_4$ produced similar results as with 10

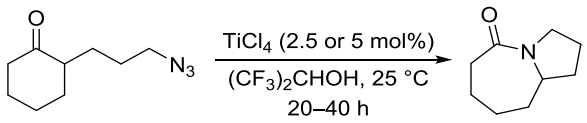
mol % $TiCl_4$ but at the expense of longer reaction times (entries 12 and 13). Changing the concentration of reaction mixture had minimal effect on yield (entries 14 and 15).

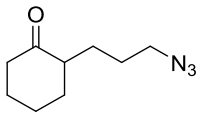
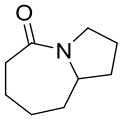
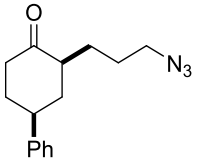
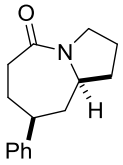
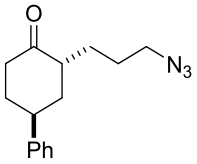
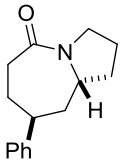
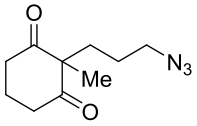
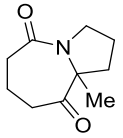
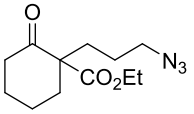
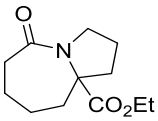
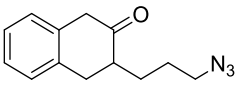
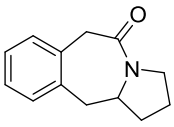
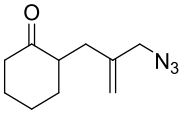
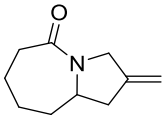
We speculated that reaction of HFIP with $TiCl_4$ might generate HCl in situ along with $Ti[OCH(CF_3)_2]_4$. If so, then 5 mol % $TiCl_4$ should be capable of generating 20 mol % HCl in situ. To test this hypothesis, we ran the reaction in the presence of 10 and 20 mol % 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a proton scavenger (Table 1, entries 16 and 17). Significant catalyst inhibition resulting in lower yields was observed, but reaction to some extent was still observed when 20 mol % DTBMP was used. This could mean that the catalytically active species is HCl generated in situ or that DTBMP, being a base, has some other deleterious effect on the reaction.[36] The reaction in HFIP with other Lewis acids provided the lactam in good yields (entries 19–26), but $Sc(OTf)_3$ provided the product in only 28% yield (entry 27). The reaction with Brønsted acids (5–20 mol %) delivered comparatively lower yield of the product than the reaction with 5 mol % $TiCl_4$ (entries 28–32). Interestingly, reaction with 20 mol % HCl in ether (entry 29) gave a lower yield than that with 5 mol % $TiCl_4$ (entry 13). The use of a chiral phosphoric acid[18b] neither provided good yield nor led to any degree of kinetic resolution (entry 33). The reaction with $Ti(O^iPr)_4$ resulted in only a trace amount of product with quantitative recovery of substrate **1f** (entry 34). Although this supported our supposition that in situ-generated HCl could be the active catalyst, it was hard to reconcile with the reduced yield obtained when HCl in ether solution was used, possibly as a result of concentration errors in the commercial product (see Table 5 and associated discussion for more on this point).

Substrate Scope

Having identified conditions that satisfied our goals (5 mol % $TiCl_4$ in HFIP), we sought to determine the scope of this substoichiometric, catalytic Schmidt reaction. We began with cyclohexanone-derived azido ketones, as previous experience had taught us that these are in general the most facile substrates (Table 3).[12-13] Indeed, the results obtained were in general as good as or better than those obtained using stoichiometric catalysts. Thus, the transformations of **1c** and cis ketone **1e** required only 2.5 mol % $TiCl_4$ (entries 1 and 2), whereas trans ketone **1f** required 5 mol % $TiCl_4$ and a longer reaction time to obtain slightly lower yield of the product (entry 3). The reaction of 1,3-diketone **1b** proceeded in higher yield than reported in the literature (entry 4; cf. Scheme 6b),[18a] while α-ester-substituted **1d**, which failed in the preliminary screening (Schemes 8 and 9), afforded an excellent yield of **2d** using the optimized protocol (entry 5). Other functionalized cyclohexanones such as β-tetralone **1g** (entry 6) and allylic azide **1h**[17m] (entry 7) also provided good yields of the corresponding lactams **2g** and **2h**.

Table 3. Initial Substrate Scope for the Catalytic Intramolecular Schmidt Reaction on Cyclohexanone-Derived Azido Ketones[a,b]

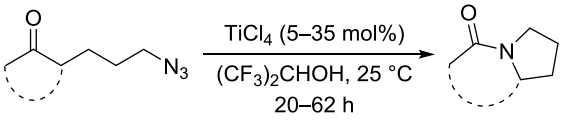


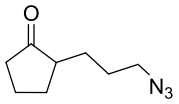
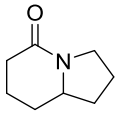
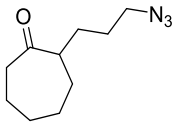
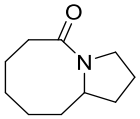
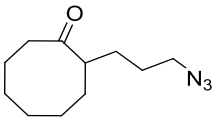
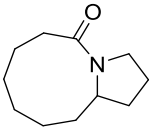
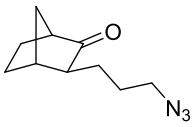
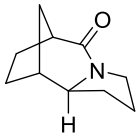
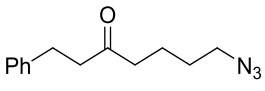
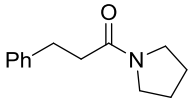
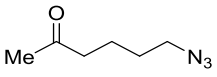
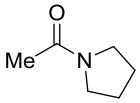
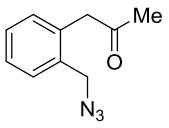
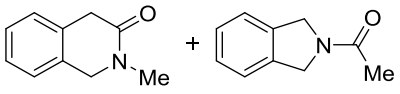
entry	substrate **1**	catalyst (mol %)	time (h)	product **2**	yield (%)[c]
1	 **1c**	2.5	20	 **2c**	94
2	 **1e**	2.5	20	 **2e**	98
3	 **1f**	5	38	 **2f**	87[d]
4	 **1b**	5	24	 **2b**	94
5	 **1d**	5 10	40 18	 **2d**	94 95
6	 **1g**	5	24	 **2g**	89
7	 **1h**	5	24	 **2h**	84

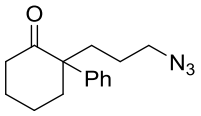
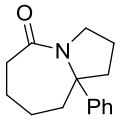
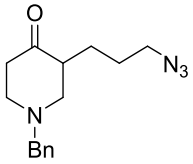
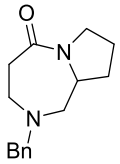
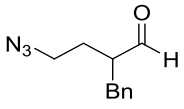
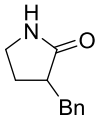
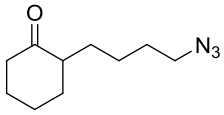
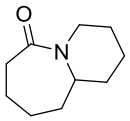
[a]To a solution of substrate (0.40 mmol) in $(CF_3)_2CHOH$ (2.0 mL) at rt was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 under nitrogen atmosphere, and the reaction mixture was stirred at 25 °C for the designated period. [b]Concn of substrate was ca. 0.20 M. [c]Isolated yields. [d]Bridged lactam **3f** was also isolated in ca. 2% yield.

We next examined a broader range of ketone types, including some that we have found challenging under previously established reaction conditions (Table 4). Although the substrate scope was broad, some recalcitrant substrates generally required higher catalyst loadings compared to cyclohexanone-derived azides. For example, cyclopentanone **1a** with 20 mol % $TiCl_4$ afforded a superior yield of indolizidinone **2a**, a structural motif found in many pharmacologically relevant alkaloids (entry 1). The reaction of seven- and eight-membered cyclic azido ketones afforded lactams of medium ring sizes in high yields (entries 2 and 3), and norcamphor-derived **1k** provided a good yield of tricyclic lactam **2k** with 25 mol % $TiCl_4$ (entry 4). *N*-Substituted pyrrolidinones **2l** and **2m** were obtained in good yields from acyclic azido ketones (entries 5 and 6), whereas benzylic azide **1n** provided a mixture of two regioisomers **2n** and **3n** in 4:1 ratio in modest yield with 15 mol % $TiCl_4$ (entry 7).

Table 4. Additional Evaluation of the Reaction Scope[a,b]



entry	substrate **1**	catalyst (mol %)	time (h)	product **2**	yield (%)[c]
1		10	44		60 (78)[d]
		15	44		79
		20	24		87
	1a			**2a**	
2		5	62		34 (85)[d]
		20	48		86[e]
	1i			**2i**	
3		25	62		90
	1j			**2j**	
4		10	62		43 (78)[d]
		25	62		87 (90)[d]
	1k			**2k**	
5		20	24		79 (96)[d,f]
		25	32		94[f]
	1l			**2l**	
6		10	36		73[g]
		15	24		77 (81)[d,g]
		20	24		86[g]
	1m			**2m**	
7		15	24		64
	1n			**2n** + **3n**	
				2n:**3n** = 4:1	

entry	substrate **1**	catalyst (mol %)	time (h)	product **2**	yield (%)[c]
8	 **1o**	25	48	 **2o**	87[h]
9	 **1p**	35	20	 **2p**	90
10	 **1q**	5	24	 **2q**	86
11	 **1r**	20	60	 **2r**	11 (20)[d]

[a]To a solution of substrate (0.40 mmol) in $(CF_3)_2CHOH$ (2.0 mL) at rt was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 under nitrogen atmosphere and the reaction mixture was stirred at 25 °C for the designated period. [b]Concn of substrate was ca. 0.20 M. [c]Isolated yields. [d]Yields in parentheses are based on recovered starting material. [e]Bridged lactam **3i** was also isolated in 2% yield (see the Experimental Section). [f]The product contained 7% 1-phenethylpiperidin-2-one **3l** (see the Experimental Section). [g]The product contained 3% *N*-methyl-2-piperidone **3m** (see the Experimental Section). [h]Bridged lactam **3o** was also isolated in 5% yield (see the Experimental Section).

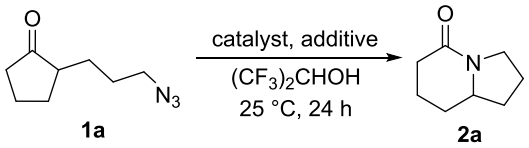
One of the most recalcitrant substrate in the series of cyclohexanone-derived azido ketones was α-phenyl-substituted **1o** (Table 4, entry 8; cf. Table 3, entries 2, 3, and 5). The transformation of **1o** required 25 mol % $TiCl_4$ and a longer reaction time to afford the corresponding fused lactam **2o** along with a small amount of bridged lactam **3o**. Previously, it was shown that the reaction of substrate **1o** with 1 equiv of methylaluminum dichloride ($MeAlCl_2$) in dichloromethane (DCM, CH_2Cl_2) preferentially afforded the fused lactam

2o.[37] Substrate **1p** containing a tertiary amine (a possible additional source of catalyst inactivation) required 35 mol % $TiCl_4$ to provide pyrrolodiazepinone **2p** (Table 4, entry 9).[38] Typically, for the intramolecular Schmidt reaction, nitrogen gas evolution is observed immediately upon addition of the catalyst. However, when $TiCl_4$ was added slowly to a solution of substrate **1p** in HFIP, a yellow precipitate was initially observed, with effervescence commencing only upon the addition of 25 mol % $TiCl_4$.[39] This observation suggests that the initial 25 mol % $TiCl_4$, which was capable of generating 100 mol % HCl, formed a salt with the basic amine, with the remaining 10 mol % $TiCl_4$ being responsible for the desired transformation into lactam **2p**. Azido aldehyde **1q** required only 5 mol % $TiCl_4$ to provide 3-benzylpyrrolidinone **2q** in good yield (entry 10). Unfortunately, extending the tether length between the carbonyl and the azide moiety from the usual four to five carbons resulted in a sluggish reaction that afforded only an 11% yield of lactam **2r**, even when 20 mol % $TiCl_4$ was employed (entry 11). This is consistent with the stringent dependence of the intramolecular Schmidt reaction on tether length observed since the initial discovery of the reaction.[6c,12-13]

Given the requirement of relatively high catalyst loading for these less reactive substrates, we sought to optimize our reaction conditions further using substrate **1a** (Table 5). After evaluation of a series of Lewis and Brønsted acids, $TiCl_4$ was still found to be the most effective catalyst for this substrate (entries 1–14). However, the combination of $TiCl_4$ with other Lewis or Brønsted acids, while not initially promising (entries 15–20 and 28) ultimately revealed acetyl chloride (AcCl, CH_3COCl) as an effective promoter of this reaction even in the absence of $TiCl_4$ (entries 21–25). Thus, the reaction with 80 mol % AcCl (entry 25) gave results comparable to those with 20 mol % $TiCl_4$ (entry 1). We realized that this would support the case that HCl is the active catalytic species, provided that we could show HFIP to be capable of generating HCl from AcCl (an ironic notion in

view of the low nucleophilicity of HFIP[30g]).[40] To address this, we combined 1 equiv of AcCl and 2 equiv of HFIP in $CDCl_3$ and monitored the reaction by ^1H NMR spectroscopy (Figure 5; see the Experimental Section for details). Within 6 min, ca. 50% conversion to HFIP acetate was observed. The rate decreased after 20 min, and the reaction took 4 h to reach >95% conversion. Conversely, we were not able to obtain any evidence for the in situ generation of HCl from $TiCl_4$.

Table 5. Further Optimization of the Reaction Conditions for 1a[a,b]



entry	catalyst	catalyst (mol %)	additive	additive (mol %)	**2a**:**1a**[c]
1	**$TiCl_4$**	**20**	**–**	**–**	**95:5**
2	$TiCl_4$	10	–	–	59:41
3	TiF_4	10	–	–	26:74
4	$TiBr_4$	10	–	–	46:54
5	$Ti(O^iPr)_4$	10	–	–	<2:98[d]
6	$SiCl_4$	10	–	–	58:42
7	$SbCl_5$	10	–	–	45:55
8	$NbCl_5$	10	–	–	44:56
9	WCl_6	10	–	–	54:46
10	HCl in ether[e]	40	–	–	45:55
11	Aqueous HCl[f]	40	–	–	59:41
12	HCl in HFIP[g]	40	–	–	57:43–75:25 (variable)
13	H_2SO_4	40	–	–	76:24
14	$TiCl_4$	5	CF_3SO_3H	5	42:58
15	–	–	CF_3SO_3H	20	49:51
16	$TiCl_4$	5	$ClSO_3H$	5	49:51
17	$TiCl_4$	10	AgOTf[h]	20	56:44

entry	catalyst	catalyst (mol %)	additive	additive (mol %)	**2a**:**1a**[c]
18	$TiCl_4$	10	$Al(O^iPr)_3$	20	50:50
19	$TiCl_4$	10	Silica gel[i]	–	47:53
20	**$TiCl_4$**	**10**	**CH_3COCl[j]**	**40**	**95:5**
21	–	–	CH_3COCl[j]	40	58:42
22	–	–	CH_3COCl[k]	40	70:30
23	–	–	CH_3COCl[k]	70	90:10
24	–	–	CH_3COCl[j]	80	94:6
25	**–**	**–**	**CH_3COCl[k]**	**80**	**97:3**[l]
26	–	–	CH_3COBr[m]	40	72:28
27	**–**	**–**	**CH_3COBr[m]**	**80**	**98:2**[n]
28	$TiCl_4$	10	$(CH_3)_3SiCl$	40	89:11
29	–	–	$(CH_3)_3SiCl$	80	92:8
30	–	–	$(CH_3)_3SiI$	80	13:87[o]

[a]To a solution of substrate **1a** (0.10 mmol) in $(CF_3)_2CHOH$ (0.50 mL) at rt was added a catalyst and/or an additive under nitrogen atmosphere, unless otherwise mentioned. For $TiCl_4$, $SiCl_4$, and $SbCl_5$, a 1.0 M solution in CH_2Cl_2 was used. [b]Concn of substrate was ca. 0.20 M. [c]^{1}H NMR ratios were determined after a brief work-up (see the Experimental Section for details). [d]Only unreacted **1a** was observed. [e]A 1.0 M solution of HCl in ether (commercial) was used. [f]Aqueous HCl (37%) was used. [g]A 0.105–0.116 M solution of HCl in HFIP was prepared and used immediately. [h]$TiCl_2(OTf)_2$ was generated in situ from $TiCl_4$ and AgOTf.[41] [i]Silica gel (50mg) was used. [j]An old container of AcCl (>5 years since initial opening) was used. [k]A new container of AcCl was used. [l]The **2a**:**1a** ratio did not change between 18 and 24 h. [m]A new container of AcBr was used. [n]The **2a**:**1a** ratio did not change between 18 and 24 h. [o]Several other unidentified byproducts/impurities were also observed.

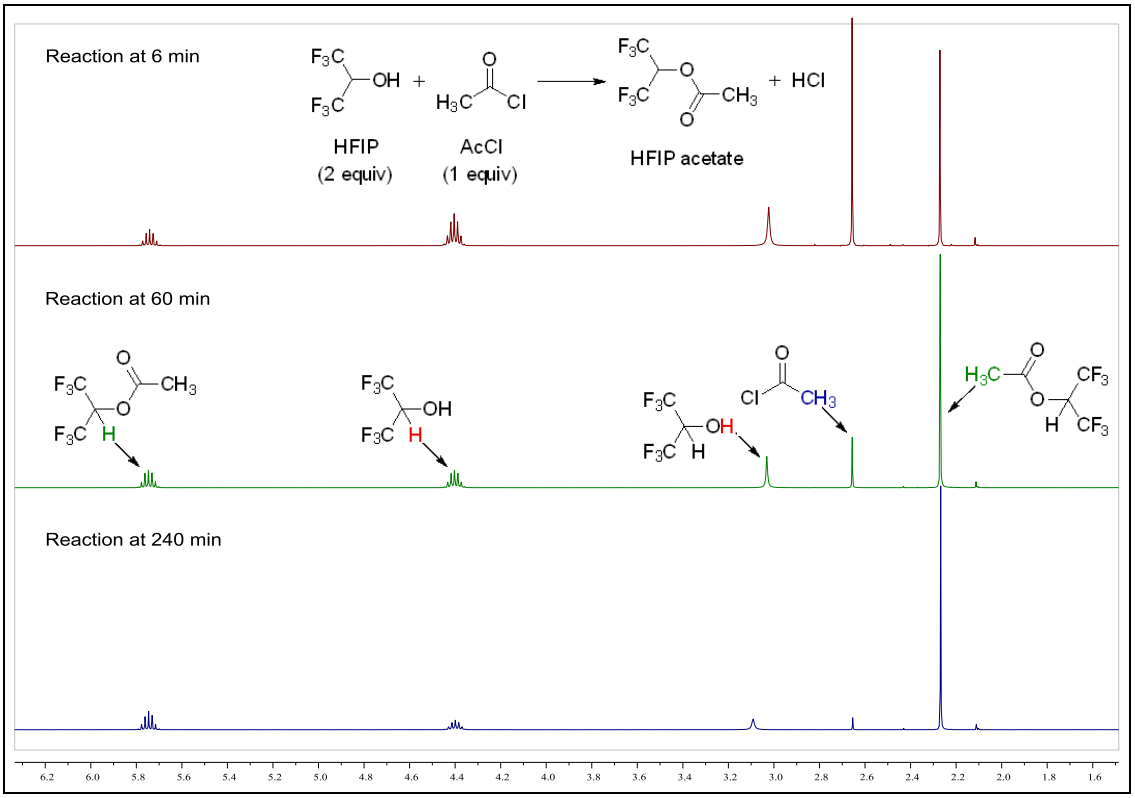


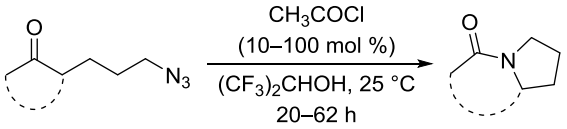
Figure 5. Results of ^{1}H NMR monitoring of the reaction of AcCl with HFIP to generate HCl in situ.

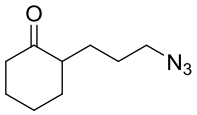
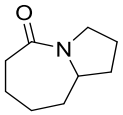
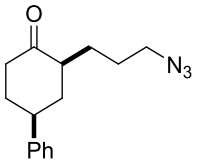
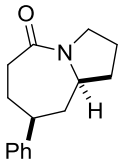
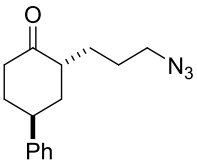
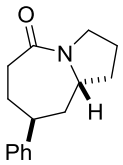
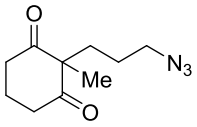
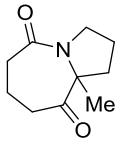
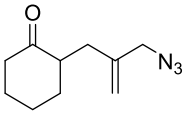
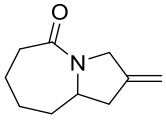
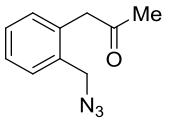
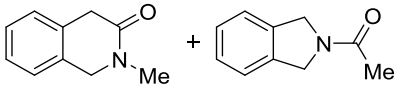
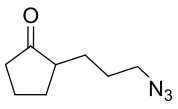
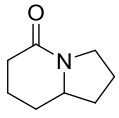
Additional experiments were carried out to gather further detail about the effect of various sources of H^{+} on these Schmidt reactions. In our initial survey, we had first tried adding commercially prepared solution of HCl in ether to the HFIP solvent (Table 1, entries 28 and 29, and Table 5, entry 10). Neither that method nor the addition of aqueous HCl[30k] (Table 5, entry 11) gave good results in our hands. On the other hand, when HCl gas was separately generated and infused into the HFIP (entry 12), a range of results were obtained. The nonreproducibility of these experiments can be blamed on the ease with which the HCl gas escaped the solution, making it difficult to gauge accurately the amount of acid present in a particular experiment. For example, markedly reduced yields (on the low end noted in entry 12) were obtained when HCl/HFIP solutions were aged for even a few minutes. We also examined whether HBr generated by the addition of acetyl bromide (AcBr, CH_3COBr)

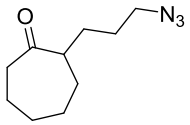
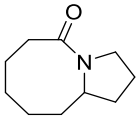
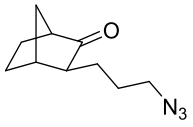
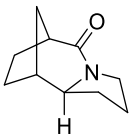
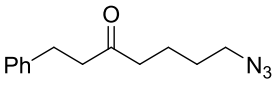
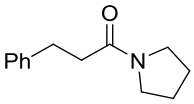
to HFIP was a suitable substitute for HCl, and the initial evidence suggested that it is (cf. entries 26 and 27 with 22 and 25). We still prefer to use AcCl-generated HCl because AcCl is generally easier to handle and more resistant to hydrolysis in air. Moreover, we observed very little difference when different sources of AcCl were used in the reaction (i.e., freshly opened vs older bottles of reagent; cf. entries 25 and 24). Taking into account both efficiency and practicality, we prefer using $TiCl_4$ or AcCl as the HCl source among all of the methods tested to date.

We decided to explore the substrate scope further under these new reaction conditions utilizing AcCl as a procatalyst. The substrate scope was comparable to that described for $TiCl_4$, and lactams were obtained in good to excellent yields (Table 6). Although higher amounts of AcCl than $TiCl_4$ were required to achieve complete conversion, the use of AcCl was convenient. In addition, both HFIP and its acetate ester byproduct are volatile, easing the work-up. Finally, no metal waste was produced.

Table 6. Scope under the Conditions Employing Acetyl Chloride[a,b]



entry	substrate **1**	catalyst (mol %)	time (h)	product **2**	yield (%)[c]
1	 **1c**	10	20	 **2c**	95
2	 **1e**	10	20	 **2e**	98
3	 **1f**	20	38	 **2f**	90[d,e]
4	 **1b**	20	24	 **2b**	95
5	 **1h**	20	24	 **2h**	77
6	 **1n**	60	24	 **2n** **3n** **2n**:**3n** = 65:35 (ca. 2:1)	68
7	 **1a**	80	24	 **2a**	90

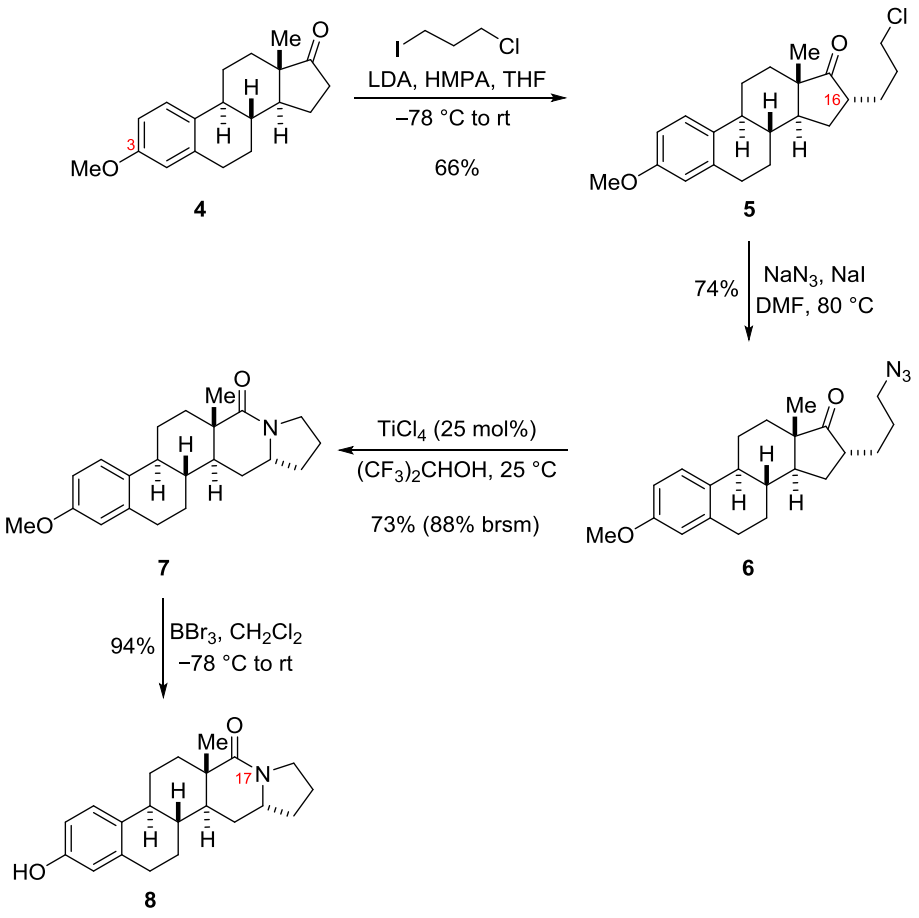
entry	substrate **1**	catalyst (mol %)	time (h)	product **2**	yield (%)[c]
8	 **1i**	80	48	 **2i**	87[f]
9	 **1k**	100	62	 **2k**	92
10	 **1l**	100	32	 **2l**	96[g]

[a]To a solution of substrate (0.40 mmol) in $(CF_3)_2CHOH$ (2.0 mL) at rt was added CH_3COCl under nitrogen atmosphere, and the reaction mixture was stirred at 25 °C for the designated period, unless otherwise noted. [b]Concn of substrate was ca. 0.20 M. [c]Isolated yields. [d]Bridged lactam **3f** was also isolated in ca. 3% yield. [e]The reaction was run on a 0.10 mmol scale. [f]Bridged lactam **3i** was also isolated in 3% yield (see the Experimental Section). [g]The product contained 7% 1-phenethylpiperidin-2-one **3l** (see the Experimental Section).

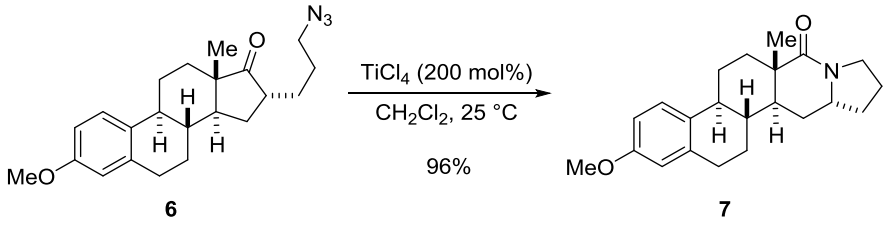
We then applied this protocol to stereochemically and structurally challenging steroidal ketones. Structurally modified steroids, in particular steroidal lactams, have been shown to possess favorable biological activities relative to their ketone precursors.[42] For example, fused (modified E-ring steroids) and C-16 substituted analogues of estrone have potential therapeutic applications as inhibitors of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD).[43] Thus, we applied our current methodology to the synthesis of a D-homo fused lactam analogue of estrone **8** (Scheme 11). Estrone 3-methyl ether **4** was alkylated under standard LDA conditions to provide a chloroalkyl substituted C16α-isomer **5** as the major product.[44] The chloro derivative **5** was converted to its corresponding azide **6** by treating with NaN_3. The azidoalkyl ketone **6** serves as a potential substrate to test the

current substoichiometric variant of the intramolecular Schmidt reaction. The low reactivity of **6** was anticipated due to the presence of a cyclic five-membered neopentyl ketone. Hence, the reaction of **6** in HFIP required 25 mol % $TiCl_4$ to achieve good conversion of the corresponding D-homo fused lactam **7** (Scheme 11). Further deprotection of the methyl ether with BBr_3 gave the 17-azaestrone analogue **8**. However, when the reaction of **6** was carried out in DCM for comparison purpose, 2 equiv (200 mol %) of $TiCl_4$ was required to obtain **7** in excellent yield (Scheme 12).

Scheme 11. Synthesis of 17-Azaestrone Analogue 8 using a Substoichiometric Variant of the Intramolecular Schmidt Reaction

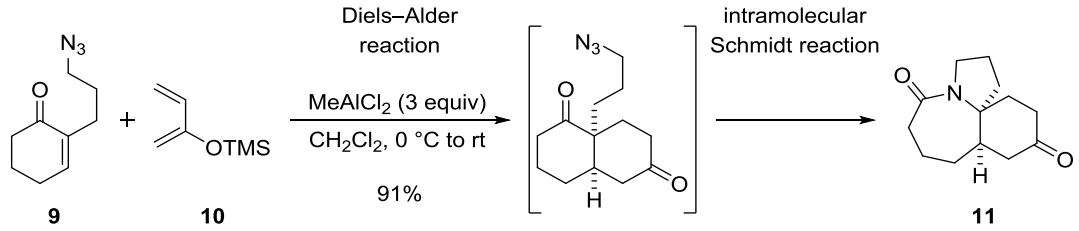


Scheme 12. Synthesis of 7 using a Conventional Intramolecular Schmidt Reaction



We and others have explored the combination of the intramolecular Schmidt reaction with other C–C bond forming processes to expediently access diverse heterocyclic ring systems with a variety of substitution patterns (for selected examples, see Figure 2).[17d,f,j,k,45] In particular, our group has developed different subtypes of Lewis acid-promoted domino intramolecular Schmidt reaction coupled with intramolecular[46] and intermolecular[17d,45a] Diels–Alder reactions. This one-pot domino process involves the initial Lewis acid-promoted Diels–Alder reaction, which reveals the ketone for the subsequent intramolecular Schmidt reaction.[45a] Since enones rarely undergo intramolecular Schmidt reactions,[47] they have been commonly utilized for the domino reaction with the Diels–Alder reaction (Scheme 13).

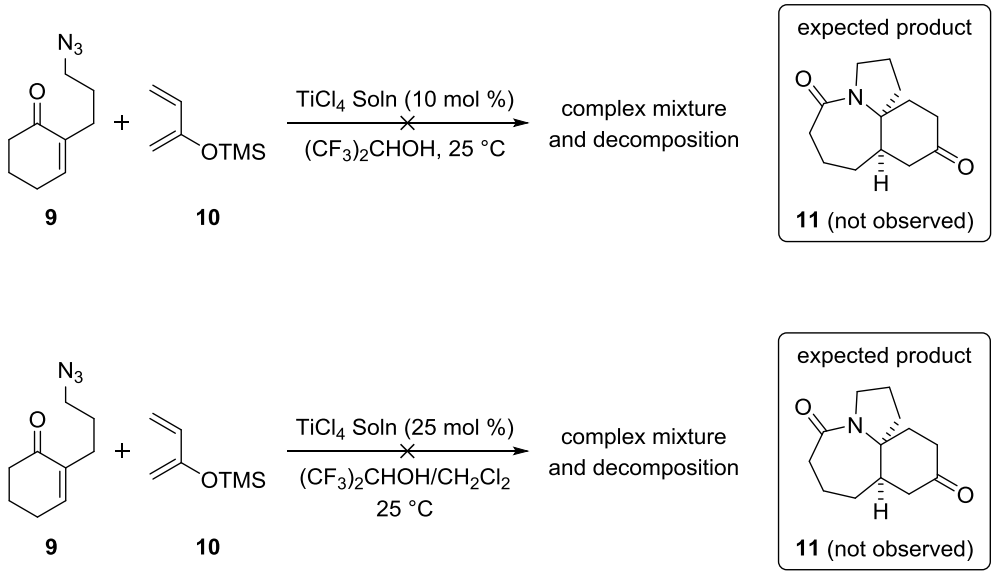
Scheme 13. Domino Intermolecular Diels–Alder/Intramolecular Schmidt Reactions



In the typical domino reaction as exemplified in Scheme 13, an excess of $MeAlCl_2$ was employed as a Lewis acid to bring about the desired transformation into tricyclic lactam **11**. The literature precedent for the catalytic Diels–Alder reaction[48] and our own

work towards the development of a catalytic intramolecular Schmidt reaction in HFIP[25] prompted us to attempt the domino reaction in a catalytic fashion. Moreover, HFIP has been shown to promote the Diels–Alder reaction without the aid of Lewis acids.[35] However, our initial efforts to render this domino reaction catalytically turned out to be unsuccessful (Scheme 14). Formation of lactam **11** was not observed when a reaction of a cyclic azido enone **9** and silyloxydiene **10** in HFIP was performed in the presence of 10 mol % $TiCl_4$. Unidentified byproducts and decomposition of **10** was observed by TLC and ^1H NMR analysis. Increasing the catalyst loading to 25 mol % $TiCl_4$ and using a mixed solvent system, HFIP/DCM, resulted in the formation of a complex mixture.

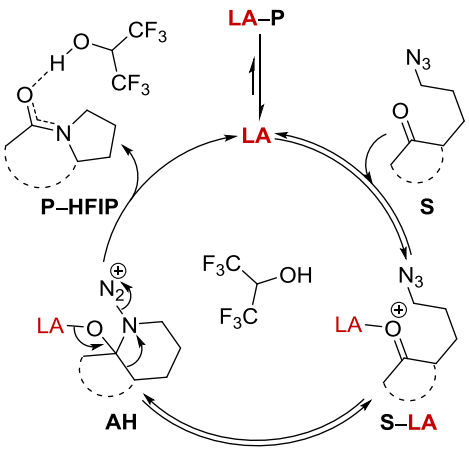
Scheme 14. Unsuccessful Catalytic Approach towards a Domino Intermolecular Diels–Alder/Intramolecular Schmidt Reaction



Mechanistic Studies

On the basis of precedent,[30g-j,33] we propose the involvement of HFIP as a strong hydrogen-bond donor to the lactam carbonyl (Figure 6). As proposed above, we believe that association of a Lewis or Brønsted acid with the Lewis basic lactam product inhibits

the catalytic reaction carried out in DCM. Hexafluoro-2-propanol as the solvent can potentially form complexes with the substrate, intermediates, and product. Critically, hydrogen bonding of HFIP with the lactam carbonyl by displacement of the Lewis or Brønsted acid allows for regeneration of the catalyst (most likely a proton). In addition, one cannot rule out coordination between HFIP and the catalyst to produce a catalytically more reactive species such as $[HFIP{\cdot}H]^{+}$.[49] We note that a cursory measurement of the pH of the reaction mixture using pH indicator strips (nonbleeding) gave a reading of pH 4.0 for the present version, as opposed to pH 1.0 for an intramolecular Schmidt reaction carried out with $TiCl_4$ in CH_2Cl_2 (the pH of pure HFIP was measured to be 5.0 by this method), suggesting an overall buffering effect of the solvent. Various experiments were designed and executed to further explore different mechanistic aspects of this substoichiometric intramolecular Schmidt reaction, such as the product inhibition by lactams and the hydrogen bonding interactions of HFIP with lactams.

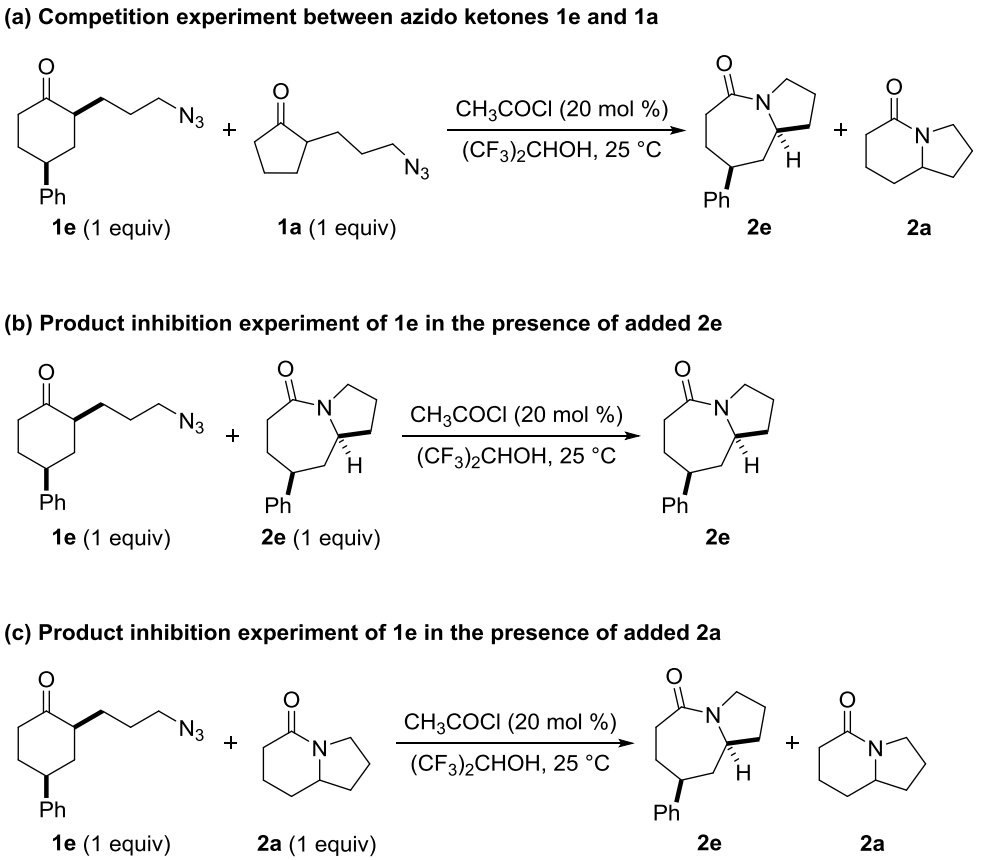


S = substrate; **P–HFIP** = product–HFIP complex; **LA** = Lewis acid/ Brønsted acid; **S–LA** = activation of substrate by Lewis acid; **AH** = azidohydrin intermediate; **LA–P** = Lewis acid–product interaction

Figure 6. Proposed catalytic cycle for the intramolecular Schmidt reaction employing HFIP as solvent.

Competition and Product Inhibition Experiments. To gain more insight into the different behaviors of different classes of azidoalkyl ketones, a competition experiment between cyclohexanone-derived **1e** and cyclopentanone-derived **1a** was performed (Scheme 15a and Figure 7). Treating an equimolar mixture of **1e** and **1a** in HFIP with 20 mol % AcCl resulted in complete conversion of substrate **1e** to lactam **2e** within 3 h (also see Table 6, entry 2). In sharp contrast, the conversion of **1a** to lactam **2a** was only 13% complete after 12 h (also see Table 6, entry 7). These results could be explained by an innate kinetic difference between the substrates, a difference in the degree of product inhibition, or a combination of the two.

Scheme 15. Competition and Product Inhibition Experiments



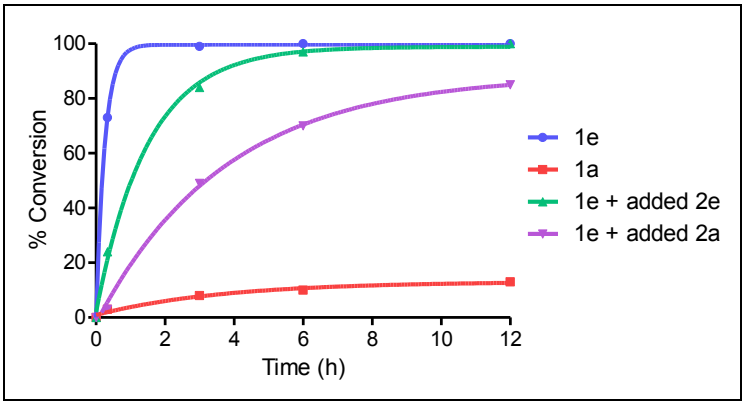
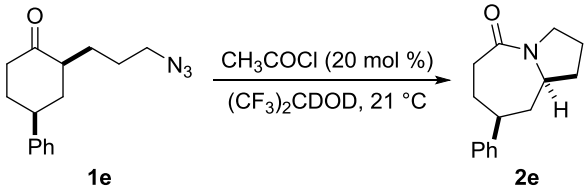


Figure 7. Relative reaction rates for **1e** and **1a** (see Scheme 15a above), **1e** with 1 equiv of **2e** added at the outset of the reaction (Scheme 15b), and **1e** with 1 equiv of **2a** added at the outset of the reaction (Scheme 15c).

With respect to the latter point, we made note of the requirement of different catalyst loadings for different substrate classes. This could probably be attributed to the difference in basicity of different lactam products, with a more basic lactam requiring higher catalyst loadings.[50] In order to demonstrate different degrees of product inhibition with different lactams, ^{1}H NMR experiments were carried out to determine the effect of adding two different product lactams at the outset of a single relatively fast reaction. For this, we chose the product of the quicker reaction leading to **2e** (and a case that succeeds with 10 mol % AcCl procatalyst) and **2a**, the product of a much slower reaction (and one that requires 80 mol % AcCl to reach completion). In the first case, the facile azido ketone substrate **1e** was combined with an equimolar amount of its lactam product **2e** and then treated with 20 mol % AcCl in HFIP (Scheme 15b and Figure 7). The time needed for quantitative conversion of **1e** to **2e** was ca. 6 h. In contrast, the reaction of a 1:1 mixture of **1e** and **2a** with 20 mol % AcCl in HFIP required >24 h to attain completion (Scheme 15c and Figure 7). These results would be consistent with significantly more product inhibition by lactam **2a** than **2e**,

which is in turn consistent with the need for higher catalyst loadings with relatively recalcitrant substrates.[19a]

The reaction rate for the conversion of **1e** to **2e** was also studied in deuterated HFIP (HFIP-d_2) with 20 mol % AcCl using ^{1}H NMR. Data collection at different time points revealed >55% conversion in 10 min, slowly reaching up to 75% in 30 min. Then the reaction further slows down requiring ca. 4 h to achieve complete conversion (Figure 8). While the initial reaction rate seems faster, the actual conversion of **1e** to **2e** correlates with the amount of time requires for the in situ generation of HCl from AcCl upon reaction with HFIP-d_2 (cf. Figures 8 and S3 in the Experimental Section). The reaction rate for **1e** in HFIP-d_2 seems slightly slower compared to HFIP (cf. Figures 7 and 8). Such difference could be simply due to experimental errors or from the use of different curve fitting softwares (see the caption for Figure 7 in the Experimental Section).



1e **2e**

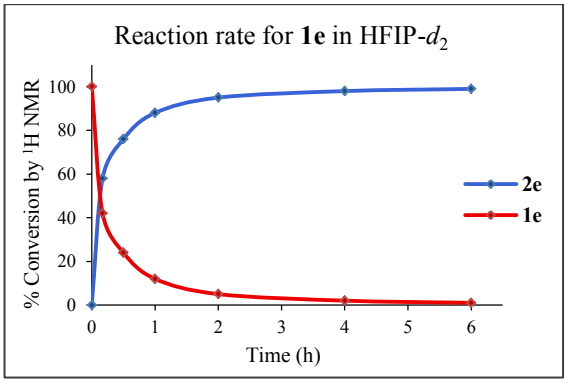


Figure 8. Reaction rate for **1e** in HFIP-d_2 (blue line represents the % conversion to **2e** and red line represents the % remaining of **1e**).

Despite the importance of the Schmidt reaction, very few kinetic studies focusing on the intermolecular reaction of ketones with azides using ^{1}H NMR and azotometry (determination of the rate of N_2 evolution) have been published.[51] This has been attributed to the considerable difficulties encountered for a quantitative study of such complex processes.[51] As shown above, reaction rate and competition experiment studies have clearly revealed that the initial rate for the intramolecular Schmidt reaction in HFIP is much faster and most of the conversion to product occurs during the first few minutes of the reaction. Toward this end, we endeavored to perform a detailed kinetic investigation to address fully the relative roles of kinetics versus product inhibition in the intramolecular Schmidt reaction.

Initial kinetic experiments were attempted on two substrates **1a** and **1b** and conversions to their corresponding products **2a** and **2b** were monitored over time using three different techniques, ^{1}H NMR, GC, and UV–visible spectrophotometry. Unfortunately, we were not able to determine the rate of the reaction using these techniques. During this trial, a cursory analysis showed that ca. 40% conversion occurred within 1 min. Since we were trying to determine the kinetic behavior at early conversion (initial rate of a reaction), manual sampling to aliquot enough number of samples in 1 min for reasonable data analysis turned out to be challenging. Moreover, different methods (such as the use of different bases and filtration through Celite) tested to quench the reaction for later analysis by GC and ^{1}H NMR proved to be ineffective and unreliable. With UV–visible study, an immediate increased in the absorbance was observed upon catalyst addition (a stock solution of $TiCl_4$ in HFIP was used) for 3–4 seconds, after which it plateaued till the end of the experiment (120 seconds). This abnormal observation during the time course of the absorbance did not allow for measurement of the rate constants. Future kinetic studies might take advantage of advanced NMR techniques and azotometric

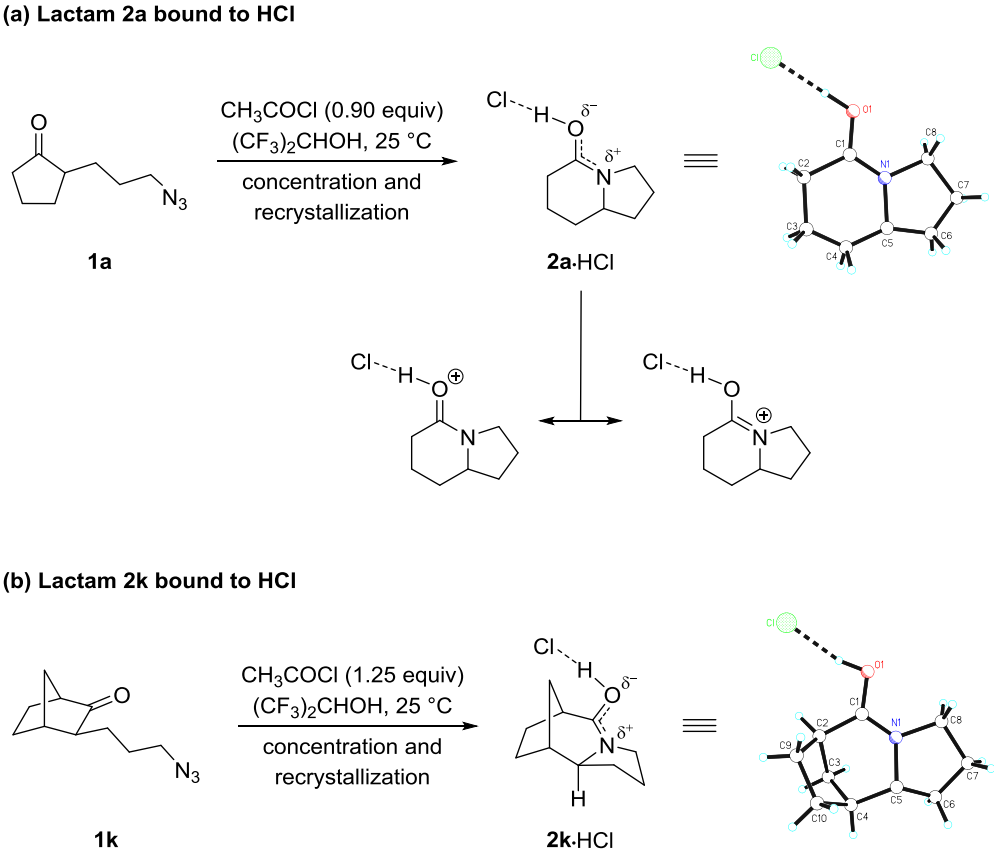
determination to overcome various problems encountered during our initial attempt. To this point, it remained a challenge to understand the details of this mechanistically complicated reaction using kinetics.

Characterization of Protonated Lactams. In general, O-protonation is significantly favored over N-protonation for amides and lactams.[1,50e] To the best of our knowledge, X-ray crystal structures of a bicyclic lactam protonated on oxygen is not known. On the other hand, structural characterizations of the highly sought N-protonated species are limited to twisted or bridged amides and lactams.[52] Thus, we attempted to isolate and characterize examples of a bicyclic lactam–catalyst complex. This would not only provide the first example of such complex but will also serve the purpose of verifying product inhibition through catalyst sequestration, which we and others have proposed in the intramolecular Schmidt reaction.[13,18a]

In order to have a successful outcome, it was necessary to carry out the experiments under conditions, which does not affect the lactam–catalyst complex. Running the experiments under AcCl and HFIP conditions seemed promising as volatile components such as HFIP and its in situ-generated acetate ester were easy to remove under vacuum, once the reaction was complete. This will apparently leave nothing but lactam product bound to HCl in the reaction vessel. Accordingly, complete conversion of **1a** to **2a** was achieved with 0.90 equiv of AcCl in HFIP (Scheme 16a). Following concentration and drying of the reaction mixture under vacuum, we were excited to see the deposition of solid particles in the vial. Several recrystallization attempts eventually afforded small diffractable crystals of protonated **2a** (**2a**·HCl) in twinned bundles. Dr. Victor W. Day was able to get a single-crystal X-ray structure of lactam **2a** bound to HCl from these poor quality crystals (Scheme 16a). Similarly, the reaction of **1k** with 1.25 equiv of AcCl in HFIP resulted in the

isolation and characterization of the protonated lactam **2k** (**2k**·HCl) by a single-crystal X-ray analysis (Scheme 16b). In this case also, twinned crystals were obtained.

Scheme 16. Single-Crystal X-Ray Structures of Lactams Bound to HCl



Crude ^{1}H NMR analysis of **2a**·HCl in $CDCl_3$ displayed a broad signal corresponding to one proton at δ_H 10.67, indicating the presence of HCl. Also, protons attached to the α-carbon of the carbonyl shifted downfield by 0.36 (from δ_H 2.11 to 2.47) and 0.41 (from δ_H 2.27 to 2.68) ppm compared to **2a**. In a similar way, HCl signal was observed at δ_H 10.11 and the α-proton of the carbonyl shifted downfield by 0.34 ppm (from δ_H 2.71 to 3.05) for **2k**·HCl compared to **2k**. A downfield shift of 2.6 ppm (from δ_C 175.2 to 177.8) was also observed for the carbonyl carbon in the ^{13}C NMR of **2k**·HCl.

In both cases, O-protonation caused a significant lengthening of the C1 to O1 bond (1.300 and 1.301 Å for **2a**·HCl and **2k**·HCl) with C–O single bond character and shortening of the C1 to N1 bond (1.288 and 1.255 Å for **2a**·HCl and **2k**·HCl) with enhanced C=N double bond character (see Table 7 for details). The short O–H bonds (1.013 and 0.9309 Å for **2a**·HCl and **2k**·HCl), typical of a covalent character in a hydroxyl group (0.967 Å) were also observed, indicating a stronger acceptor strength (basicity) of the amide oxygen. The preferred O-protonation results from the stabilization of the positive charge on the O-protonated species by partial charge delocalization from the nitrogen atom through enhanced resonance phenomenon (Scheme 16). This charge delocalization is favored because the less electronegative nitrogen can bear the positive charge more readily than the amide oxygen.[53] On the other hand, the presence of long (O–)H···Cl bonds (1.85 and 1.93 Å for **2a**·HCl and **2k**·HCl) compared to HCl (1.274 Å) suggested a short hydrogen bond with a relatively strong intermolecular hydrogen bonding, characteristic of a O–H donor and chloride (Cl^-) acceptor (Table 7).[53-54] The bond angles (O–H···Cl) of 176.0° and 164.3° for **2a**·HCl and **2k**·HCl were indicative of nearly linear hydrogen bonds.[54c]

Table 7. Geometric Details of the Lactam·HCl Complex

lactam	bond length (Å)				bond angle (°)
	C=O (C–OH)	C–N (C=N)	O–H	H···Cl	O–H···Cl
typical bond length[55]	1.233[a] (1.333)[b]	1.352[c] (1.279)[d]	0.967[e]	1.274 (for H–Cl)	–
2a·HCl	1.300(18)	1.288(19)	1.013	1.85	176.0
2k·HCl	1.301(6)	1.255(7)	0.9309	1.93	164.3

[a](C*)$_2$–N–**C=O** (in δ-lactams). [b]C=**C–OH** (in enols). [c](C*)$_2$–**N–C**=O (in δ-lactams). [d]C_{ar}–**C=N**–C (in general for Csp^2=N). [e]C***–O–H** (in alcohols). ar = aromatic. [a–e] The values for bond lengths were taken from ref. 55.

Undoubtedly, we were able to provide a clear proof of evidence for the Lewis basic lactam based catalyst sequestration through characterizations of protonated forms of lactams as HCl salts by single-crystal X-ray analysis.

Determination of Association Constants for HFIP–Lactam Complexes using NMR Titration. HFIP has been shown to form aggregates, such as trimers, having potential hydrogen bonds with strengths comparable to those of covalent linkages.[30h] Such strong hydrogen bonding could well explain the role of HFIP in the catalysis of the intramolecular Schmidt reaction. NMR technique could provide a useful means to investigate this exceptional hydrogen-bond donor ability of HFIP with different lactams. A study has been reported for the determination of association constants (K_a) for the hydrogen-bonded complexes of HFIP with ethers.[30h] Determination of K_a using the NMR technique might offer further insight into the relative basicities of various lactams, which evoke different degrees of product inhibition.

When a host (H) and a guest (G) species interacts to form a host–guest complex (HG), which is held together via weak intermolecular forces such as hydrogen bonding, the equilibrium constant is often referred to as a binding constant (K) or an association constant (K_a) (equation (1)).[56] NMR spectroscopy is the most widely used technique for studying intermolecular binding or reversible complexation between a host (H) and a guest (G) species and determining K_a in host–guest complexes.[56-57] Besides being an important method in supramolecular chemistry,[56b,c] the NMR technique has also been used in the determination of protein–ligand dissociation constants.[58] The most common NMR experiment for quantifying interactions is a titration of the guest to a solution of the host, noting a change in the chemical shift. NMR titration methods are mostly useful to study K_a

in the range 10–10^4 M^{-1}. To get reliable K_a, it is necessary to design the experiment in a way so that the complexation ratio for a binding curve ranges from 20 to 80%.[56a,b]

$$H + G \rightleftharpoons HG$$

$$K_a = \frac{[HG]}{[H][G]} \quad (1)$$

[H] = Concentration of Host, [G] = Concentration of Guest, and [HG] = Concentration of Host–Guest Complex.

Despite the apparent simplicity of the NMR titration approach, several issues need to be addressed carefully in order to obtain reliable results.[56,57b] Some of the common issues involve: (1) different type of approximations such as determining the value for δ_c or $\Delta\delta_{max}$ (the difference between the chemical shift of the free host and the theoretical signal shift in the host–guest complex at 100% complexation), (2) careful choice of graphical methods (e.g., NMR vs UV–visible) such as Benesi–Hildebrand, Rose–Drago, etc. as each method has limitations in different applications, (3) finding a right concentration of host/guest for a particular system as carrying out titrations at concentrations unsuitable for the equilibrium often lead to systematic errors, (4) ensuring a constant host concentration during the course of the experiment; it is best to prepare a guest solution in the host solution with the same concentration of the host for the titration, (5) it is always necessary to determine the stoichiometry of binding before any determination of K_a for the host–guest complex as different graphical methods required for the determination of K_a depend on the ratio of binding, and (6) use of a reliable non-linear regression or curve-fitting methods.[56,57b] Commercial software packages for fitting data to binding models such as GraphPad Prism[59] are relatively user-friendly compared to custom written programs that often run along with generic data and mathematical programs such as Microsoft Excel or Matlab.[56c] Advantages

of using GraphPad Prism involve no requirement for approximations, accounts for estimation of uncertainties, and allows for unrestricted distribution of experimental data points (concentrations).[56a,c] Results obtained are more reliable and provides more accurate measurements of K_a. Equilibrium binding or dissociation constant (K_d), which is defined as the guest concentration needed to achieve a half-maximum binding at equilibrium is generally obtained in the GraphPad Prism upon data processing and K_a could be easily determined from K_d using the following equation, $K_a = 1/K_d$.

Equation (2) describes the complexation-induced shift of an NMR signal for a fast equilibrium and the change in a chemical shift with a change in the concentration forms the basis of NMR titration for the determination of K_a.[56,57b,60] All of the graphical methods and curve fitting programs designed to find solutions for this general equation (2) for the archetypical 1:1 binding system (two parameters fit) produce a hyperbolic binding curve (titration curve). $[H]_0$ and $[G]_0$ are two known parameters and the two unknown parameters, K_a and $\Delta\delta_{max}$ could be obtained by non-linear curve fitting of the titration data.

$$\delta_{obs} = \delta_0 + \frac{\Delta\delta_{max}}{2[H]_0}\left[\frac{1}{K_a} + [H]_0 + [G]_0 - \sqrt{\left(\frac{1}{K_a} + [H]_0 + [G]_0\right)^2 - 4[H]_0[G]_0}\right] \qquad (2)$$

δ_{obs} = an experimentally measured chemical shift, δ_0 = the chemical shift of the free host, $\Delta\delta$ = measured change in chemical shift (upon addition of guest species) referenced to that of the uncomplexed host, $\Delta\delta_{max}$ = the difference between δ_0 and the theoretical signal shift at 100% complexation, K_a = the association constant, $[H]_0$ = the initial concentration of host, and $[G]_0$ = the initial concentration of guest. Equation taken from refs. 56, 57b, and 60.

Job′s method of continuous variation was used to first determine the stoichiometry of binding for HFIP–product and HFIP–substrate complexes (Figure 9).[30h,61] The Job plots based on the ^{1}H NMR data provide good evidence that HFIP forms a 1:1 complex with both

product **2a** and substrate **1a**, as can be observed from the peak abscissa values of 0.52 for **2a** and 0.50 for **1a.** Although the stoichiometries of binding were similar, the complexation shift ($\Delta\delta$) of the HFIP hydroxyl resonance upon complexation of lactam **2a** was significantly higher than for azido ketone **1a**, consistent with the expected stronger complexation of HFIP with the lactam than with the ketone.

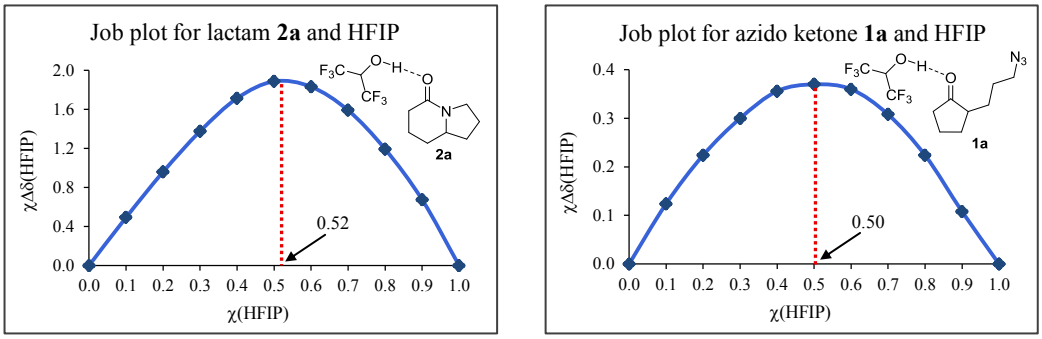


Figure 9. Job plots for the complexation of lactam **2a** and azido ketone **1a** with HFIP.

With this information in hand about the stoichiometry of binding for HFIP with the lactam and the azido ketone, a simple 1:1 binding model could be employed to treat the NMR data for finding out the K_a in order to study the strength of the hydrogen bonding interaction. Initial NMR titration experiments were carried out following a slight modification of the reported procedure used for studying hydrogen bonding complexes of HFIP with ethers.[30h] Initial experiments, which involved measuring a change in the chemical shift of the carbonyl carbon using ^{13}C NMR in $CDCl_3$ were erroneous, thus unsuccessful (Figure 10). In these attempts, azido ketones **1a** and **1e**, and lactam **2e** were treated as host and HFIP was treated as guest. Several problems were encountered. First, the high concentrations initially used were unsuitable for the equilibriums being measured. Second, we learned that concentration errors were introduced upon successive additions of the guest to the NMR tube, in which the titration experiment was being performed. Since

we did not have any custom-written curve-fitting programs for the determination of K_a, we sought help of Dr. Justin Douglas to develop a process for fitting the NMR titration data to a 1:1 binding model based on equation (2) using Microsoft Excel. Unfortunately, processing the NMR data using Microsoft Excel was unreliable as correct approximations for $\Delta\delta_{max}$ could not be made.[30h,56,57b,60,61b] Due to errors in the experimental design, reliable values for K_a were not obtained. Moreover, saturation plots obtained were erroneous as concentration ratios for HFIP (guest) to **1e** and **2e** (hosts) were inaccurate because concentrations of hosts did not remain constant during the titration experiments (Figure 10).

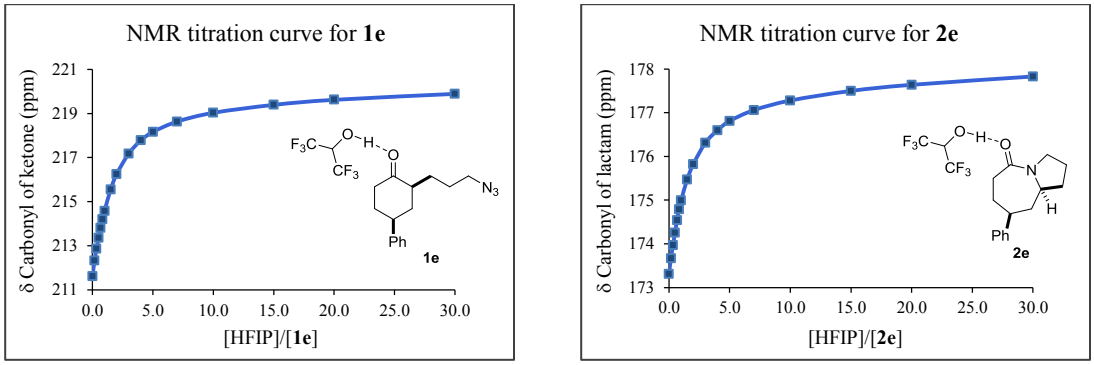


Figure 10. Saturation plots for unsuccessful NMR titration experiments of **1e** and **2e** with HFIP.

Given these issues, we approached Dr. Blake R. Peterson for his help and insights in to designing the experiment, since his laboratory routinely determines K_d in biological settings. He guided us on how to run the NMR titration and helped to process the titration data using GraphPad Prism software. Here, the NMR titration experiment was performed with HFIP as a host and azido ketone **1a** as a guest and the change in the chemical shift of the hydroxyl proton of HFIP was monitored using ^{1}H NMR. Since sufficient quantity of azido ketone **1a** was available compared to lactam **2a**, **1a** was used for preliminary titration experiments to find the concentration range for the host and the guest.

Trial titration experiments were run at 20 and 2 mM concentrations of HFIP. To avoid the concentration error, individual NMR tubes were used for each dilution step. The titration at 20 mM concentration of HFIP was accomplished by preparing a series of 11 different concentrations (titration points), where increasing amounts of **1a** was added up to 15 equiv in to individual NMR tubes. The stock solution of **1a** was prepared with a stock solution of HFIP in $CDCl_3$ and the final volume in the NMR tube was kept constant at 0.60 mL. The change in the chemical shift (δ) of the hydroxyl proton of HFIP was determined by ^{1}H NMR. A significant downfield shift of the hydroxyl proton was observed with increasing concentrations of **1a**. The presence of only one hydroxyl proton signal was indicative of a hydrogen-bonded complex with a fast equilibrium on a NMR time scale. A titration curve was obtained by plotting the absolute value of the observed chemical shift change ($\Delta\delta$) against the concentration of **1a** (Figure 11). Non-linear regression analysis with one site specific binding model using GraphPad Prism gave a K_d of 151 mM for **1a**, from which K_a was calculated to be 0.00662 mM^{-1}. NMR titration at 2 mM concentration of HFIP failed to give reliable data points because the concentration of HFIP was too low to detect the hydroxyl proton signal accurately at increasing concentrations of **1a** by ^{1}H NMR.

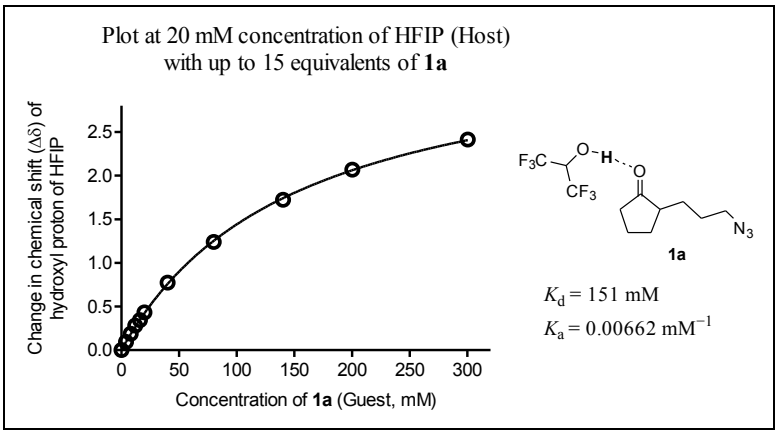


Figure 11. Titration curve of HFIP at 20 mM concentration with up to 15 equiv of **1a** (11 titration points).

In practice, the experiments are generally designed to set the constant host concentration much lower than the K_d and that was the case observed here (Figure 11). In addition, 20 mM concentration gave an appropriate signal to noise ratio for measuring the chemical shift of the hydroxyl proton of HFIP by ^{1}H NMR, so other concentrations of HFIP were not explored further. To validate the consistency of the result obtained in the first experiment, NMR titration at 20 mM concentration of HFIP was repeated, but with a series of 10 different concentrations up to 20 equiv of **1a**. Processing the data in a similar way using GraphPad Prism gave a K_d of 130 mM and K_a of 0.00769 mM^{-1} for **1a** (Figure 12).

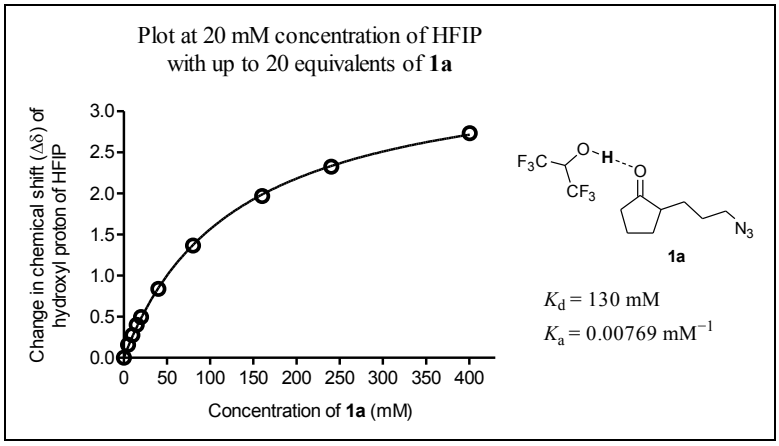


Figure 12. Titration curve of HFIP at 20 mM concentration with up to 20 equiv of **1a** (10 titration points).

Since good results were obtained for **1a**, a titration experiment was run with the corresponding lactam **2a** in a similar way as per our initial goal of determining the K_a for different lactams in order to assess their hydrogen-bond acceptor abilities with HFIP. When HFIP was titrated with up to 20 equiv of **2a** (10 titration points), GraphPad Prism based treatment of the titration data provided a K_d of 16.8 mM and K_a of 0.0595 mM^{-1} for **2a** (Figure 13a).

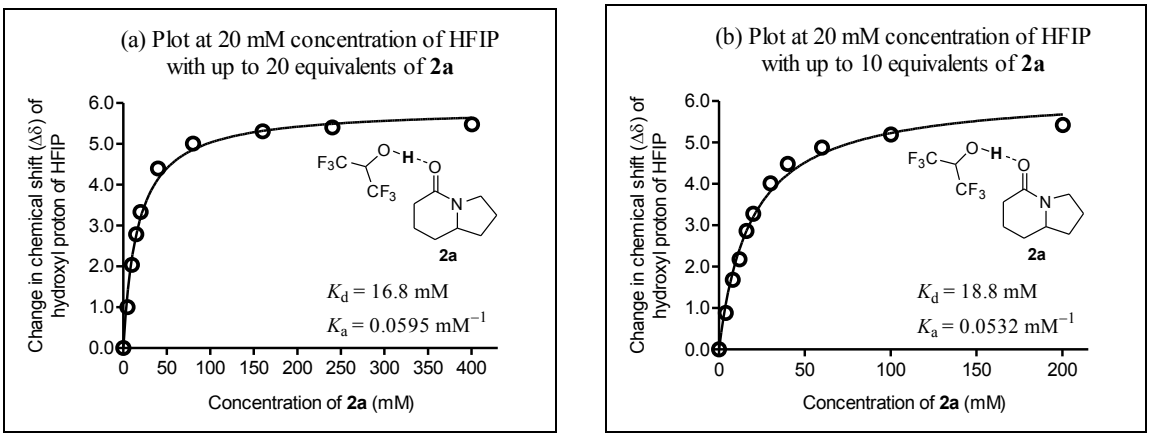


Figure 13. NMR titration curves of HFIP with **2a**.

The carbonyl oxygen of lactam **2a**, being strongly Lewis basic is a much better hydrogen-bond acceptor compared to the ketone **1a**. Hence, a higher affinity of **2a** towards a hydrogen-bond donor such as HFIP was expected. A lower K_d for lactam **2a** is indicative of a stronger complexation of **2a** with HFIP compared to a weaker interaction observed for **1a** (cf. Figures 12 and 13a). Because of the stronger hydrogen bonding interaction between HFIP and lactam, a lower concentration of lactam should be sufficient to achieve a half-saturation point, where 50% of the HFIP is bound to the lactam. Hence, titration was repeated at 20 mM concentration of HFIP with up to 10 equiv of **2a** (11 titration points) (Figure 13b). GraphPad Prism based data treatment provided a titration curve with a K_d of 18.8 mM and K_a of 0.0532 mM^{-1} for **2a** (Figure 13b). Since the lower concentration of the lactam **2a** gave a value of K_d within the range of an experimental error than that carried out at the higher concentration, NMR titration studies for other lactams were carried out at lower concentrations. The main advantage lies in the requirement of a lesser amount of a given lactam for carrying out the experiment. With the optimized experimental procedure, NMR titrations for lactams **2e**, **2f**, and **2k** were carried out at 20 mM concentration of HFIP. Dissociation constants, K_d (association constants, K_a) were ascertained to be 21.3

mM (0.0469 mM^{-1}), 19.6 mM (0.0510 mM^{-1}), and 20.5 mM (0.0488 mM^{-1}) for lactams **2e**, **2f**, and **2k**, respectively (Figure 14).

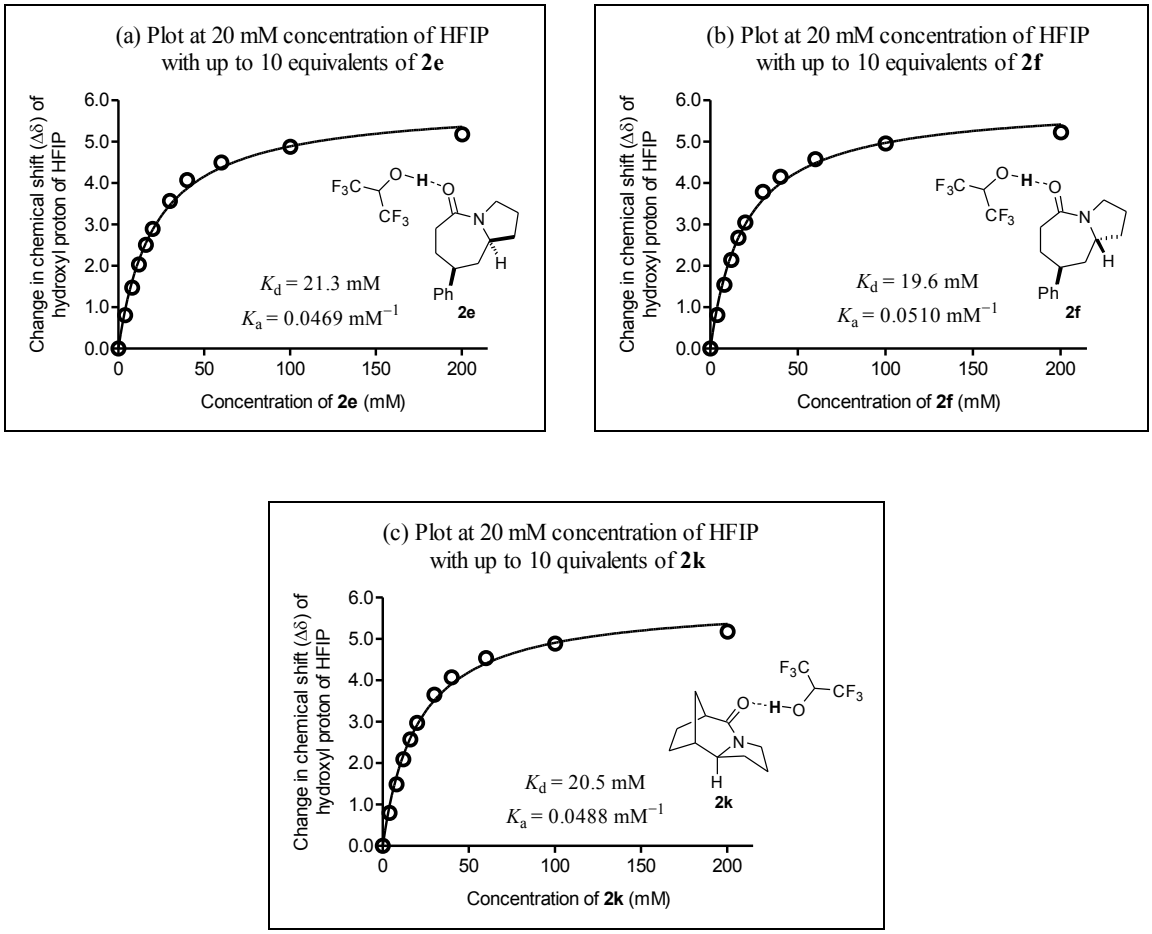


Figure 14. NMR titration curves of HFIP with lactams **2e**, **2f**, and **2k**.

The complexation or association constants (K_C or K_a) for hydrogen-bonded complexes of HFIP with THF and 1,4-dioxane have been reported to be 0.065 and 0.033 mM^{-1} respectively.[30h] These authors also showed that the pK_C (pK_C = $\log_{10}K_C$) of these ethers correlate well to the hydrogen-bond basicity pK_{HB} data available in the literature[62] (pK_C for THF and 1,4-dioxane were reported to be 1.81 and 1.52).[30h] The pK_{HB} scale, which utilizes *p*-fluorophenol (pK_a = 9.91 and hydrogen-bond acidity (α_2^H) = 0.629)[30d] as the reference hydrogen-bond donor is a well-established thermodynamic hydrogen-bond

basicity scale for organic bases, which serve as corresponding acceptors (pK_{HB}, pK_C, and pK_a are all similar terms except determined in different ways).[30h,50f,62] Increasing efforts have been made to build a pK_{HB} scale for the quantitative measurement of the strength of organic Lewis bases such as ketones, ethers, amides, and lactams.[62c] The basicity of various lactams as pK_{HB} or pK_a (pK_a = $\log_{10}K_a$; not to be confused with the logarithm of the acid dissociation constant) have also been determined by titration with phenols using IR spectroscopy.[50a,f] In one of this study, the basicities of unsubstituted lactams followed the following trend based on the ring size: 6-membered > 7-membered > 5-membered (pK_a of piperidone, caprolactam, and pyrrolidone was found to be 0.75, 0.36, and –0.30).[50a] The presence of *N*-substituents had a significant influence on the basicity of these lactams.

In an analogous way as reported in the literature,[30h] we calculated the pK_a value for the lactam from their corresponding K_a (Table 8). All four lactams (**2a**, **2e**, **2f**, and **2k**) under study showed very close hydrogen-bond basicities (pK_a or pK_{HB}). Thus, no clear correlation was observed between the basicity of different lactams and the amount of catalyst loading required for their conversion. This conflicts with the hypothesis set forth in the discussion with respect to Figure 7 and Scheme 15. Likewise, the chemical shift (δ) of the lactam carbonyl carbon did not compare well both with K_d and pK_a values and the need for a specific amount of catalyst loading for a particular azidoalkyl ketone substrate for their conversion to the corresponding lactam (Table 8).

Table 8. Correlation of K_d, K_a, and pK_a Values Obtained from NMR Titration Experiments with the Observed Catalyst Loading Requirements[a]

lactam **2**	K_d (mM)	K_d (M)	K_a (mM^{-1})	K_a (M^{-1})	pK_a	δ of carbonyl carbon (ppm)	$TiCl_4$ catalyst loading (mol %)[b]
2a	18.8	0.0188	0.0532	53.2	1.73	168.9	20
2f	19.6	0.0196	0.0510	51.0	1.71	172.3	5
2k	20.5	0.0205	0.0488	48.8	1.69	175.2	25
2e	21.3	0.0213	0.0469	46.9	1.67	173.4	2.5

[a] pK_a = $\log_{10}K_a$. pK_a has been compared to pK_{HB} (hydrogen-bond basicity).[30h] [b] See Tables 3 and 4.

As noted above, we have proposed that product inhibition due to lactam–catalyst interaction is responsible for the need of superstoichiometric amounts of catalysts under most conditions (i.e., those using solvents other than HFIP). Since it was difficult to determine the pK_{HB} value for the lactam using HCl as a hydrogen-bond donor, we sought to measure the inherent hydrogen-bond interactions of lactams with HFIP. However, the strength of the hydrogen-bonded complexes between HFIP and lactams determined using NMR titration experiments did not reflect the different degrees of product inhibition observed in the intramolecular Schmidt reaction. One explanation would be that the lactam–catalyst interaction does not correlate the hydrogen bonding interaction observed between lactam and HFIP. Because HFIP is a better hydrogen-bond donor than *p*-fluorophenol (cf. pK_a and α_2^H values; see discussion above and Table 2), it is less likely that using *p*-fluorophenol as the reference hydrogen-bond donor will provide a better determination of pK_{HB} value for the lactam and in turn correlate with the different catalyst loading requirement. Moreover, we cannot rule out the dependance of product inhibition on unknown and unanticipated factors other than basicity, such as fused ring strain.[63] Future elaborative studies might reveal comprehensive understandings in to the complex scenario of product inhibition, informing future synthetic efforts.

Conclusions

We have demonstrated a catalytic intramolecular Schmidt reaction with broad substrate scope and utility. Two versions of the reaction, one using $TiCl_4$ and the other with AcCl, have been identified as having strong synthetic utility that is as good or better than all previous versions of this process. In either case, the strong hydrogen bonding ability of HFIP was critical to the development of these substoichiometric reactions. The discovery of conditions employing AcCl as a procatalyst in the presence of HFIP provided evidence that HCl is an active catalytic species as well as providing a metal-free catalytic reaction. Prior to this discovery, the primary metal-free variations of the intramolecular Schmidt reaction used either TFA as the solvent or TfOH or $ClSO_3H$ as a stoichiometric reagent.

The most favorable examples utilized attractively low loadings of catalyst, as low as 2.5 mol % for the $TiCl_4$-promoted version or 10 mol % AcCl. Although some of the least cooperative substrates needed as much as 100 mol % of "H^+" catalyst added (via either the addition of 25 mol % $TiCl_4$ or the straight-ahead addition of 100 mol % AcCl), we note that these conditions still measure up very favorably to those previously reported for analogous substrates. For example, the reaction of **1a** in CH_2Cl_2 needed 4.5 equiv of $TiCl_4$ to afford a 67% yield,[13] while the same reaction carried out with 20 mol % $TiCl_4$ or 80 mol % AcCl gave a product yield of 87% or 90%, respectively. Although we did not quantitatively compare the purities of the products obtained in these various reactions, we note informally that the presently reported procedures tended to provide products requiring little additional purification.

Catalyst sequestration by the lactam resulting in product inhibition was evidently proved by the single-crystal X-ray analysis of the lactam bound to catalyst. In addition, ^1H NMR experiments were performed to exhibit different degrees of product inhibition with different lactams. That such structurally similar lactams have substantially different effects

on the rate of a given reaction is provocative and might lead to increased understanding of the role of product inhibition in this and other reactions that afford lactam or amide products. Our effort to correlate the basicity and the extent of product inhibition exhibited by various lactams using NMR titration was unsuccessful. Elucidation of further mechanistic details such as the determination of initial reaction rate will be a part of prospective study. Extensions of this reaction methodology to other variants of the Schmidt reaction in terms of scope, applications, and limitations are subjects of the following sections in this chapter.

A chiral BINOL-derived *N*-triflylphosphoramides has been used to promote the enantioselective desymmetrization in the intramolecular Schmidt reaction of 2-substituted-2-azidopropylcyclohexane-1,3-dione.[18b] However, 1.5 equiv of a chiral Brønsted acid was required to promote the reaction with acceptable yields and modest enantioselectivities. The chiral Lewis or Brønsted acid catalysts and ligands are often expensive and thus, their use in stoichiometric amounts will have limited applications, especially on an industrial scale. This substoichiometric variant sets up an avenue for the further development of asymmetric version of this chemistry utilizing a substoichiometric amount of chiral acid catalysts.

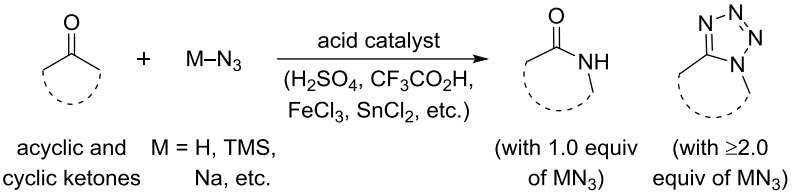
Our laboratory has also recently reported the in situ conversion of halo ketones to azido ketones and their corresponding conversion to lactams via the intramolecular Schmidt reaction in a microwave-assisted continuous flow format.[64] The main limitations of this continuous flow reaction system were the requirement of high temperature, limited substrate scope, and laborious isolation procedure. Suitable reaction conditions, such as the use of AcCl and HFIP could be instrumental in enabling a safe and efficient continuous flow Schmidt chemistry, which is currently under development in our laboratory.

1.3 Catalysis of the Intermolecular Schmidt Reaction of Ketones with $TMSN_3$

The Schmidt reaction represents one of the most powerful tools in organic chemistry for the conversion of carbonyl-containing compounds into their nitrogenous products.[6b,c] Since its discovery,[6a,65] the Schmidt reaction has been widely used for the synthesis of amides or lactams from ketones (Scheme 15). This formal nitrogen-insertion process has received considerable attention in the past few decades and has evolved to include variants expanding its scope and utility.[6c,12-13,16b,17g,m,45a,b,47,66] Although widely useful, a major limitation for the Schmidt reaction and its variants in general as discussed in the previous Section 1.2 is the necessity of superstoichiometric amounts of acid catalysts, often as a solvent, for the reaction to reach completion.[6b,c] This limitation particularly hinders its application to large scale processes and to acid-sensitive substrates, and contributes to acid and metal waste impacting the environment. We discovered that a strong hydrogen-bond-donating solvent, HFIP, promotes catalysis in the intramolecular Schmidt reaction (see Section 1.2).[25] This result sparked our interest to revisit other variants of the Schmidt family in order to identify milder reaction conditions that utilize significantly less amounts of preferably metal-free acid catalyst, in the presence of HFIP.

To achieve this objective, we primarily targeted the intermolecular Schmidt reaction of ketones with $TMSN_3$. The Schmidt reaction of ketones with an azide (HN_3, NaN_3, or $TMSN_3$) typically yields amides or lactams as the major product and tetrazoles as a minor byproduct. The formation of tetrazoles can generally be increased by using larger amounts of azides (Scheme 17), but the success of this strategy is highly dependent on the reaction conditions and the structure of ketones.[6c,67] Hence, exploratory efforts were concentrated toward the optimization of reaction conditions in HFIP for the synthesis of tetrazoles.

Scheme 17. Schmidt Reaction of Ketones with Azides



Tetrazoles have found widespread applications as organocatalysts,[68] ligands,[69] precursors for other nitrogen-containing heterocycles,[70] and in material science.[71] From a medicinal chemistry perspective, tetrazoles have become increasingly relevant, especially 5-substituted 1*H*-tetrazoles as carboxylic acid bioisosteres and 1,5-disubstituted tetrazoles as conformational mimics of cis amide bonds.[72] In addition, tetrazole-based compounds possess numerous pharmacological activities such as anticancer[73] and human growth hormone secretagogue (GHS).[72b,e,74] Noteworthy examples include Losartan®, an angiotensin-II receptor antagonist for the treatment of hypertension[75] and Cardiazole (PTZ, **13a**), a $GABA_A$ receptor antagonist and a prototypical anxiogenic drug[76] (Figure 15).[72f]

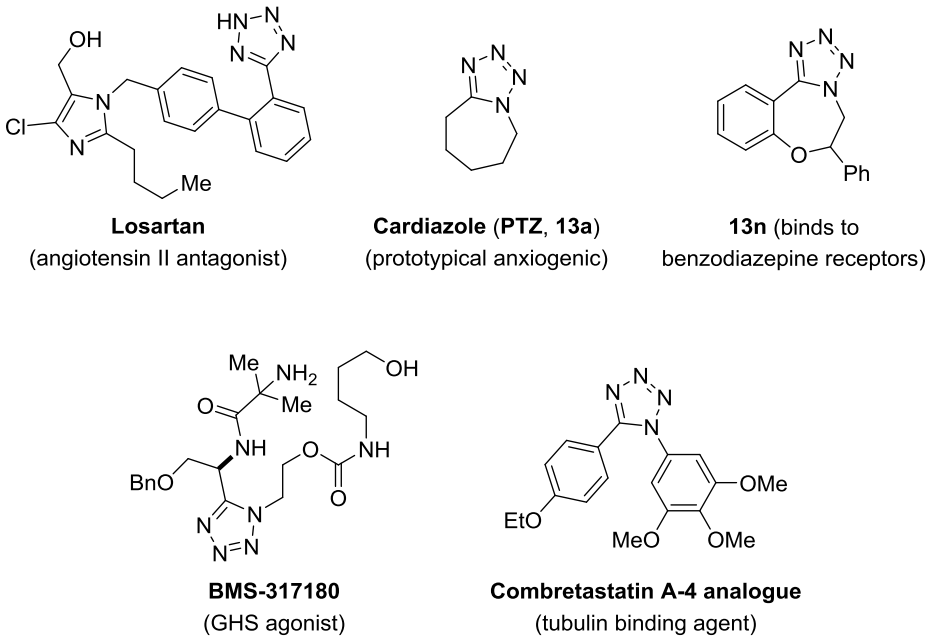


Figure 15. Representative examples of pharmacologically active tetrazoles.

Besides the Schmidt reaction of ketones with azides,[67,77] numerous methods for the synthesis of substituted tetrazoles are known.[72b,c,78] Some common strategies to prepare 1,5-disubstituted tetrazoles entail intramolecular cycloaddition reaction of nitriles and azides,[72f,79] reaction of in situ-generated nitrilium ion with $TMSN_3$,[72d,78b] reactions of amides with NaN_3 in the presence of PCl_5 or triflic anhydride through the intermediacy of imidoyl chlorides[80] or triflates,[81] and reaction of amides with $TMSN_3$ in the presence of triphenylphosphine and diethyl azodicarboxylate.[80a,82] Despite such advancements, most methods either require more than one step and/or high reaction temperatures (>100 °C) to obtain the tetrazole.[72b,78a,b,79c] High reaction temperatures often pose a safety concern due to explosion hazards of azides and tetrazoles, especially on a large scale.[6c,78a,83] As well, tedious work-ups due to the use of polar aprotic solvents such as DMF, long reaction times, and the requirement of the pre-designed starting materials often limits their applications as a general method for the synthesis of tetrazoles.

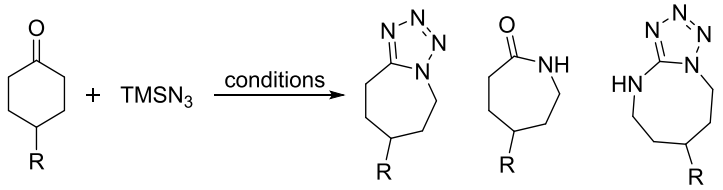
On the contrary, the synthesis of 1,5-disubstituted tetrazoles (mostly fused) using the Schmidt reaction have received considerably less attention; the main limitations being the use of excess acid and long reaction times, often rendering it unsuitable for functionalized substrates.[67] In addition, due to the instability and hazardous nature of HN_3, its in situ generation from NaN_3 in the presence of excess acid catalyst often presents a safety concern.[6c,83b,84] The use of surplus acid catalyst also necessitates basic work-up to remove leftover acid components.[6c] Trimethylsilyl azide ($TMSN_3$) has emerged as a safer and convenient alternative to HN_3 and NaN_3 as an organic solvent soluble azide source for various synthetic transformations.[84b,85] Our efforts to overcome some of these limitations by developing conditons that employ $TMSN_3$ and substoichiometric catalyst for the synthesis of 1,5-disubstituted tetrazoles is described here.

Optimization of Reaction Conditions

Prior to this work, the only report of a Schmidt reaction being carried out under substoichiometric catalysis was reported by Nishiyama, who described the synthesis of tetrazoles using 10 mol % $SnCl_2{\cdot}2H_2O$ under solvent-free conditions.[77b] Though attractive in terms of catalyst loading, the reaction only proceeded at higher temperature of 55 °C over an extended period of 16 h. In our hands, following the procedure described by Nishiyama, the neat reaction of cyclohexanone **12a** and $TMSN_3$ with 10 mol % $SnCl_2{\cdot}2H_2O$ at 55 °C afforded tetrazole **13a** in 87% yield compared to the reported yield of 71%[77b] (Table 9, entry 1). However, the reaction of **12a** and $TMSN_3$ with 5 mol % $SnCl_2{\cdot}2H_2O$ in HFIP at 55 °C turned out to be slightly less effective (entry 2). For the ease of reaction monitoring by TLC, we decided to carry out the optimization studies on 4-phenylcyclohexanone **12b**. Screening of different Lewis and Brønsted acids in HFIP identified TfOH as the optimal acid catalyst for this transformation; 25 mol % TfOH provided the maximum yield of 84% for tetrazole **13b** and 7% of aminotetrazole **15b** in just 1 h (entries 3–9). The use of TfOH over other strong acids such as H_2SO_4 (commonly employed in the Schmidt reaction) offers an additional advantage in that it resists oxidation, minimizing side reactions in few cases.[86] The reaction of **12b** with 1.5 equiv of $TMSN_3$ in HFIP afforded **13b** as the major product, which was contrary to previous reports, where two or more equivalents of the azide nucleophile were generally needed to obtain a tetrazole as the major product (entry 3).[6b,67,77a] HFIP seemed to play a role in promoting the formation of tetrazole over lactam, and the modest yield of **13b** in this reaction was due to incomplete conversion. The reaction with iron(III) chloride in HFIP also delivered tetrazole **13b** (entry 7), which was interesting since the reaction of a ketone with 1.5 equiv of $TMSN_3$ in DCE

has been reported to provide lactam.[84b] Nevertheless, the reaction with 2.5 equiv of $TMSN_3$ in the presence of 50 μL of water afforded lactam **14b** as a major product (entry 10).

Table 9. Optimization of Reaction Conditions for Tetrazole Synthesis[a,b]



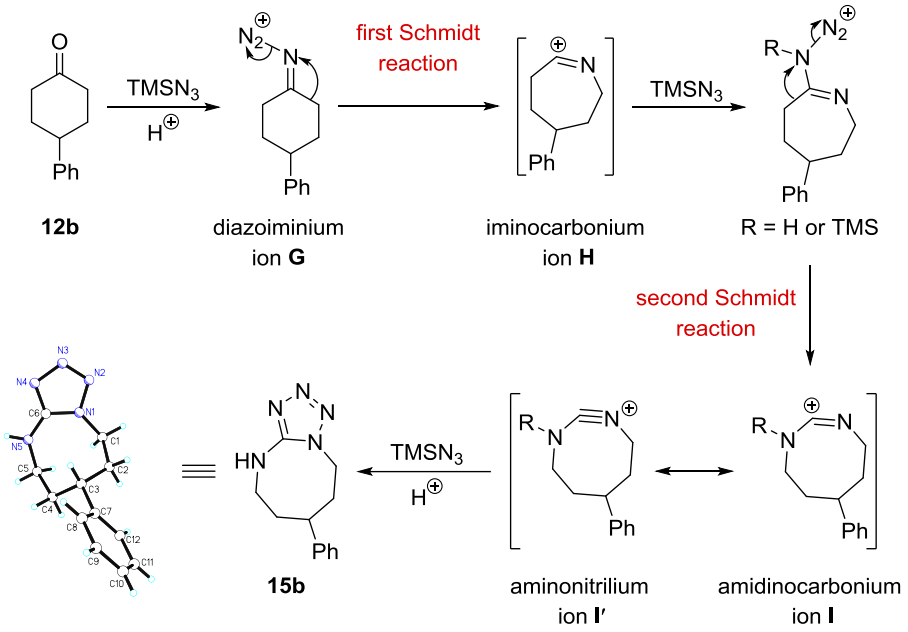
entry	R **12**	$TMSN_3$ (equiv)	catalyst	catalyst (mol %)	solvent	temp, time	yield (%)[c] **13**	**14**	**15**
1	H	3.0	$SnCl_2{\cdot}2H_2O$	10	neat	55 °C, 16 h	87 (71)[d]	ND	ND
2	H	3.0	$SnCl_2{\cdot}2H_2O$	5	$(CF_3)_2CHOH$	55 °C, 16 h	66	ND	ND
3	Ph	1.5	CF_3SO_3H	10	$(CF_3)_2CHOH$	rt, 20 h	49	ca. 7[e]	ca. 6[e]
4	Ph	2.5	CF_3SO_3H	20	$(CF_3)_2CHOH$	rt, 2 h	75	ND	ND
5	Ph	2.5	CH_3COCl[f]	20	$(CF_3)_2CHOH$	rt, 18 h	31	ND	ND
6	Ph	2.5	$BF_3{\cdot}OEt_2$	20	$(CF_3)_2CHOH$	rt, 22 h	16	ND	ND
7	Ph	2.5	$FeCl_3{\cdot}6H_2O$	20	$(CF_3)_2CHOH$	rt, 22 h	60	ND	ND
8	Ph	3.0	$ClSO_3H$[g]	20	$(CF_3)_2CHOH$	rt, 2 h	51	ND	ND
9	**Ph**	**2.5**	**CF_3SO_3H**	**25**	**$(CF_3)_2CHOH$**	**rt, 1 h**	**84**	**ND**	**7**
10	Ph	2.5	CF_3SO_3H	25	$(CF_3)_2CHOH$[h]	rt, 5 h	13	53	ND
11	H	3.0	CF_3SO_3H	5	$(CF_3)_2CHOH$	55 °C, 16 h	85	ND	ND
12	Ph	2.5	$SnCl_2{\cdot}2H_2O$	25	neat	rt, 2 h	trace	–	–
13	Ph	2.5	CF_3SO_3H	25	neat	rt, 2 h	34	ca. 12[e]	ca. 3[e]

[a]To a solution or a suspension of ketone **12a** (0.40 mmol) or **12b** (0.20 mmol) and $TMSN_3$ in $(CF_3)_2CHOH$ (1.0 or 0.50 mL) or under neat conditions was added a catalyst and the reaction was allowed to stir at a specified temperature for a designated period of time unless otherwise mentioned (see the Experimental Section for details). [b]Concn of ketone was ca. 0.40 M. [c]Isolated yields. [d]Yield in parentheses refers to the reported yield in ref. 77b. [e]Corrected yield for **14b** and **15b** from a slightly impure inseparable mixture as determined by ^1H NMR. [f]Could generate 20 mol % of HCl in situ (ref. 25). [g]The reaction was carried out under argon atmosphere. [h]50 μL of deionized water was added before the addition of TfOH. ND = Not determined.

The reaction of **12a** with 5 mol % TfOH in HFIP at 55 °C provided comparable yield as with 10 mol % $SnCl_2 \cdot 2H_2O$ without solvent (Table 9, cf. entries 11 and 1). Conversely, when the neat reaction of **12b** was carried out with 25 mol % $SnCl_2 \cdot 2H_2O$ at room temperature, only a trace amount of tetrazole **13b**, in addition to unidentified byproducts and some unreacted **12b**, were observed by crude ^1H NMR (entry 12). Very poor conversion could be due to the heterogeneity of the reaction mixture as the catalyst ($SnCl_2 \cdot 2H_2O$) was insoluble. As per the report by Nishiyama, the reaction of ketones and $TMSN_3$ with $SnCl_2 \cdot 2H_2O$ at room temperature provided only trace amounts of tetrazoles for cyclic ketones and diazido intermediates for acyclic ketones.[77b] As diazido compounds are high-energetic materials and explosive in nature, their build-up in a reaction should be avoided.[6c,87] Moreover, it is best to avoid tin due to toxicity concerns.[88] Still, the neat reaction of **12b** and $TMSN_3$ with 25 mol % TfOH at room temperature was somewhat effective and **13b** was obtained in 34% yield along with a small amount of **14b** and **15b** as a mixture and unreacted **12b** (entry 13).

Mechanistically, the formation of aminotetrazole **15b** is intriguing since likely migrations of both the carbonyl substituents occur via two consecutive Schmidt reactions to afford an amidinocarbonium ion **I** or aminonitrilium ion **I'** (Scheme 18). Subsequent addition of the third molecule of azide to either resonance structures of the reactive intermediate **I** leads to the formation of aminotetrazole **15b**, the structure of which was confirmed by single-crystal X-ray diffraction analysis. Although substituted 5-aminotetrazoles are known in the literature,[78a,89] they are rarely prepared from the Schmidt reaction.[6b] The formation of iminodihydrotetrazole (tautomer of aminotetrazole)[78b,90] from benzophenone was the only example of such a Schmidt reaction.[6a,67]

Scheme 18. Proposed Mechanism for the Formation of Aminotetrazole 15b

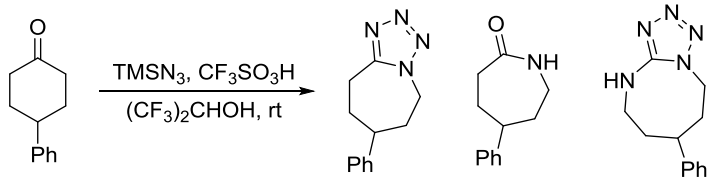


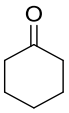
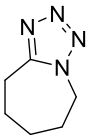
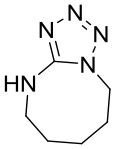
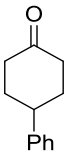
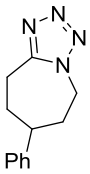
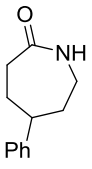
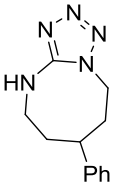
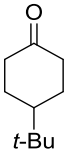
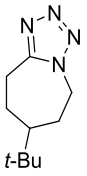
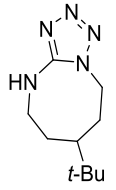
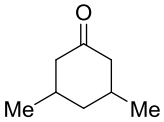
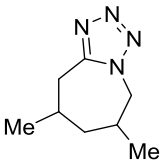
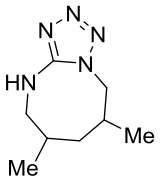
Substrate Scope and Limitations

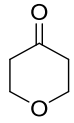
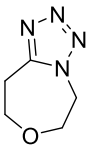
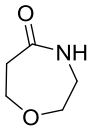
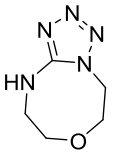
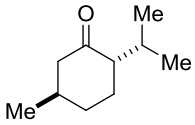
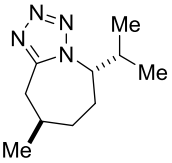
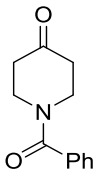
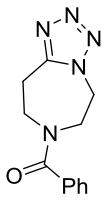
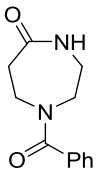
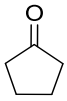
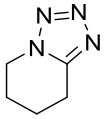
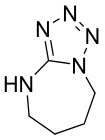
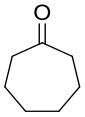
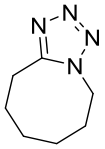
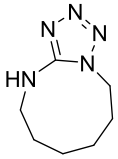
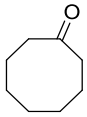
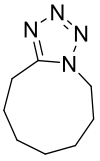
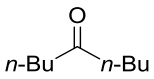
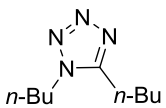
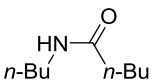
The scope and limitations of various cyclic and acyclic ketones were investigated under the optimized reaction conditions (Table 10). Unsubstituted and substituted cyclohexanones worked well, with 25 mol % TfOH delivering good yields of tetrazoles and <15% combined yields of aminotetrazoles and lactams (entries 1–4). Functionalized and sterically hindered cyclohexanones required 45–65 mol % TfOH to afford the desired transformation in good yields (entries 5–7). Given the possibility for the isomerization of an α-center under the strong acidic conditions, the formation of a single tetrazole product **13f** from L-menthone **12f** with a high level of regio- and diastereoselectivity was remarkable (entry 6). On the other hand, both methyl and isopropyl substituents in **12f** are equatorial. A similar buffering effect of HFIP was also observed in our previous work on the catalytic intramolecular Schmidt reaction (see Table 1 and the associated discussion in Section 1.2).[25] The requirement of 65 mol % TfOH for piperidone substrate **12g** was in agreement with the decreased catalytic turnover due to an additional site (amide) of catalyst

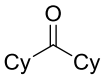
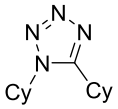
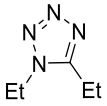
deactivation (entry 7). Reactions of smaller and medium ring ketones provided moderate to excellent yields of tetrazoles (entries 8–10). In contrast, the reaction of aliphatic ketones required close to a stoichiometric amount of acid catalyst to afford the corresponding tetrazoles in moderate to good yields (entry 11–13).

Table 10. Substrate Scope of Ketones for the Synthesis of Tetrazoles [a,b]



entry	ketone **1**	catalyst (mol %)	time (h)	yield (%)[c] **2**	**3**	**4**
1		25	2		–	
	12a			**13a** (91%)	ND	**15a** (4%)
2		25	2			
	12b			**13b** (84%)	**14b** (3%)	**15b** (9%)
3		25	2		–	
	12c			**13c** (83%)	ND	**15c** (9%)
4		25	1.5		–	
	12d[d]			**13d** (83%)[e]	ND	**15d** (3%)[e]

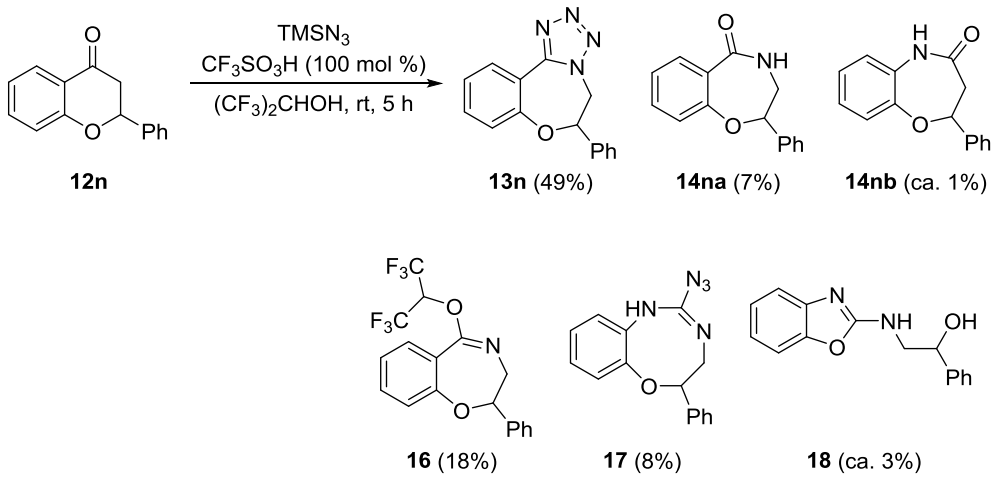
entry	ketone **1**	catalyst (mol %)	time (h)	yield (%)[c] **2**	**3**	**4**
5		45	2.5		 +	
	12e			**13e** (53%)	**14e** (3%)[f]	**15e** (7%)[f]
6		50	6		–	–
	12f			**13f** (87%)	ND	ND
7		65	2.5			–
	12g			**13g** (50%)[g]	**14g** (14%)[g]	ND
8		50	6		–	
	12h			**13h** (51%)	ND	**15h** (7%)
9		60	2		–	
	12i			**13i** (93%)	ND	**15i** (ca. 2%)
10		60	2		–	–
	12j			**13j** (86%)	ND	ND
11		80	3			–
	12k			**13k** (40%)[h]	**14k** (19%)[h]	ND

entry	ketone **1**	catalyst (mol %)	time (h)	yield (%)[c]		
				2	**3**	**4**
12		90	6		–	–
	12l			**13l** (74%)[i]	ND	ND
13		90	6		–	–
	12m			**13m** (66%)	ND	ND

[a]To a solution of ketone (0.40 mmol) and $TMSN_3$ (1.0 mmol) in $(CF_3)_2CHOH$ (1.0 mL) was added TfOH and the reaction was allowed to stir at room temperature for a specified period. [b]Concn of ketone was ca. 0.40 M. [c]Isolated yields. [d]Mixture of isomers (ca. 95% major isomer). [e]Corrected yield of the major isomer from a mixture of isomers (see the Experimental Section for details). [f]Corrected yield for **14e** and **15e** from an inseparable mixture as determined by ^{1}H NMR. [g]Mixture of rotamers (see the Experimental Section for details). [h]Corrected yield for **13k** and **14k** from an inseparable mixture as determined by ^{1}H NMR (see the Experimental Section for details). [i]Corrected yield of **13l**, contains a small amount of byproduct (probably amide) as determined by ^{1}H NMR and HRMS (See the Experimental Section). ND = Not determined.

The Schmidt reaction of aromatic ketones, in particular chromanones and flavanones, has been extensively studied with respect to the synthesis of benzoheterazepine analogues as potential psychotropic agents.[77a,d,h,91] The reaction of less reactive aromatic ketones requires excess acid catalysts, often as solvents, and long reaction times to provide lactam isomers as major products in most cases.[77a,h] Although the reaction of flavanone **12n** using our HFIP methodology required a full equiv of TfOH, the reaction time was much shorter and tetrazole **13n** was furnished in moderate yield along with only a small amount of lactam regioisomers **14na** and **14nb** (Scheme 19). Moreover, three unusual products **16**, **17**, and **18** were obtained through intra- and intermolecular trapping of carbonium ion intermediates with different nucleophiles en route to the tetrazole and aminotetrazole products.

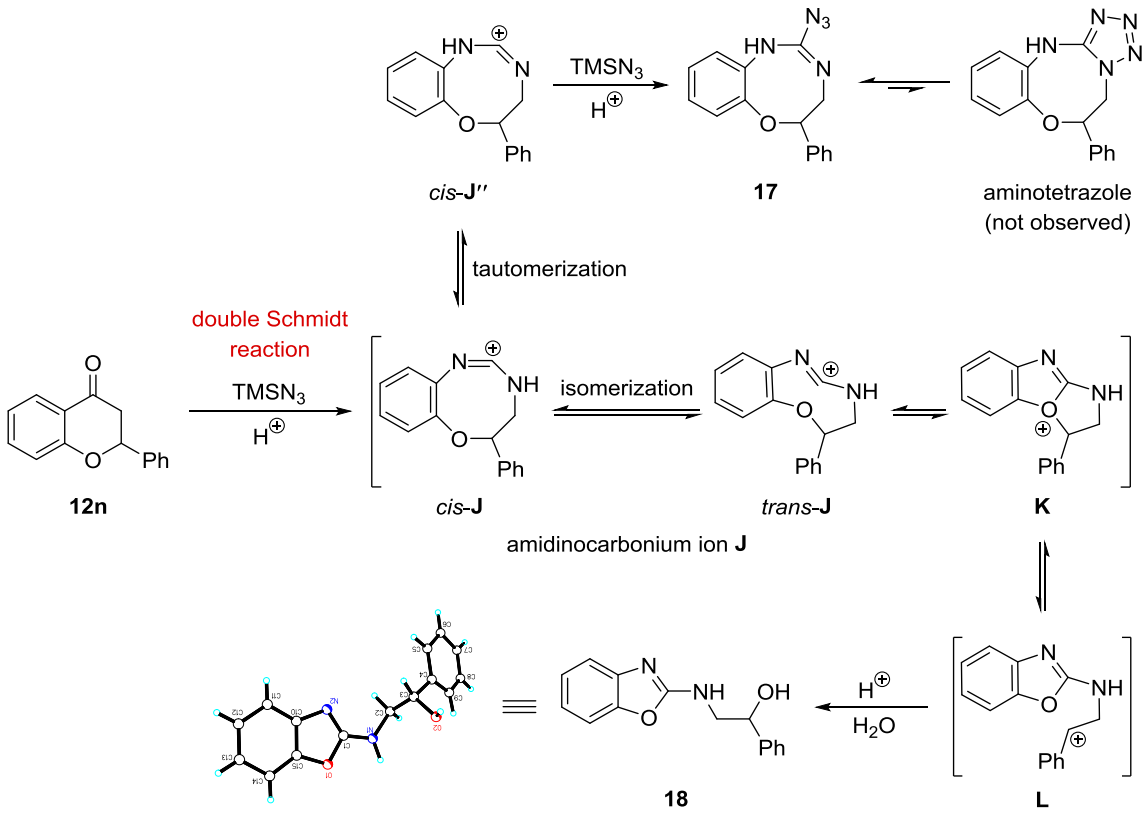
Scheme 19. Unusual Products Formation from Flavanone 12n



Iminoether **16** was obtained through the trapping of iminocarbonium ion with HFIP. The formation of iminoesters as major products upon treatment of flavanone with NaN_3 in TFA and trichloroacetic acid has been documented (see Scheme 33b; Section 1.7.2).[77a] A *cis*-isomer **J''** of an eight-membered amidinocarbonium ion formed after two sequential Schmidt reactions was intermolecularly trapped with $TMSN_3$ leading to the formation of guanyl azide **17**, which in theory could cyclize into the aminotetrazole. However, the corresponding aminotetrazole product was not observed (Scheme 20). This result was counterintuitive since cyclization into the aminotetrazole is generally the thermodynamically more favored process.[89a,92] The thermal isomerization of aminotetrazoles is believed to proceed via a transient guanyl azide intermediates.[89a,92a] However, in our system, guanyl azide is favored, presumably due to stabilization of **17** by the aromatic ring or due to internal hydrogen bonding between the oxygen and guanidino "–NH–" group, which made its isolation possible.[78b,92a] Moreover, the isolation of guanyl azide **17** provides strong evidence for the involvement of intermediate **J** (also see amidinocarbonium ion **I** and aminonitrilium ion **I'** in Scheme 18). Guanyl azide **17** was

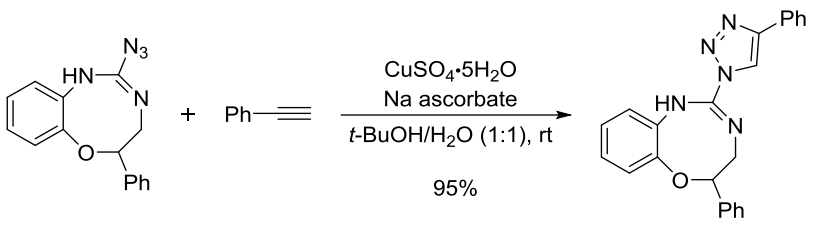
subsequently subjected to copper-promoted click reaction with phenyl acetylene to provide a unique guanidino triazole **19** that further confirmed the structure of **17** (Scheme 21).

Scheme 20. Proposed Mechanism for the Formation of Guanyl Azide 17 and Aminobenzoxazole 18



Mechanistically fascinating was the formation of a small amount of aminobenzoxazole **18** (Schemes 19 and 20). Presumably, isomerization of *cis*-**J** to *trans*-**J**, followed by its intramolecular trapping by the oxygen atom present in the ring would generate an oxonium ion **K**. Bicyclic ring-opening of **K** affords a benzylic carbocation **L**, which upon hydration leads to **18**. Formation of aminobenzoxazoles have also been reported by Misiti in few instances from the Schmidt reaction of substituted flavanones with NaN_3.[91b]

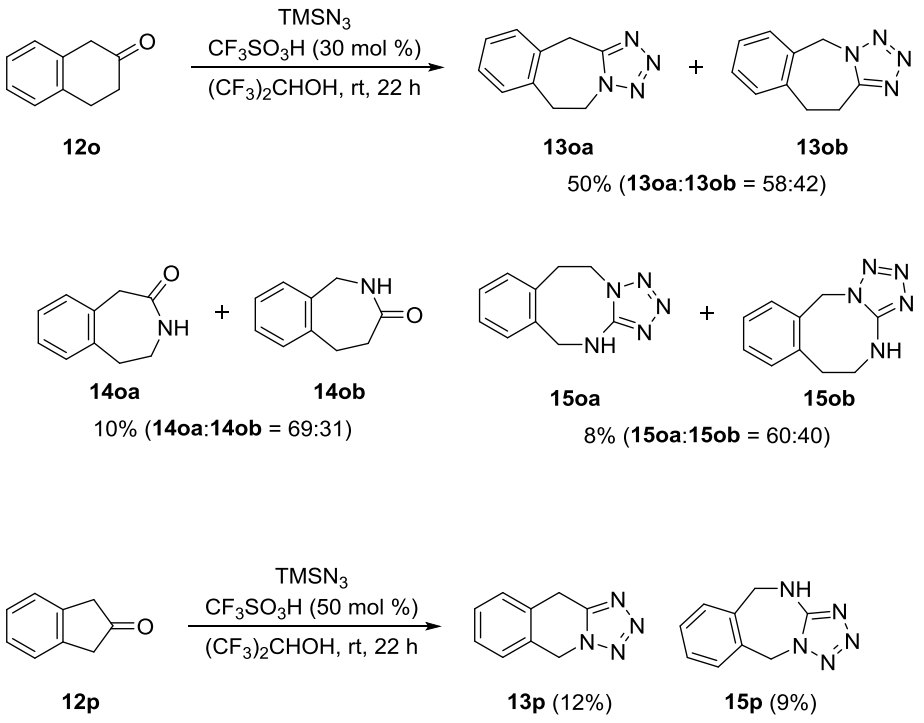
Scheme 21. Copper-Catalyzed Alkyne-Azide Cycloaddition (CuAAC) of 17 to Guanidino Triazole 19



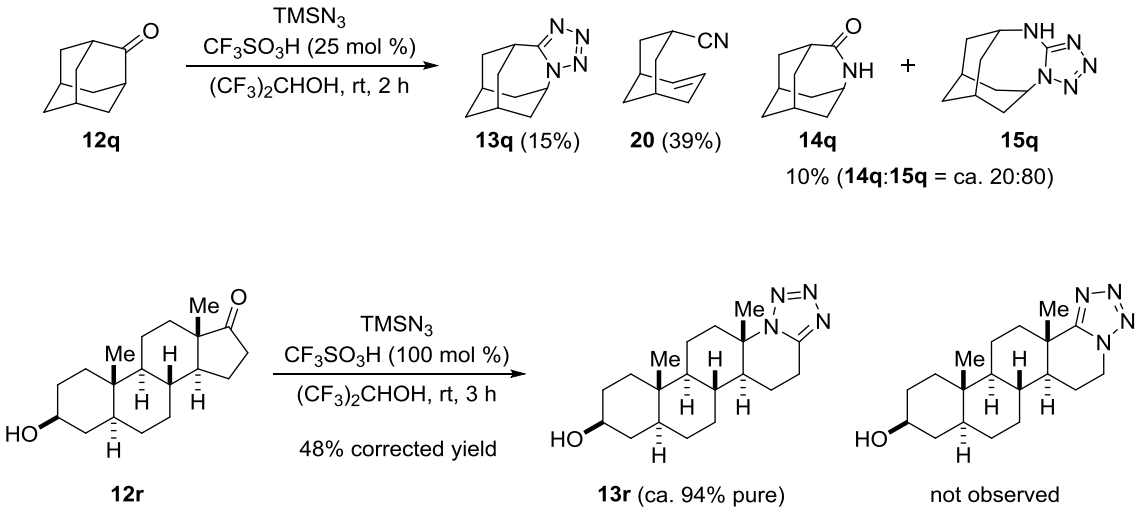
17 19

The scope of this methodology was further extended to more challenging substrates such as benzylic and steroidal ketones (Schemes 22 and 23). Low yields of tetrazoles have been reported for the Schmidt reaction of β-tetralone **12o** with HN_3.[77d] The reaction of **12o** in HFIP using the optimized conditions provided tetrazoles **13oa** and **13ob** in modest yield in addition to small amounts of lactams **14oa** and **14ob**, and aminotetrazoles **15oa** and **15ob** (Scheme 22). On the other hand, the reaction of 2-indanone **12p** afforded a complex mixture, from which tetrazole **13p** and aminotetrazole **15p** were isolated in low yields (Scheme 22). Similarly, the reaction of adamantanone **12q** gave the desired tetrazole product **13q** in low yield; however, it was obtained in twice the yield than the reported procedure using NaN_3 and methanesulfonic acid ($MeSO_3H$; Scheme 23).[93] Carbonitrile **20** was obtained as a major product in this reaction, which was in consistent with the literature report and resulted likely from either diazoiminium or nitrilium ion intermediates via fragmentation.[93] In addition, a small amount of an inseparable mixture of lactam **14q** and aminotetrazole **15q** was obtained along with some unreacted **12q**. The reaction of *trans*-androsterone **12r** with 1 equiv of TfOH gave a mixture of several unidentified and inseparable byproducts from which it was possible to isolate a single tetrazole isomer **13r** in ca. 48% corrected yield and ca. 94% purity (Scheme 23).

Scheme 22. Schmidt Reaction of Benzylic Ketones



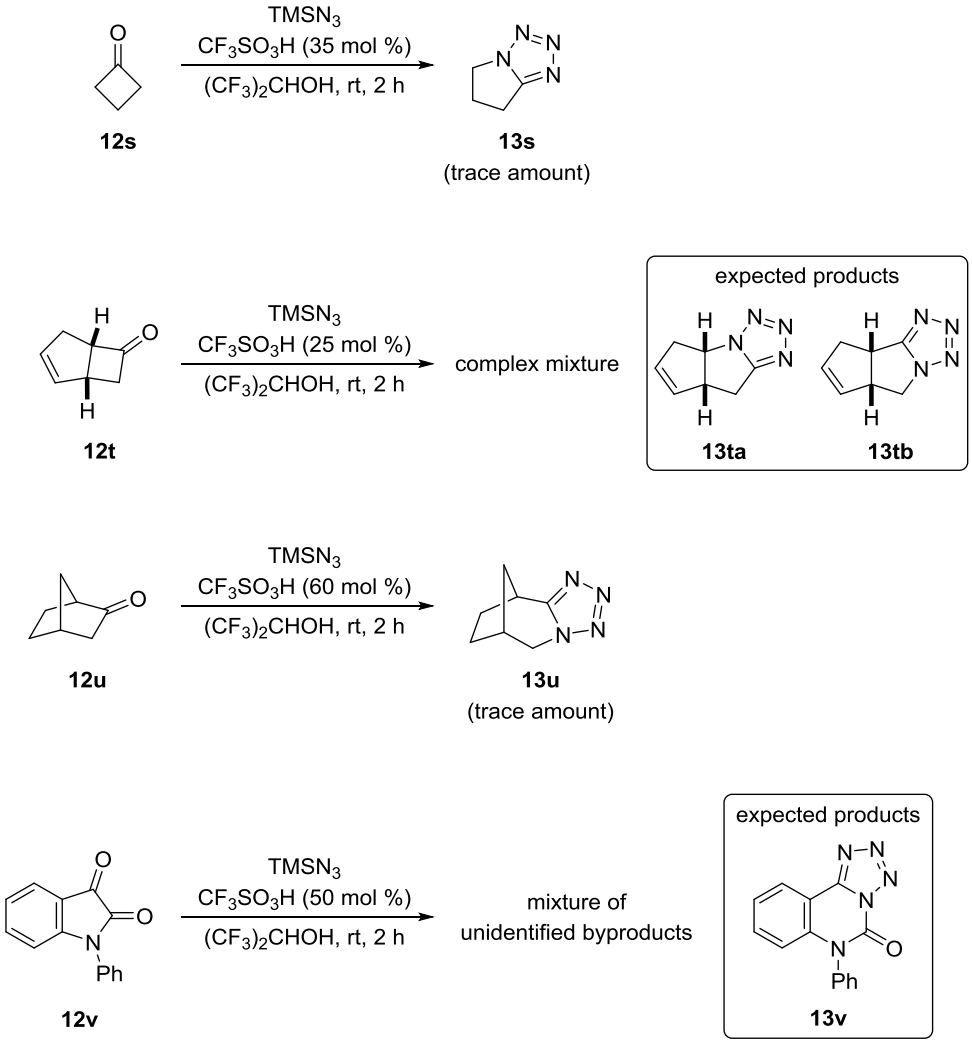
Scheme 23. Schmidt Reaction of Adamantanone 12q and *trans*-Androsterone 12r



The methodology was found to be substrate dependent (Scheme 24). The reaction of cyclobutanone **12s** showed a trace amount of tetrazole in an isolated mixture. An initial effervescene indicative of a nitrogen gas evolution suggests divergence to a non-productive

reaction pathway such as fragmentation (similar to that observed for **12q**). This might have led to the formation of volatile byproducts as no tractable product was observed in this reaction. The reaction of bicycloheptenone **12t** resulted in a complex mixture. In a similar way as **12s**, the reaction of norcamphor **12u** gave an impure sample of a small amount of what is believed to be a single tetrazole isomer **13u**. Additionally, a mixture of several byproducts was obtained. The reaction of 1-phenylisatin **12v** gave a mixture of several unidentified byproducts of which the non-polar byproduct was the major component.

Scheme 24. Unsuccessful Examples Attempted



Conclusions

The current protocol for the synthesis of tetrazoles has addressed many limitations of the older methods such as high temperatures, making it superior in terms of operational practice. The use of a considerably less amount of the acid catalyst and short reaction times for most cases were the key highlights of this methodology. A relatively broad substrate scope was also demonstrated.

1.4 Catalysis of the Intermolecular Schmidt Reaction of Aldehydes with $TMSN_3$

The importance of nitriles as a versatile functional group not only lies in their synthetic utility as building blocks or precursors to other functionalities such as acids, amines, amides, aldehydes, and tetrazoles but also because they are important structural motifs in many natural products,[94] pharmaceuticals,[95] agrochemicals, dyes, etc.[96] In pharmaceuticals, aryl nitriles contributes heavily to the total number of nitrile-containing drugs, for examples, letrozole, pericyazine, escitalopram, dapivirine, and the list goes on (Figure 16).[95] Nitrile groups on the aromatic ring can serve many functions such as ketone bioisosteres and increased resistance of aromatic system to the oxidative metabolism.[95]

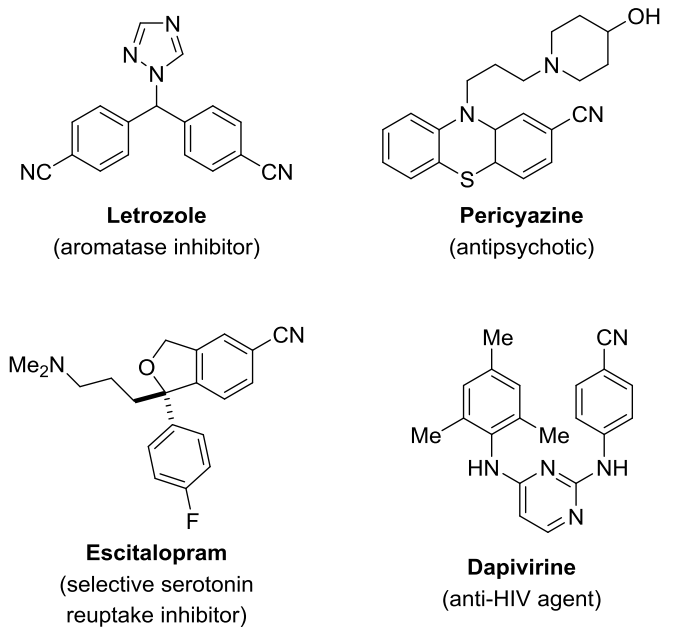


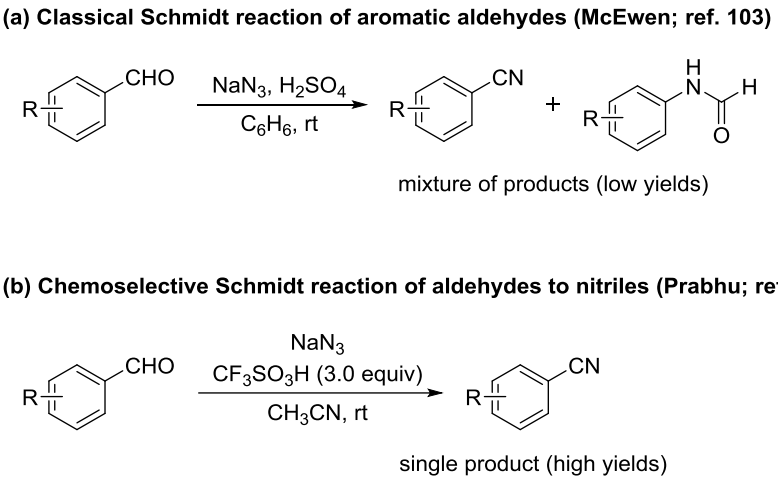
Figure 16. Drugs containing aryl nitriles.

General strategies for the synthesis of aryl nitriles involve the Sandmeyer reaction of aryldiazonium salts,[96d,97] Rosenmund–von Braun reaction from aryl halides,[97c,98] transition metal-catalyzed cyanation of aryl halides[99] or direct cyanation through C–H bond functionalization of arenes,[100] and ammoxidation of methyl arenes, which is a preferred

industrial process.[101] Major drawbacks for most of these processes are the use of stoichiometric to excess amounts of toxic cyanide source, generation of heavy metal waste, requirement of relatively high temperatures (>100 °C), long reaction times, requirement of a reactive aryl halide source (aryl iodides and bromides are generally preferred), and the scarcity of the commercially available substrates such as methyl arenes.[99c,102]

Given the limitations for these existing protocols, development of a mild and practically simple process for the synthesis of aryl nitriles would be attractive. In a similar sense as described in Section 1.3 for the outcome of the Schmidt reaction of ketones with an azide, the Schmidt reaction of aromatic aldehydes is known to provide a mixture of nitriles and formanilides (Scheme 25a).[103] Due to such non-selective transformations, the utility of the Schmidt reaction for the synthesis of aromatic nitriles has been limited. Recently, Prabhu and co-workers demonstrated that the Schmidt reaction of aldehydes with NaN_3 in the presence of TfOH as a catalyst and ACN as solvent, exclusively affords corresponding nitriles (Scheme 25b).[66j] In order to achieve this chemoselective reaction, 3 equiv of TfOH was minimally required for an instantaneous reaction to obtain a high yield of the aromatic nitrile. A conversion of mere 6% was observed when 1.5 equiv of TfOH was used during the optimization studies. The utility of this chemoselective Schmidt process would improve if substoichiometric amount of acid catalyst could be used. In order to further expand the scope of the methodology developed for the Schmidt reaction in HFIP (see Sections 1.2 and 1.3), we sought to test those reaction conditions on aromatic aldehydes.

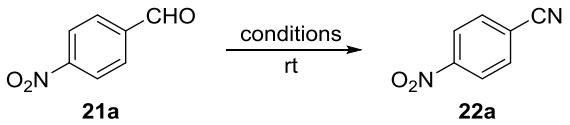
Scheme 25. Intermolecular Schmidt Reaction of Aromatic Aldehydes



Optimization of Reaction Conditions

As reported by Prabhu,[66j] we also began our optimization on 4-nitrobenzaldehyde **21a** with NaN_3 and TfOH, however with HFIP as a solvent instead of ACN (Table 11, entry 1). Low conversion to **22a** with 50 mol % TfOH (entry 1) and 80 mol % AcCl (entry 2) indicated a solubility issue with NaN_3 in HFIP, resulting in low reactivity. Changing to a soluble azide source such as $TMSN_3$ drastically improved the yield with 25 mol % of catalysts (entries 3 and 4). However, reactions did not go to completion even after longer periods and few polar byproducts were observed by TLC during reaction monitoring. Even though the reaction with 30 mol % TfOH offered complete conversion in 2 h, only a modest yield was obtained due to the formation of polar unidentified byproducts (entry 5). Gratifyingly, a 1:1 combination of HFIP and ACN as a solvent significantly increased the yield, but complete conversion was not observed even after 4 h (entry 6). Finally, the reaction of **21a** with 40 mol % TfOH proved to be optimal, providing a slightly better yield of **22a** along with a much shorter reaction time (entry 7).

Table 11. Optimization of the Schmidt Reaction of 4-Nitrobenzaldehyde 21a[a,b]



21a **22a**

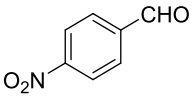
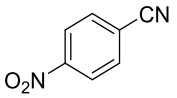
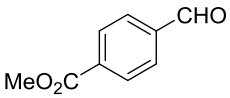
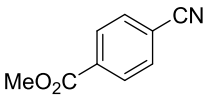
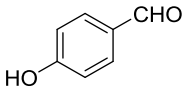
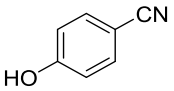
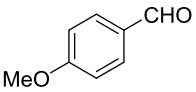
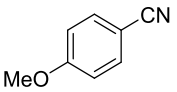
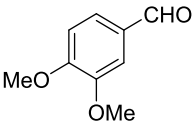
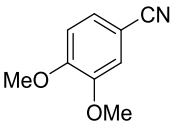
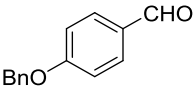
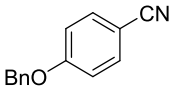
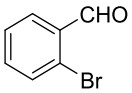
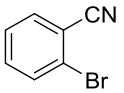
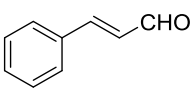
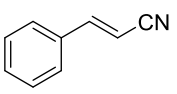
entry	azide source	azide (equiv)	catalyst	catalyst (mol %)	solvent	time (h)	NMR ratio (**22a**:**21a**)[c]	yield (%)[d] **22a**
1	NaN_3	1.5	CF_3SO_3H	50	$(CF_3)_2CHOH$	16	30:70[e]	ND
2	NaN_3	1.5	CH_3COCl[f]	80	$(CF_3)_2CHOH$	8	19:81	ND
3	$TMSN_3$	1.5	$TiCl_4$[g]	25	$(CF_3)_2CHOH$	24	ND	75
4	$TMSN_3$	1.5	CF_3SO_3H	25	$(CF_3)_2CHOH$	8	ND	68
5	$TMSN_3$	2.0	CF_3SO_3H	30	$(CF_3)_2CHOH$	2	ND	65[h]
6	$TMSN_3$	2.0	CF_3SO_3H	30	$(CF_3)_2CHOH$/ CH_3CN (1:1)	4	ND	81
7	**$TMSN_3$**	**2.0**	**CF_3SO_3H**	**40**	**$(CF_3)_2CHOH$/ CH_3CN (1:1)**	**45 min**	**ND**	**83**

[a]To a solution of 4-nitrobenzaldehyde **21a** (0.25 or 0.50 mmol) and azide in a solvent (0.50, 1.0, or 2.0 mL) was added a catalyst and the reaction was allowed to stir at rt (23 or 25 °C) for a designated period of time, unless otherwise mentioned. [b]Concn of **21a** was ca. 0.25 or 0.50 M. [c]^{1}H NMR ratio determined on a crude reaction mixture. [d]Corrected isolated yields of **22a** (**22a** was contaminated with a small amount (ca. 3–6%) of **21a**). [e]Other byproducts were also observed. [f]Capable of generating 80 mol % HCl in situ. [g]A 1.0 M solution of $TiCl_4$ in CH_2Cl_2 was used. [h]^{1}H NMR only showed peaks of **22a**. ND = Not determined

Substrate Scope

Various aromatic aldehydes were subjected to the optimized reaction conditions (Table 12). In general, a variety of aldehydes containing different functional groups were well tolerated and their corresponding nitriles were obtained in good to excellent yields. Benzaldehydes containing electron-withdrawing (entries 1 and 2) and electron-donating groups (entries 3–5) underwent a facile reaction to furnish the corresponding nitriles. Even cinnamaldehyde **21h** reacted smoothly to afford cinnamonitrile **22h** in excellent yield (entry 8).

Table 12. Scope of Aromatic Aldehydes[a,b]

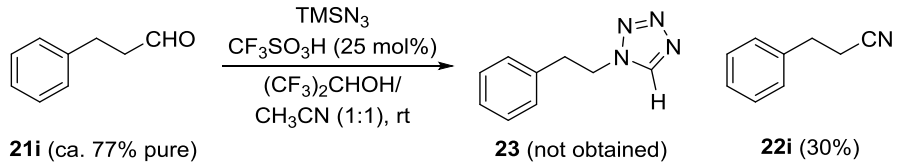
entry	aldehydes **21**	time (min)	nitriles **22**	yield (%)[c]
1	 **21a**	45	 **22a**	83[d]
2	 **21b**	30	 **22b**	78
3	 **21c**	30	 **22c**	95
4	 **21d**	30	 **22d**	82
5	 **21e**	20	 **22e**	86
6	 **21f**	20	 **22f**	71
7	 **21g**	30	 **22g**	68
8	 **21h**	45	 **22h**	90

[a]To a solution of aldehyde **21** (0.50 mmol) and $TMSN_3$ (1.0 mmol) in a premixed $(CF_3)_2CHOH/CH_3CN$ solvent mixture (2.0 mL, 1:1) was added TfOH (0.20 mmol) and the reaction was allowed to stir at rt for a designated period.

[b]Concn of aldehyde was ca. 0.25 M. [c]Isolated yields. [d]Contains ca. 4% of unreacted **21a** (same as entry 7 in Table 3; see the Experimental Section for details).

After successfully demonstrating the utility of this methodology for the synthesis of aromatic nitriles, we then focused on preparing tetrazoles from aliphatic aldehydes and $TMSN_3$.[104] The reaction of hydrocinnamaldehyde **21i** with 3 equiv of $TMSN_3$ in the presence of 25 mol % TfOH resulted in a complex mixture from which 3-phenylpropionitrile **22i** was isolated in low yield (Scheme 26). The formation of the complex mixture could be possibly due to the use of excess $TMSN_3$ and impure **21i**, which was realized later. Moreover, the presence of tetrazole **23** in the mixture could not be determined.

Scheme 26. Intermolecular Schmidt Reaction of Aliphatic Aldehyde 21i with $TMSN_3$



21i (ca. 77% pure) **23** (not obtained) **22i** (30%)

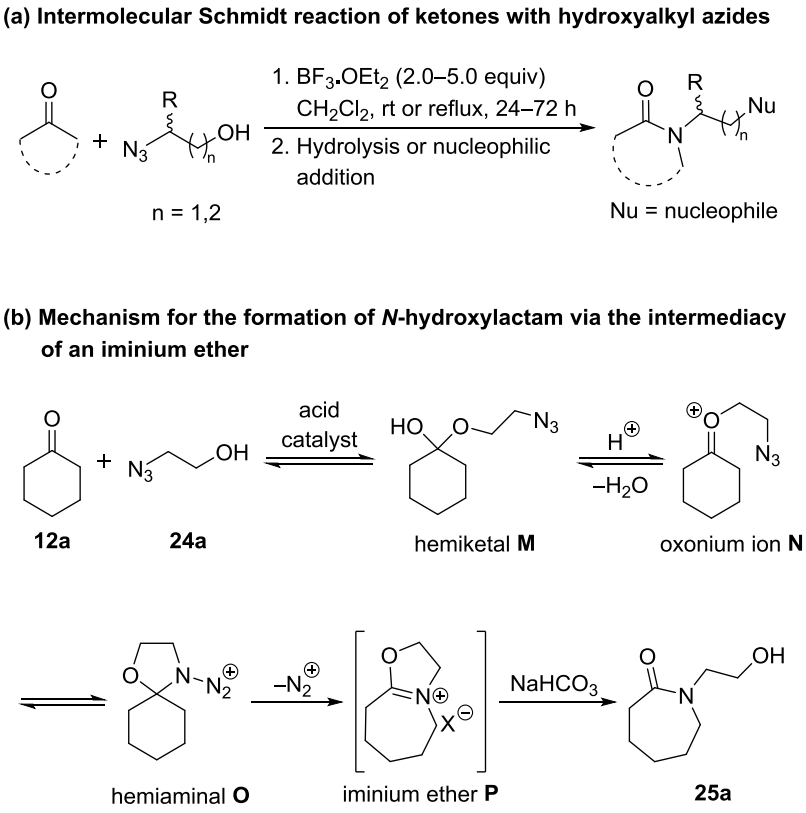
Conclusions

We have clearly shown that HFIP promotes this acid-catalyzed intermolecular Schmidt reaction, allowing for the use of only 40 mol % TfOH for the conversion of aromatic aldehydes to aromatic nitriles. A wide range of functional group compatibility was observed. Additional optimization of the reaction conditions might facilitate the extension of the scope to aliphatic aldehydes.

1.5 Improved Protocol for the Intermolecular Schmidt Reaction with Hydroxyalkyl Azides

Boyer was the first to utilize hydroxyalkyl azides in the intermolecular Schmidt reaction with aromatic aldehydes to afford oxazolines and dihydrooxazines (see Section 1.1; Boyer reaction).[11a,b] Professor Aubé further exploited this in situ tethering of hydroxyalkyl azides (azido alcohols) to ketones for the synthesis of *N*-hydroxyalkyl lactams (also known as the Boyer–Aubé reaction;[83b] Scheme 27a).[66c,105] Mechanistically, the hydroxyl group of a hydroxyalkyl azide **24a** attacks the activated carbonyl group of **12a** promoting the formation of a hemiketal **M**, which upon dehydration generates an oxonium ion intermediate **N** (Scheme 27b).[66c,g,105a] Subsequent intramolecular attack by the azido group results in a hemiaminal species **O**. Antiperiplanar migration of one of the alkyl groups with concomitant loss of N_2 then yields an iminium ether intermediate **P** that upon hydrolysis with aqueous base affords *N*-hydroxyalkyl lactam **25a**, which could be seen as the formal product of direct insertion of the azide end of **24a** into the ketone **12a**. This intermolecular Schmidt variant has been utilized for nitrogen asymmetric ring-expansion reactions,[66g,106] construction of γ-turn-like peptidomimetic libraries,[107] and syntheses of functionalized lactams[108] and *N*-alkyl heterocycles[66i,109] via nucleophilic additions to iminium ethers. The increased reactivity and stability of hydroxyalkyl azides compared to alkyl azides under acidic conditions has considerably expanded the scope and utility of this variant.

Scheme 27. Intermolecular Schmidt Reaction of Ketones with Hydroxyalkyl Azides

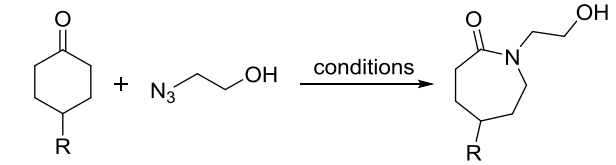


Typically, the reaction of ketones with hydroxyalkyl azides requires 2–5 equiv of $BF_3{\cdot}OEt_2$ in DCM to achieve successful iminium ether formations over extended periods (Scheme 27a).[66c,105,110] However, in principle, only 1 equiv of acid catalyst should be sufficient to promote the reaction to completion as only 1 equiv of the counter ion (X^-) is required to stabilize the isolable iminium ether intermediate (Scheme 27b).[66c,105a] Thus, carrying out this transformation with 1 equiv of Brønsted acid catalyst in a short period is attractive, both in terms of metal-free transformation and acid waste minimization. It would also provide an easy access to the isolation of iminium ethers for further functionalization when necessary; in this case, its hydrolysis to afford *N*-hydroxyalkyl lactam.

Optimization of Reaction Conditions on Ketones

We initially utilized the substoichiometric amount of $BF_3{\cdot}OEt_2$ and $TiCl_4$ to promote the reaction of cyclohexanone **12a** with 2-azidoethan-1-ol **24a** in the presence of HFIP (Table 13, entries 1 and 2). However, low to partial conversion to the desired lactam **25a** was observed suggesting the necessity for a full equiv of the acid catalyst. Reaction with 25 mol % $TiCl_4$ (capable of generating a full equiv of HCl) resulted in a satisfactory yield of **25a** (entry 3). Employing 1 equiv of TfOH for the reaction of **12b** with **24a** in HFIP turned out to be preferable, affording a quantitative yield of the corresponding lactam **25b**. Substrate scope of diverse ketones with these conditions has been further investigated by Manwika Charaschanya.

Table 13. Preliminary Optimization Studies for the Intermolecular Schmidt Reaction of Ketones with 2-Azidoethanol 24a in HFIP[a,b]



12a; R = H
12b; R = Ph

24a

25a; R = H
25b; R = Ph

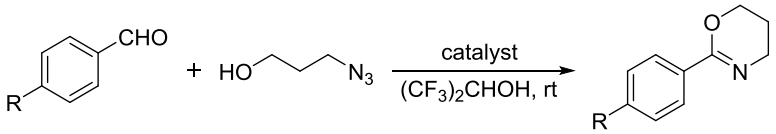
entry	R **12**	catalyst	catalyst (mol %)	solvent	temp, time	yield (%)[c] **25**
1	H	$BF_3{\cdot}OEt_2$	25	$(CF_3)_2CHOH$	rt, 30 min	20
2	H	$TiCl_4$[d]	10	$(CF_3)_2CHOH$	25 °C, 24 h	40
3	H	$TiCl_4$[d]	25	$(CF_3)_2CHOH$	rt, 30 min	76
4	**Ph**	**CF_3SO_3H**	**100**	**$(CF_3)_2CHOH$**	**rt, 1 h**	**99**

[a]To a solution of ketone **12** (1.0 equiv) and 2-azidoethanol **24a** (1.3 or 1.5 equiv) in HFIP (1.6 or 2.5 mL) was added a catalyst (0.10–1.0 equiv) and the reaction mixture was stirred at a specified temperature for a designated period of time. Further hydrolysis with a saturated aqueous $NaHCO_3$ solution for 6–20 h followed by purification afforded **25**. [b]Concn of **12** was ca. 0.25 or 0.40 M. [c]Isolated yields. [d]10 and 25 mol % $TiCl_4$ could generate 40 and 100 mol % HCl in situ, respectively.

Limitations with Aromatic Aldehydes

Boyer′s initial work for the synthesis of oxazolines and dihydrooxazines from aromatic aldehydes and hydroxyalkyl azides in H_2SO_4 have met several limitations.[11a,b] Professor Aubé showed that the modification of the original reaction conditions by employing Lewis acid such as $BF_3{\cdot}OEt_2$ substantially extended the scope of the process.[66e] The modified reaction conditions required 2 equiv of $BF_3{\cdot}OEt_2$ to provide good to quantitative yields of oxazolines and dihydrooxazines from a variety of aldehydes. We sought to optimize the modified reaction conditions by employing HFIP with a hope to utilize a substoichiometric amount of an acid catalyst. In general, aldehydes are more reactive than ketones and the reaction of aldehydes with hydroxyalkyl azides does not involve the formation of iminium ether. Thus, one could envision that less than 1 equiv of the acid catalyst should be capable of promoting the desired reaction.

Table 14. Initial Screening of Conditions for the Intermolecular Schmidt Reaction of Aldehydes with 3-Azidopropanol 24b in HFIP[a,b]



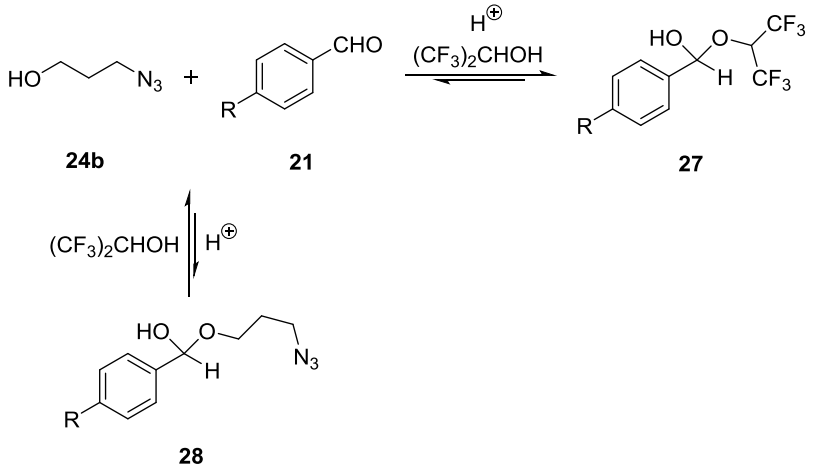
21a; R = NO_2 **24b** **26a**; R = NO_2
21j; R = H **26j**; R = H

entry	R **21**	catalyst	catalyst (mol %)	solvent	temp, time	yield (%) **26**
1	NO_2	$BF_3{\cdot}OEt_2$	25	$(CF_3)_2CHOH$	rt, 6 h	ca. 9[c]
2	NO_2	$TiCl_4$[d]	25	$(CF_3)_2CHOH$	rt, 6 h	ca. 5[e]
3	NO_2	CF_3SO_3H	25	$(CF_3)_2CHOH$	rt, 6 h	ca. 12[c]
4	H	CF_3SO_3H	10	$(CF_3)_2CHOH$	rt, 24 h	ca. 10[f]

[a]To a solution of aldehyde **21** (0.20 mmol) and 3-azidopropanol **24b** (0.30 mmol) in HFIP (0.50 mL) was added a catalyst (0.020–0.050 mmol) and the reaction mixture was allowed to stir at rt for a designated period. [b]Concn of **21** was ca. 0.40 M.

[c]Isolated yield (contains trace amounts of unidentified impurities). [d]Could generate 100 mol % HCl in situ. [e]Corrected isolated yield (contains ca. 50% of unidentified impurities). [f]Corrected isolated yield (contains ca. 10% of unidentified impurities).

Scheme 28. Competitive Hemiacetal Formation of Aldehydes 21



Given our success on the reaction of ketones with **24a** in HFIP (see Table 13 above), we carried out a similar optimization study on aromatic aldehydes **21** with 3-azidopropan-1-ol **24b** for the synthesis of dihydrooxazines **26** (Table 14). Unfortunately, screening of few acid catalysts in HFIP only resulted in very low yields of **26** (entries 1–4). A potential reason for the low reactivity of the aromatic aldehydes under these conditions could be attributed to facile formation of a relatively stable hemiacetal **27** with HFIP compared to the formation of hemiacetal **28** with **24b** (Scheme 28). Hence, the intermolecular Schmidt reaction with hydroxyalkyl azides in HFIP has so far been limited to ketone substrates.

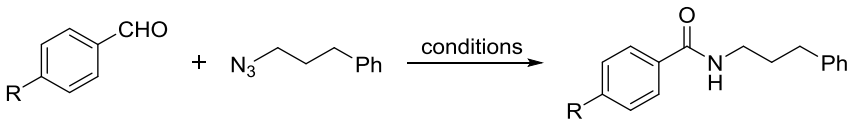
Conclusions

We have identified an improved protocol for the synthesis of *N*-hydroxyalkyl lactams from ketones. The protocol is attractive even with its use of a full equiv of TfOH. High yields and short reaction times were additional main features of this HFIP-promoted reaction. We found that this reaction methodology was limited to ketone substrates and its utilization for the synthesis of dihydrooxazines from aldehydes was unfruitful.

1.6 Intermolecular Schmidt Reaction with Alkyl Azides

As discussed previously (see Section 1.1; Boyer reaction), alkyl azides are known not to react with ketones under standard Schmidt conditions.[9-10] Severe limitations were also observed for the intermolecular Schmidt reaction of aromatic aldehydes with alkyl azides.[11] Professor Aubé reported for the first time the $TiCl_4$-catalyzed Schmidt reaction of *n*-hexyl azide and benzyl azide on facile cyclic ketones to give *N*-substituted lactams.[66a] Although useful, the reaction suffered from a very limited substrate scope. Similarly, for the Schmidt reaction of alkyl azides with aliphatic aldehydes, some improvements were achieved; however, with a very narrow substrate scope to access useful quantities of amides.[111] Given our success in the development of mild and efficient reaction conditions employing HFIP for the different variants of Schmidt family (see Sections 1.2–1.5), we decided to explore those conditions for the intermolecular Schmidt reaction with alkyl azides.

Table 15. Exploration of Reaction Conditions for the Intermolecular Schmidt Reaction of Benzaldehydes 21 with Alkyl Azide 29[a,b]



21j; R = H
21c; R = OH

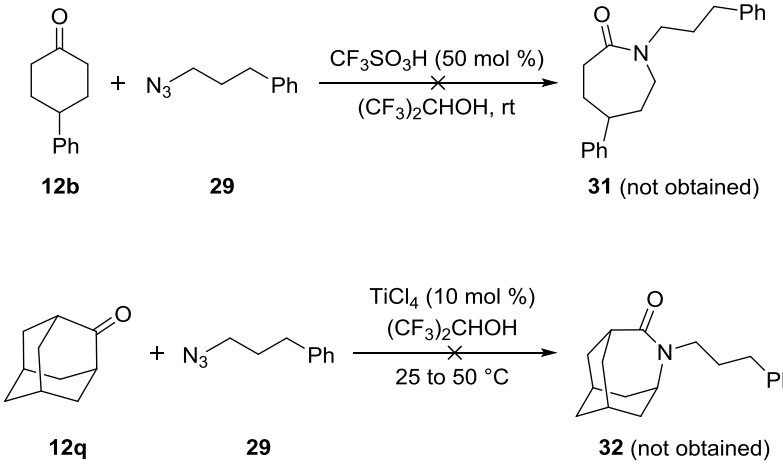
29

30j; R = H
30c; R = OH

entry	R **21**	catalyst	catalyst (mol %)	solvent	temp, time	reaction outcome[c,d]
1	H	$TiCl_4$	10	$(CF_3)_2CHOH$	25 °C, 16 h to 50 °C, 7 h	no reaction
2	OH	CF_3SO_3H	50	$(CF_3)_2CHOH$	rt, 5 h	no reaction
3	OH	CF_3SO_3H	50	$(CF_3)_2CHOH$/ CH_3CN (1:1)	rt, 5 h	no reaction
4	OH	CF_3SO_3H	50	$(CF_3)_2CHOH$/ CH_3CN (1:4)	rt, 5 h	no reaction

[a]To a solution of benzaldehyde **21** (0.17 mmol) and (3-azidopropyl)benzene **29** (0.33 mmol) in solvent (0.83 mL) was added a catalyst and the reaction was allowed to stir at a specified temperature for a designated period of time. [b]Concn of **21** was ca. 0.20 M. [c]^{1}H NMR of a crude reaction mixture was used to determine the reaction outcome. [d]Trace amounts of unidentified byproducts were observed.

Scheme 29. Unsuccessful Attempts towards the Intermolecular Schmidt Reaction of Ketones with Alkyl Azide 29



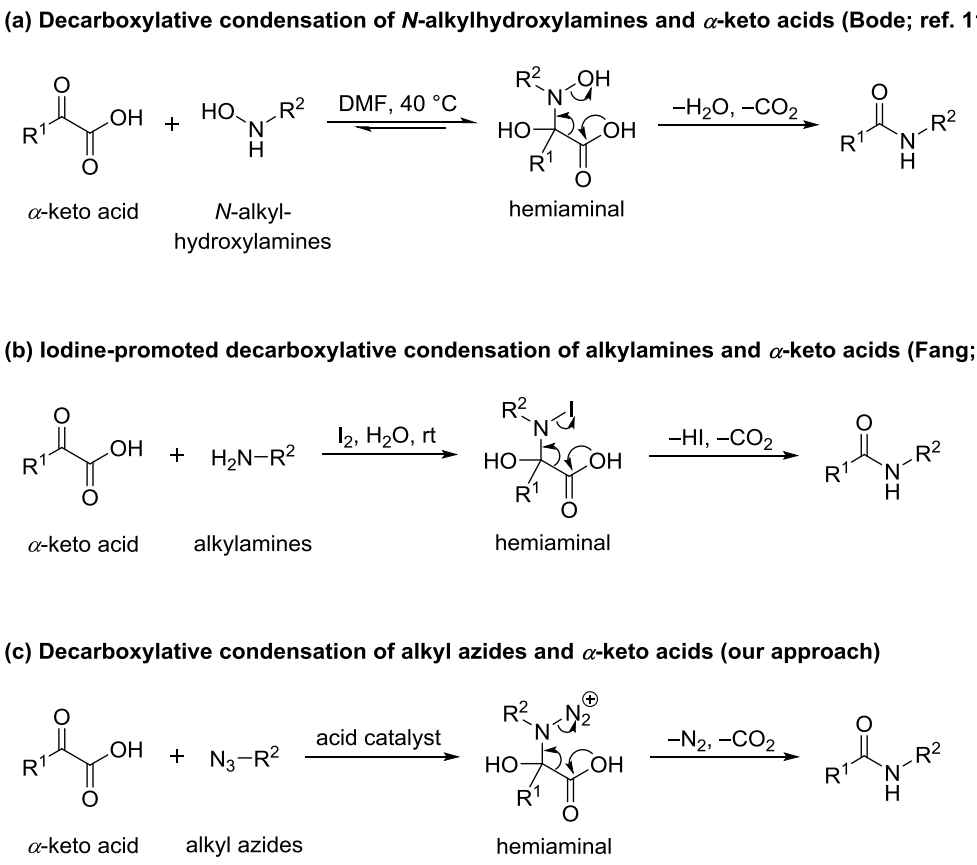
Initial exploration using substoichiometric amounts of acid catalysts in HFIP were disappointing as no amide products **30** were obtained when benzaldehydes **21** were reacted with (3-azidopropyl)benzene **29** (Table 15). Replacing the aldehydes with cyclic ketones **12b** and **12q** also resulted in similar failure (Scheme 29). The ^{1}H NMR of a crude reaction mixture of **12b** with **29** apparently showed the presence of a trace amount of product **31** along with other byproducts. Since initial results were discouraging, no further efforts were made in these regards.

1.7 Development of New Variants in the Schmidt Family

1.7.1 Decarboxylative Condensation of Azides and α-Keto Carboxylic Acids

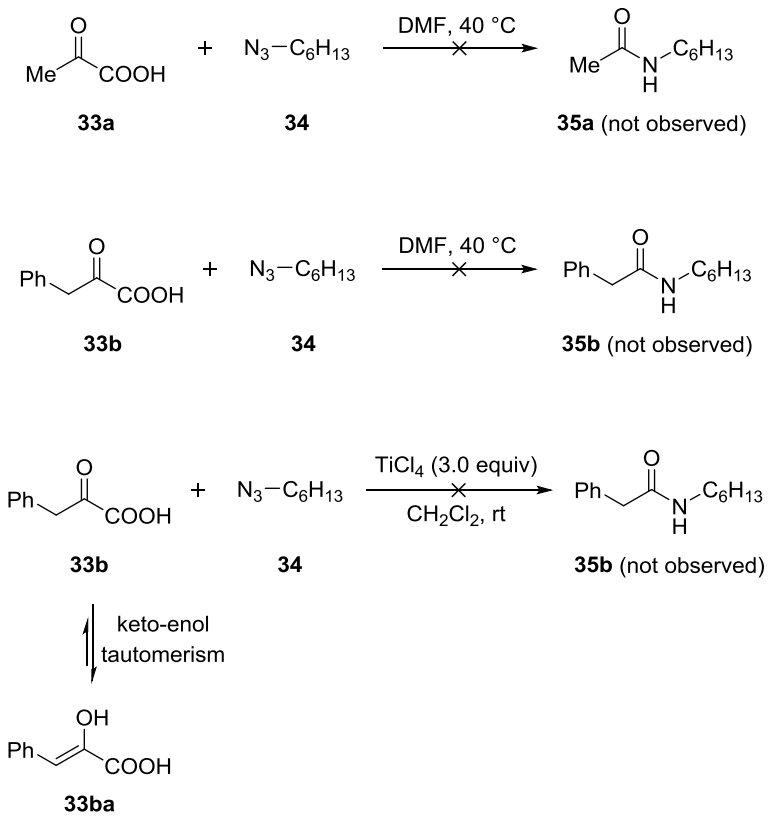
As discussed in the introduction of this chapter (Section 1.1), the conventional approach for the synthesis of amides involves the condensation of amines and carboxylic acids. Although various methods for amide formation have been introduced, the discovery of the native chemical ligation of C-terminal peptide thioesters and N-terminal cysteines has revolutionized the field of protein synthesis.[4,112] In 2006, Bode and co-workers discovered a chemoselective approach to amide synthesis by the decarboxylative condensation of *N*-alkylhydroxylamines and α-keto carboxylic acids (Scheme 30a).[113] The efficiency of this process was reflected in the mild reaction conditions, which requires no reagents or catalysts, and the fact that only water and carbon dioxide were generated as byproducts. Furthermore, this strategy was applied to the chemoselective ligation of unprotected-peptide fragments. Alternatively, Fang and co-workers reported the decarboxylative amidation of α-keto carboxylic acids and alkylamines using iodine as an oxidant (Scheme 30b).[114] This methodology was successfully applied for the amidation of monosaccharides containing α-keto carboxylic acids such as sialic acid with simple alkylamines.

Scheme 30. Decarboxylative Amidation of α-Keto Acids



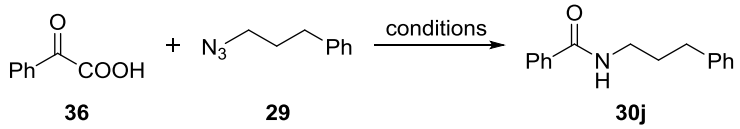
In *N*-alkylhydroxylamines (R^2NHOH), *N*-iodinated alkylamines (R^2NHI), and alkyl azides (R^2N_3), the nitrogen has a same oxidation state of –1. Hence, it should be possible to employ alkyl azides for the decarboxylative amidation reaction of α-keto carboxylic acids in the presence of an acid catalyst (Scheme 30c). To this hypothesis, we began our initial optimization study on pyruvic acids **33** with *n*-hexyl azide **34** (Scheme 31). Running the amidation reaction of **33** and **34** under Bode′s conditions (DMF, 40 °C) did not afford any amide product **35**. While working with phenylpyruvic acid **33b**, it was observed that **33b** predominantly exists in enol form **33ba** (Scheme 31). The combination of enolization of α-keto acids **33** and decreased nucleophilicity and volatile nature of **34** resulted in an unproductive reaction outcome. Even under strong Lewis acid conditions by employing 3 equiv of $TiCl_4$, no product formation was observed.

Scheme 31. Initial Failed Optimization towards the Decarboxylative Amidation Reaction of *α*-Keto Acids 33 and *n*-Hexyl Azide 34



In order to avoid the enolization process, phenylglyoxylic acid **36** was used in the decarboxylative amidation reaction along with **29**, a non-volatile source of alkyl azide. A short screening of different acid catalysts in stoichiometric to excess amount under various conditions showed that the desired amidation reaction was very sluggish (Table 16). The desired amide product, *N*-(3-phenylpropyl)benzamide **30j** was only obtained in a very low yield upon reaction of **36** and **29** in the presence of excess $BF_3{\cdot}OEt_2$ (entry 1). Running the reaction with other acid catalysts, at higher temperature or both in order to drive the reaction to completion either resulted in no reaction or the formation of a complex mixture (entries 2–7).

Table 16. Optimization Studies for the Decarboxylative Amidation Reaction[a]

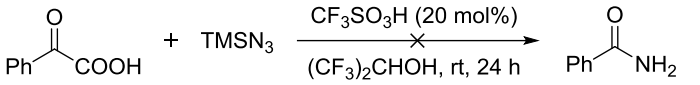


36 **29** **30j**

entry	catalyst	catalyst (equiv)	solvent	temp, time	yield (%) **30j**
1	$BF_3{\cdot}OEt_2$	3.5	CD_2Cl_2	rt, 52 h	16[b]
2	$BF_3{\cdot}OEt_2$	3.5	CD_2Cl_2	100 °C (μW), 0.5 h	mixture[c]
3	CF_3SO_3H	3.5	CD_2Cl_2	rt, 2 h	mixture[c]
4	$Sc(OTf)_3$	0.95	CH_3CN	rt to 160 °C (μW), 6.7 h	complex mixture
5	CF_3CO_2H	2.0	CH_2Cl_2	rt, 24 h to 40 °C, 48 h	no reaction[d]
6	none	–	H_2O/THF	100 °C (μW), 1.7 h	no reaction[d]
7	$SnCl_4$	4.0	CH_2Cl_2	rt, 24 h	no reaction[d]

[a]To a solution of phenylglyoxylic acid **36** (0.20–0.33 mmol) and (3-azidopropyl)benzene **29** (0.40–0.45 mmol) in solvent (1.0–2.5 mL) was added a catalyst and the reaction mixture was allowed to stir at a specified temperature for a designated period of time. [b]Isolated yield. [c]Mixture of unidentified byproducts/impurities along with unreacted starting materials. [d]Mostly unreacted starting materials were observed by TLC analysis.

Scheme 32. Failed Decarboxylative Amidation Reaction of 36 and $TMSN_3$



36 **37** (not observed)

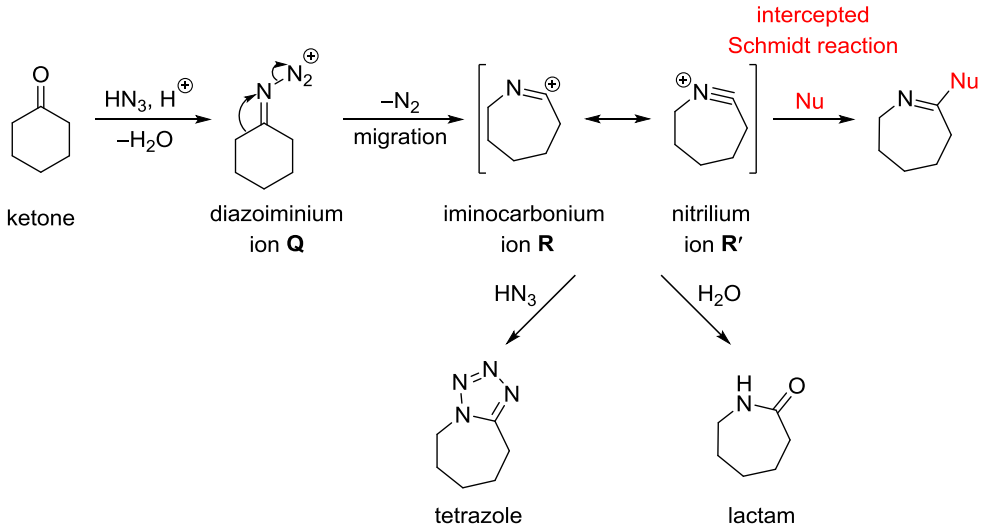
A reaction of **36** and $TMSN_3$, a stronger nucleophilic azide source with a substoichiometric amount of TfOH in HFIP did not yield any desired benzamide **37** (Scheme 32). Mostly unreacted **36** in addition to trace amounts of unidentified byproducts/impurities were observed upon crude ^{1}H NMR analysis. So far we have been unable to find suitable conditions for the decarboxylative amidation reaction of α-keto acids and azides.

1.7.2 Intercepted Schmidt Reaction

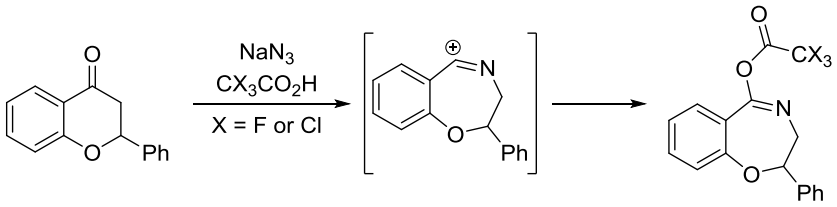
The Schmidt reaction of a ketone with an azide involves the formation of a iminocarbonium ion intermediate (Schemes 2 and 33a).[6c] In a typical example, cyclic ketone such as cyclohexanone reacts with HN_3 under acidic conditions to generate diazoiminium ion **Q**. The concurrent migration of one of the alkyl substituent and the loss of nitrogen gas yields a iminocarbonium species **R**, which can also exist as a nitrilium ion **R'** (although strained in case of cycloheptyne[115]). The iminocarbonium ion could be trapped either with water to afford a lactam (caprolactam in this case) or with another molecule of the azide to yield a tetrazole (Scheme 33a). Traditionally, in the Schmidt reaction, iminocarbonium ions have only been intercepted with water and azide nucleophiles. Besides our own encounter of the interception of a iminocarbonium ion with HFIP to generate iminoether **16** (see Scheme 19; Section 1.3), we could only find one report where a iminocarbonium ion was incidentally trapped with trifluoroacetate and trichloroacetate ions to give iminoesters (Scheme 33b).[77a] Iminocarbonium or nitrilium ions have also been implicated in the Beckmann rearrangement.[116] These intermediates have been trapped with nucleophiles other than water in both intramolecular and intermolecular fashions to generate useful variants of the Beckmann reaction (Scheme 34).[5b,116-117]

Scheme 33. Trapping of Iminocarbonium Ion Intermediate in the Schmidt Reaction

(a) Mechanism for the Schmidt reaction of a ketone



(b) Trapping of a iminocarbonium ion intermediate by trihaloacetates in the Schmidt reaction of flavanone 12n

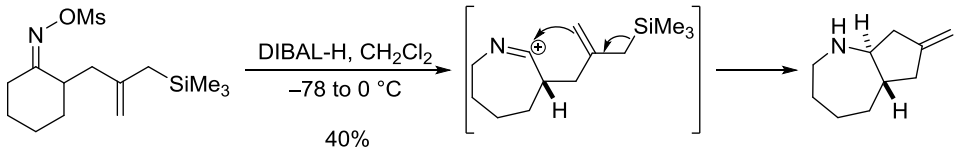


12n

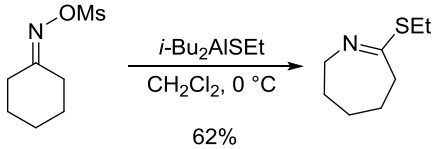
iminoesters
(>90% yield)

Scheme 34. Representative Examples of Intercepted Beckmann Reactions

(a) Intramolecular interception (Schinzer; ref. 117a)

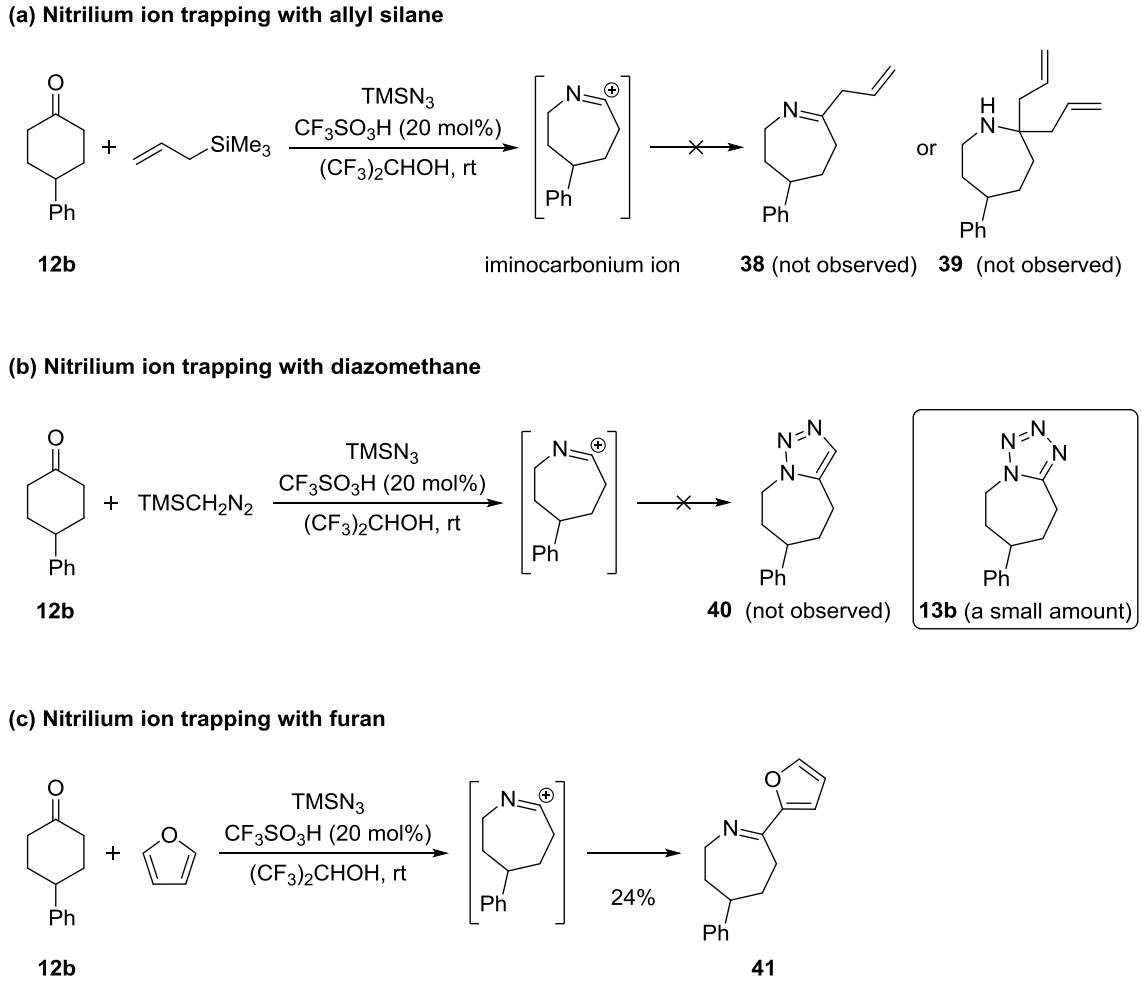


(b) Intermolecular interception (Yamamoto; ref. 117b)



We found an opportunity to discover and develop the intercepted Schmidt reaction from the niche in scientific literature. One could envisage the utility of this variant and the products resulting from the trapping of iminocarbonium ions by a variety of nucleophiles, further expanding the scope of the Schmidt reaction. We put our thoughts into action and ran reactions with three different nucleophiles to test our premise (Scheme 35). The reaction was performed with a premixed solution of 4-phenylcyclohexanone **12b**, $TMSN_3$, and a nucleophile in HFIP and then treated with a substoichiometric amount of TfOH. The reaction with allyl silane nucleophile in theory should have led to monoallyl azepine **38**, diallyl azepane **39**, or both (Scheme 35a). However, desired allyl substituted products were not observed and a small amount of tetrazole product **13b** was obtained along with mixtures of unidentified byproducts. Similarly, we had hoped to get the triazole product **40** from the cycloaddition of diazomethane to the iminocarbonium ion (Scheme 35b). Nevertheless, instead of the desired triazole **40**, again tetrazole **13b** arising from the cycloaddition of another molecule of $TMSN_3$ to the iminocarbonium ion was obtained in a small amount. We observed a violent exothermic reaction during the addition of diazomethane to the reaction mixture, which suggests that HFIP reacted with diazomethane to form a methyl ether of HFIP.[118] It is very probable that none of the diazomethane was left in the reaction mixture to form the anticipated cycloaddition product **40**.

Scheme 35. Interception of the Iminocarbonium Ion Generated from 4-Phenyl-cyclohexanone 12b and $TMSN_3$



On the contrary, we were delighted to observe the expected furan-substituted azepine product **41**, when the reaction was carried out with a furan nucleophile (Scheme 35c). Although, **41** was obtained in low yield, its formation validated the proof of concept that the interception of the iminocarbonium ion in the Schmidt reaction is feasible. Future efforts will be directed toward identifying suitable conditions with a hope to achieve a broader substrate scope and high yields for the intercepted products.

1.8 Experimental Section

General Information. Reactions were performed under an inert atmosphere (argon or nitrogen) either in flame-dried or oven-dried glassware, or glass sample vials with TFE-lined cap. The stainless steel needles used for handling anhydrous solvents and reagents were oven dried and flushed with nitrogen prior to use. Plastic syringes were flushed with nitrogen before use. All chemicals were used as received from commercial source without further purification, except L-menthone and β-tetralone, which were purified on RediSep normal-phase silica flash columns using a CombiFlash Rf system (Teledyne Isco). A new container of HFIP was used. New containers were also used for most catalysts such as $BF_3{\cdot}OEt_2$, $TiCl_4$, and TfOH. Methylene chloride (CH_2Cl_2) and THF were dried by passage through neutral alumina columns using a commercial solvent purification system prior to use. TLC was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Preparative TLC was carried out using silica gel GF TLC plates (UV 254 nm, 1000 microns). Visualization was accomplished with UV light and Seebach's stain or aqueous $KMnO_4$ by heating. Purification was achieved by flash chromatography either on a standard grade silica gel (40–63 μm particle size, 230 × 400 mesh) with compressed nitrogen as a source of positive pressure or on a CombiFlash Rf (automated flash chromatography/medium pressure liquid chromatography, MPLC) system with RediSep normal-phase silica flash columns (4, 12, 24, 48, or 80 g). IR spectra were acquired as thin films or solids. All NMR spectra (^1H, ^{13}C, APT, COSY, HSQC, HMBC, and NOESY) were acquired on either a 400 MHz or a 500 MHz with a dual carbon/proton cryoprobe instrument. NMR samples were mostly recorded in deuterated chloroform ($CDCl_3$) with few exceptions, where deuterated methanol (CD_3OD), deuterated HFIP ($(CF_3)_2CDOD$), and deuterated DCM (CD_2Cl_2) were used. Chemical shifts are reported in parts per million

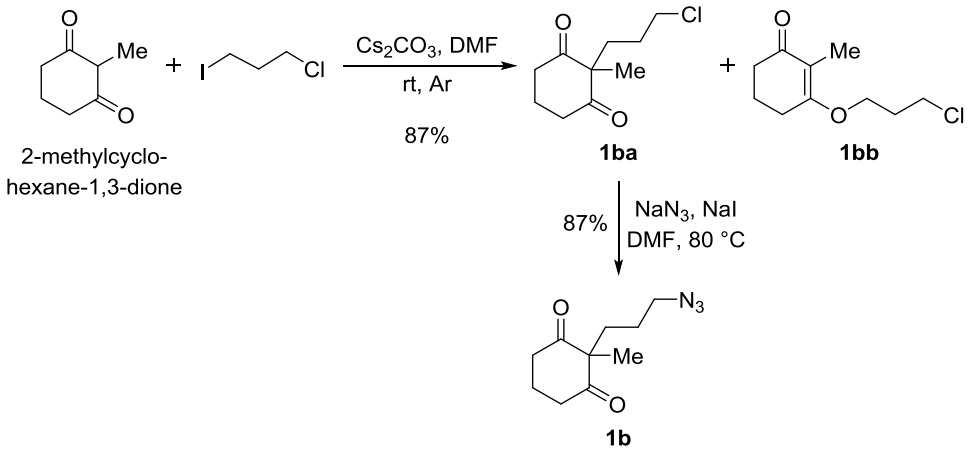
(ppm) and are referenced to the center line of the solvent (For $CDCl_3$, δ 7.26 ppm for ^1H NMR and δ 77.23 ppm for ^{13}C NMR, and for CD_2Cl_2, δ 5.32 ppm for ^1H NMR and δ 54.00 ppm for ^{13}C NMR). Coupling constants are given in Hertz (Hz). $CDCl_3$ with tetramethylsilane as an internal standard (TMS, δ 0.00 ppm for ^1H NMR) was used to record NMR for Job plots and NMR titration experiments. HRMS data were collected with a LCT Premier time-of-flight mass spectrometer and an electrospray ion source. Melting points were determined in open capillary tubes using an automated melting point apparatus and are uncorrected. Reaction mixtures were concentrated under nitrogen gas using a sample concentrator. Microsyringes (flushed with nitrogen prior to use) or calibrated micropipettes were used to measure and deliver volumes between 1.00–100 μL. Single-crystal X-ray analyses were performed using Cu Kα radiation (λ = 1.54178 Å) with either Bruker APEX2 or Platinum 135 CCD detector. X-rays were provided by a Bruker MicroStar microfocus rotating anode equipped with Helios multilayer optics.

In general, complete spectroscopic data (^1H NMR, ^{13}C NMR, IR, and HRMS) are provided for compounds, which are reported in the literature with partial or no characterization data.

Experimental Procedures for Section 1.2

List of Known Compounds. The following substrates, 2-(3′-azidopropyl)-cyclopentanone (**1a**),[12-13] 2-(3′-azidopropyl)-2-methylcyclohexane-1,3-dione (**1b**),[18a] 2-(3′-azidopropyl)cyclohexanone (**1c**),[12-13] ethyl 1-(3′-azidopropyl)-2-oxocyclohexane-carboxylate (**1d**),[12-13] 3-(3′-azidopropyl)-3,4-dihydronaphthalen-2(1*H*)-one (**1g**),[12-13,119] 2-(2′-(azidomethyl)allyl)cyclohexanone (**1h**),[17m,64] 2-(3′-azidopropyl)cycloheptanone (**1i**),[13] 2-(3′-azidopropyl)cyclooctanone (**1j**),[13] 6-azidohexan-2-one (**1m**),[13] 1-(2′-(azidomethyl)-phenyl)propan-2-one (**1n**),[64] 2-(3′-azidopropyl)-2-phenylcyclohexan-1-one (**1o**),[37] 4-azido-2-benzylbutanal (**1q**),[111] and 2-(4′-azidobutyl)cyclohexanone (**1r**)[13] are known and were either synthesized according to the literature procedures or with slight modification thereof. Details for syntheses of compounds **1b**, **1m**, and **1n** are described below.

Spectroscopic data for the following lactams, hexahydroindolizin-5(1*H*)-one (**2a**),[12-13] 9a-methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione (**2b**),[18a] hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2c**),[12-13] ethyl 5-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepine-9a-carboxylate (**2d**),[12-13] 2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2g**),[12-13,119] 2-methylenehexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2h**),[17m,64] octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one (**2i**),[13] octahydro-1*H*-pyrrolo[1,2-*a*]azonin-5(6*H*)-one (**2j**),[13] 3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (**2l**),[120] 1-phenethylpiperidin-2-one (**3l**),[121] 1-(pyrrolidin-1-yl)ethanone (**2m**),[13] *N*-methyl-2-piperidone (**3m**),[122] 2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (**2n**),[123] 1-(isoindolin-2-yl)ethanone (**3n**),[124] 9a-phenyloctahydro-5*H*-pyrrolo[1,2-*a*]azepin-5-one (**2o**),[37] 2-benzylhexahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-5(2*H*)-one (**2p**),[64] 3-benzylpyrrolidin-2-one (**2q**),[111] and octahydropyrido[1,2-*a*]azepin-6(2*H*)-one (**2r**)[13] prepared according to the catalytic methodology described in Section 1.2 matches with those reported in the literature.

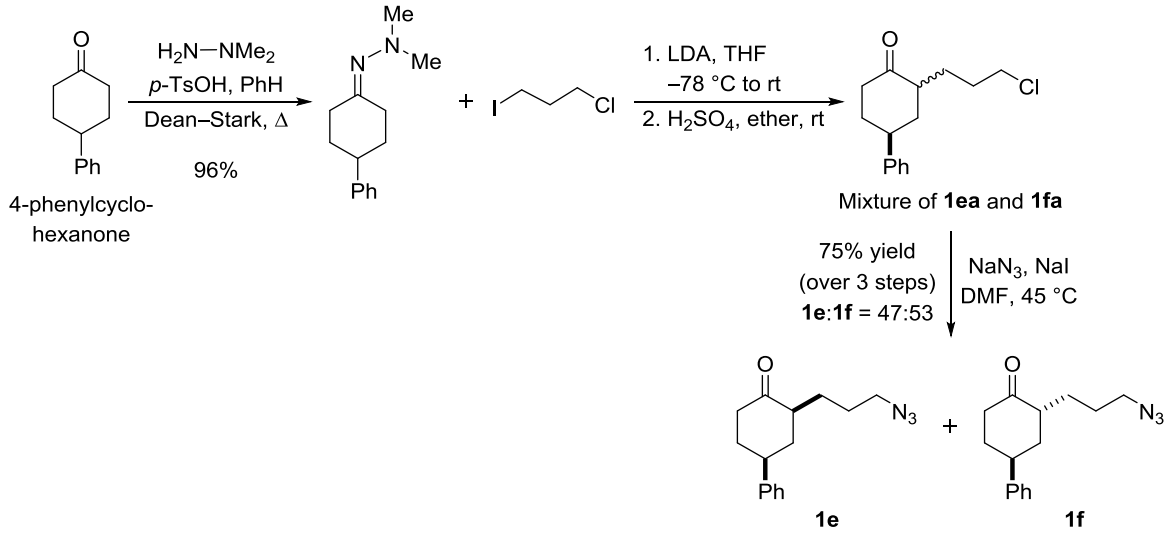


2-(3′-Azidopropyl)-2-methylcyclohexane-1,3-dione (1b).[18a] Following the literature procedure,[125] 2-(3′-chloropropyl)-2-methylcyclohexane-1,3-dione (chloro diketone) **1ba** was prepared from 2-methylcyclohexane-1,3-dione in the following manner:

To a pale yellow solution of 2-methylcyclohexane-1,3-dione (6.30 g, 49.9 mmol, 1.0 equiv) in anhydrous DMF (70 mL) in a flame-dried flask at rt under argon atmosphere was added Cs_2CO_3 (17.9 g, 54.9 mmol, 1.1 equiv) and the resulting pale orange suspension was stirred at rt for 15 min. 1-Chloro-3-iodopropane (16.1 mL, 150 mmol, 3.0 equiv) was added at once and a cream-colored suspension was stirred at rt for 14 h. The reaction mixture was diluted with water and extracted with EtOAc (5 × 40 mL). The combined organic extracts were washed with water (4 × 50 mL), brine (2 × 50 mL), dried over sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. Purification using a 80 g flash column on a CombiFlash Rf system (0–40% EtOAc/hexanes over 90 min) afforded chloro diketone **1ba**[125] as a pale yellow oil in 39% yield (3.92 g, 19.3 mmol) and 3-(3′-chloropropoxy)-2-methylcyclohex-2-enone **1bb**[125] as a yellow oil in 48% yield (4.86 g, 24.0 mmol).

To a solution of chloro diketone **1ba** (2.30 g, 11.3 mmol, 1.0 equiv) in anhydrous DMF (15 mL) at rt under nitrogen atmosphere was added sodium iodide (NaI; 2.21 g, 14.8 mmol, 1.3 equiv) followed by sodium azide (NaN_3; 1.62 g, 25.0 mmol, 2.2 equiv) and the resulting yellow suspension was stirred at 80 °C for 1.5 h. The reaction mixture was cooled

to rt, diluted with water and extracted with ether (Et_2O) (4 × 25 mL). The combined organic extracts were washed with water (3 × 80 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification using a 40 g flash column on a CombiFlash Rf system (0–20% EtOAc/hexanes over 65 min) afforded azido ketone **1b** as a yellow oil in 87% yield (2.07 g, 9.89 mmol).



(2*S*,4*S*)-*rel*-2-(3′-Azidopropyl)-4-phenylcyclohexanone (*cis*-1e) and (2*R*,4*S*)-*rel*-2-(3′-Azidopropyl)-4-phenylcyclohexanone (*trans*-1f). A solution of 4-phenyl-cyclohexanone (15.0 g, 86.1 mmol, 1.0 equiv), *N*,*N*-dimethylhydrazine (19.6 mL, 258 mmol, 3.0 equiv) and PTSA (0.818 g, 4.30 mmol, 0.050 equiv) in benzene (100 mL) was vigorously refluxed for 28 h under nitrogen atmosphere with removal of water by a Dean–Stark apparatus. The reaction mixture was concentrated under reduced pressure and the crude hydrazone obtained as an orange oil was used for the next alkylation reaction without further purification.

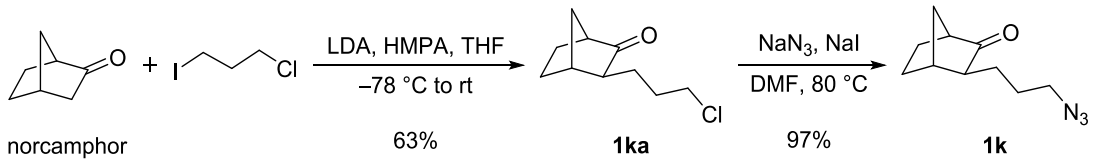
To a cooled 1.0 M LDA solution (94.7 mL, 94.7 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added a solution of hydrazone (18.6 g, 86.1 mmol, 1.0 equiv) in THF (40 mL) slowly over 25 min, and the reaction mixture was allowed to stir at

0 °C for 5 h. The reaction mixture was then cooled to –78 °C and a solution of 1-chloro-3-iodopropane (10.9 mL, 103 mmol, 1.2 equiv) in THF (30 mL) was added slowly over 25 min. The reaction was warmed to rt and stirred for 15 h. The reaction mixture was diluted with ether (50 mL) and then treated with an ice-cold solution of dilute H_2SO_4 (50 mL) and the resulting reddish-orange solution was stirred at rt for 1 h to hydrolyze the hydrazone. The reaction mixture was diluted with water and extracted with ether (3 × 60 mL). The combined organic extracts were washed with water (2 × 60 mL), saturated aqueous sodium bicarbonate ($NaHCO_3$) solution (1 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The reddish-orange oil was dried under vacuum to afford a crude mixture of cis and trans chloro ketone (**1ea** and **1fa**), which was used for the subsequent nucleophilic displacement reaction without further purification.

To a solution of a crude mixture of cis and trans chloro ketone, **1ea** and **1fa** (21.0 g, 83.8 mmol, 1.0 equiv) in anhydrous DMF (60 mL) at rt under nitrogen atmosphere was added sodium iodide (15.1 g, 101 mmol, 1.2 equiv) followed by sodium azide (10.9 g, 168 mmol, 2.0 equiv) and the resulting yellow suspension was stirred at 45 °C for 18 h. The reaction mixture was cooled to rt, diluted with water and extracted with ether (4 × 75 mL). The combined organic extracts were washed with water (4 × 250 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on a silica gel (4–6% EtOAc/hexanes) afforded a mixture of **1e** and **1f** and a partial separation of **1e**. Subsequent purifications of the mixture using a 40 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 50 min) afforded the partial separation of **1e** and **1f** as pale pinkish-orange oils and a mixture of **1e** and **1f** as a pale orange oil (16.7 g, 75% combined yield; **1e**:**1f** = 47:53 by ^{1}H NMR or UPLC). Azido ketone (*cis*-**1e**): R_f = 0.56 (10% EtOAc/hexanes, run for four times); IR (neat) 2091, 1709, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.33 (m, 1H), 1.52–1.70 (m, 3H), 1.83–1.96 (m, 2H), 2.21–2.29 (m,

2H), 2.47–2.58 (m, 3H), 3.12 (tt, J = 12.3, 3.2 Hz, 1H), 3.21–3.31 (m, 2H), 7.21–7.24 (m, 3H), 7.30–7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 26.5, 34.9, 41.3, 41.7, 43.3, 49.4, 51.5, 126.62, 126.66, 128.6, 144.5, 211.5; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ [M + H – N_2]$^+$ 230.1545, found 230.1550.

Azido ketone (*trans*-**1f**): R_f = 0.50 (10% EtOAc/hexanes, run for four times); IR (neat) 2094, 1708, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52–1.66 (m, 3H), 1.87–2.10 (m, 3H), 2.13–2.23 (m, 2H), 2.39 (dtd, J = 14.7, 4.5, 1.1 Hz, 1H), 2.44–2.50 (m, 1H), 2.54–2.62 (m, 1H), 3.18 (m, 1H), 3.30 (t, J = 6.4 Hz, 2H), 7.21–7.28 (m, 3H), 7.31–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 28.4, 33.2, 37.3, 38.3, 38.4, 48.7, 51.1, 126.5, 126.7, 128.6, 144.2, 213.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ [M + H – N_2]$^+$ 230.1545, found 230.1546.



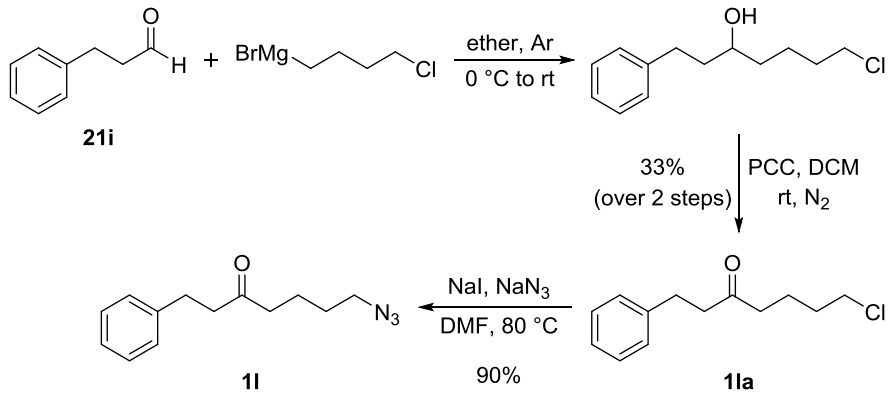
norcamphor **1ka** **1k**

(1*S*,3*S*,4*R*)-*rel*-3-(3′-Azidopropyl)bicyclo[2.2.1]heptan-2-one (1k).[17i] To a cooled 1.0 M LDA solution (32.7 mL, 32.7 mmol, 1.2 equiv) in THF at −78 °C in a flame-dried flask under argon atmosphere was added a solution of norcamphor (3.00 g, 27.2 mmol, 1.0 equiv) in THF (10 mL) slowly over 10 min and the reaction mixture was allowed to stir at –78 °C for 1 h. To the resulting white suspension was added HMPA (20 mL) followed by 1-chloro-3-iodopropane (5.85 mL, 54.5 mmol, 2.0 equiv) over 10 min. The yellow suspension was stirred at –78 °C for 1 h, warmed to rt, and stirred for 1 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride (NH_4Cl) (50 mL) and diluted with water (50 mL) followed by extraction with ether (3 × 40 mL). The combined organic extracts were washed with water (1 × 70 mL), brine (1 × 70 mL), dried over

Na_2SO_4, and concentrated under reduced pressure. Purification using a 40 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 40 min) afforded **1ka** as an impure material. Subsequent purification of impure **1ka** using a 40 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 100 min) afforded the partial separation of **1ka** as a pale yellow oil. Vacuum distillation (ca. 1.3 mbar) at ca. 93 °C of the remaining impure **1ka** afforded sufficiently pure **1ka** as a pale yellow oil (3.22 g, 17.2 mmol, 63% combined yield). (1*S*,3*S*,4*R*)-*rel*-3-(3′-Chloropropyl)bicyclo[2.2.1]heptan-2-one (chloro ketone) **1ka**: R_f = 0.57 (10% EtOAc/hexanes, run twice); IR (neat) 1738, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27–1.44 (complex, 4H), 1.48–1.60 (m, 2H), 1.65–1.82 (complex, 5H), 2.30 (m, 1H), 2.41–2.42 (m, 1H), 3.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 26.5, 27.8, 31.0, 34.7, 39.4, 44.6, 49.3, 52.8, 219.2; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}ClO$ $[M + H]^+$ 187.0890, found 187.0892.

To a solution of chloro ketone **1ka** (1.84 g, 9.86 mmol, 1.0 equiv) in anhydrous DMF (12 mL) at rt under nitrogen atmosphere was added sodium iodide (1.77 g, 11.8 mmol, 1.2 equiv) followed by sodium azide (1.28 g, 19.7 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 2 h. The reaction mixture was cooled to rt, diluted with water (75 mL) and extracted with ether (3 × 35 mL). The combined organic extracts were washed with water (4 × 60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification using a 40 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 80 min) afforded **1k** as a colorless oil in 97% yield (1.84 g, 9.52 mmol). Azido ketone **1k**: R_f = 0.51 (10% EtOAc/hexanes, run twice); IR (neat) 2090, 1738, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.45 (complex, 4H), 1.46–1.55 (m, 1H), 1.58–1.68 (complex, 3H), 1.69–1.79 (complex, 3H), 2.33 (m, 1H), 2.45 (m, 1H), 3.20 (m,

2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 26.3, 27.5, 27.9, 34.7, 39.4, 49.4, 51.1, 53.2, 219.3; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}NO$ $[M + H - N_2]^+$ 166.1232, found 166.1247.



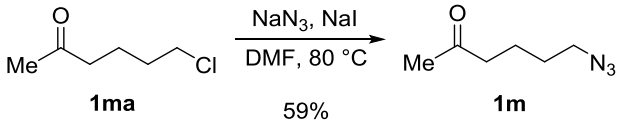
7-Azido-1-phenylheptan-3-one (1l). To a stirring suspension of magnesium turnings (0.434 g, 17.9 mmol, 1.2 equiv) in ether (12 mL) in a flame-dried flask under argon atmosphere was added five drops of 1-bromo-4-chlorobutane and the mixture was gently refluxed for 30 min. A solution of 1-bromo-4-chlorobutane (2.06 mL, 17.9 mmol, 1.2 equiv) in ether (8 mL) was then added slowly over 20 min via a syringe. After refluxing gently for another 30 min, the reaction mixture was cooled to 0 °C and a solution of hydrocinnamaldehyde **21i** (2.00 g, 14.9 mmol, 1.0 equiv) in ether (10 mL) was added slowly over 10 min. The reaction mixture was stirred at 0 °C for 15 min, warmed to rt over 15 min, and stirred at rt for 1 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with ether (2 × 30 mL). The combined organic extracts were washed with brine (2 × 75 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude alcohol as a pale yellow oil, which was used for the next oxidation step without further purification.

To a stirring solution of crude alcohol in CH_2Cl_2 (40 mL) under nitrogen atmosphere was added PCC (6.42 g, 29.8 mmol, 2.0 equiv) and Celite (7.00 g), and the reaction was stirred at rt for 1.5 h. The reaction mixture was concentrated under reduced pressure and the

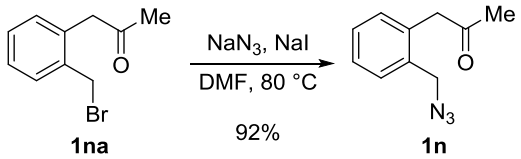
brownish-black residue obtained was suspended in ether (20 mL). The suspension was sonicated for few minutes and filtered through Celite. The residue was rinsed with several portions of ether (6 × 15 mL) and the combined filtrates were concentrated under reduced pressure. Purification using a 40 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 55 min) afforded **1la** as an impure material. Subsequent purification of impure **1la** using a 40 g flash column on a CombiFlash Rf system (0–5% EtOAc/hexanes over 50 min) afforded **1la**[126] as a colorless oil in 33% yield over two steps (1.12 g, 4.98 mmol). 7-Chloro-1-phenylheptan-3-one (chloro ketone) **1la**: R_f = 0.57 (10% EtOAc/hexanes, run twice); IR (neat) 1711, 1453, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66–1.78 (m, 4H), 2.41 (t, J = 6.8 Hz, 2H), 2.73 (t, J = 7.5 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 3.50 (m, 2H), 7.17–7.21 (m, 3H), 7.26–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 29.8, 31.9, 42.0, 44.3, 44.7, 126.2, 128.4, 128.5, 141.1, 209.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}ClO$ $[M + H]^+$ 225.1046, found 225.1083.

To a solution of chloro ketone **1la** (1.08 g, 4.81 mmol, 1.0 equiv) in anhydrous DMF (10 mL) at rt under nitrogen atmosphere was added sodium iodide (0.864 g, 5.77 mmol, 1.2 equiv) followed by sodium azide (0.625 g, 9.61 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 1 h. The reaction mixture was cooled to rt, diluted with water and extracted with ether (3 × 30 mL). The combined organic extracts were washed with water (3 × 60 mL), brine (1 × 60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification using a 24 g flash column on a CombiFlash Rf system (0–5% EtOAc/hexanes over 40 min) afforded **1l** as a colorless oil in 90% yield (0.995 g, 4.30 mmol). Azido ketone **1l**: R_f = 0.50 (10% EtOAc/hexanes, run twice); IR (neat) 2090, 1711, 1453, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50–1.58 (m, 2H), 1.59–1.67 (m, 2H), 2.41 (t, J = 7.0 Hz, 2H), 2.72 (t, J = 7.5 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 3.24 (t, J = 6.6

Hz, 2H), 7.17–7.21 (m, 3H), 7.26–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 28.3, 29.8, 42.2, 44.3, 51.2, 126.2, 128.4, 128.5, 141.0, 209.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ $[M + H - N_2]^+$ 204.1388, found 204.1386.

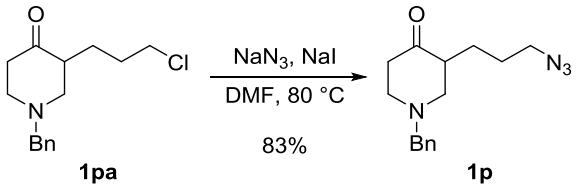


6-Azidohexan-2-one (1m).[13] To a solution of 6-chlorohexan-2-one **1ma** (1.50 g, 11.1 mmol, 1.0 equiv) in anhydrous DMF (10 mL) at rt under nitrogen atmosphere was added sodium iodide (2.00 g, 13.4 mmol, 1.2 equiv) followed by sodium azide (1.45 g, 22.3 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 2 h. The reaction mixture was cooled to rt, diluted with water and extracted with ether (3 × 30 mL). The combined organic extracts were washed with water (4 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification using a 24 g flash column on a CombiFlash Rf system (0–15% EtOAc/hexanes over 25 min) afforded pure azido ketone **1m** as a pale yellow oil in 59% yield (0.920 g, 6.52 mmol). The product was found to be slightly volatile.



1-(2′-(Azidomethyl)phenyl)propan-2-one (1n).[64] To a solution of 1-(2′-(bromomethyl)phenyl)propan-2-one **1na**[64] (0.540 g, 2.38 mmol, 1.0 equiv) in anhydrous DMF (5 mL) at rt under nitrogen atmosphere was added sodium iodide (0.427 g, 2.85 mmol, 1.2 equiv) followed by sodium azide (0.309 g, 4.76 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 40 min. The reaction mixture was cooled to rt,

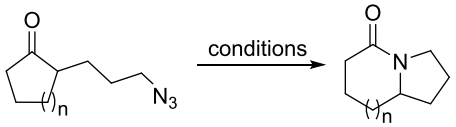
diluted with water (40 mL), and extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (2 × 40 mL), brine (1 × 40 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification using a 12 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 35 min) afforded azido ketone **1n** as a pale orange oil in 92% yield (0.415 g, 2.19 mmol).



3-(3′-Azidopropyl)-1-benzylpiperidin-4-one (1p).[64] To a solution of 1-benzyl-3-(3′-chloropropyl)piperidin-4-one **1pa**[64] (0.195 g, 0.734 mmol, 1.0 equiv) in anhydrous DMF (5 mL) at rt under nitrogen atmosphere was added sodium iodide (0.132 g, 0.880 mmol, 1.2 equiv) followed by sodium azide (0.0954 g, 1.47 mmol, 2.0 equiv) and the resulting suspension was stirred at 80 °C for 1 h. The reaction mixture was cooled to rt, diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 30 min) afforded **1p** as a pale yellow oil in 83% yield (0.166 g, 0.609 mmol). Azido ketone **1p**: R_f = 0.42 (2% MeOH/CH_2Cl_2, run twice); IR (neat) 2092, 1712, 1453, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (m, 1H), 1.55 (m, 2H), 1.82 (m, 1H), 2.22 (m, 1H), 2.36 (m, 1H), 2.43–2.59 (m, 3H), 2.97–3.05 (m, 2H), 3.24 (m, 2H), 3.56 (1/2 AB, J = 13.1 Hz, 1H), 3.64 (1/2 AB, J = 13.1 Hz, 1H), 7.25–7.29 (m, 1H), 7.30–7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.7, 41.1, 49.4, 51.5, 53.7, 58.9, 61.9, 127.4, 128.5, 128.9, 138.2, 210.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{21}N_2O$ $[M + H - N_2]^+$ 245.1654, found 245.1645.

Preliminary Screening of Reaction Conditions for the Intramolecular Schmidt Reaction

Table S1. Preliminary Screening with 5 and 10 mol % $Sc(OTf)_3$ by Sze-Wan Li



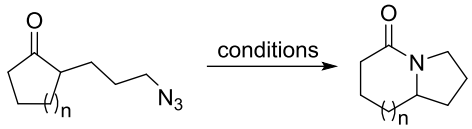
n = 1, **1a**
n = 2, **1c**

n = 1, **2a**
n = 2, **2c**

entry	n	conditions	product conversion (%)[a,b]
1	2	5 mol % $CuSO_4 \cdot H_2O$, H_2O, 180 °C, 4 h	37
2	2	10 mol % $Sc(OTf)_3$, CH_3CN, 80 °C, 16 h	47
3	2	5 mol % $Sc(OTf)_3$, *t*-BuOH, 140 °C, 4 h	26
4	2	5 mol % $Sc(OTf)_3$, H_2O, 160 °C, 4 h	80
5	2	5 mol % $Sc(OTf)_3$, H_2O, 180 °C, 4 h	>95 (78)
6	2	5 mol % $Sc(OTf)_3$, H_2O/CH_3CN (1:1), 180 °C, 4 h	>95 (88)
7	2	10 mol % $Sc(OTf)_3$, CH_2Cl_2, DBU (20 mol %), rt, O/N	9
8	2	5 mol % $Sc(OTf)_3$, CH_2Cl_2, rt, O/N	10
9	2	5 mol % $Sc(OTf)_3$, $C_2H_4Cl_2$, reflux, O/N	16
10	2	5 mol % $TiCl_4$, CH_2Cl_2, rt, 16 h	8
11	1	10 mol % $Sc(OTf)_3$, H_2O, 180 °C, 4 h	42

[a]Product conversion was determined by ^1H NMR. [b]Yield in parentheses represents isolated yield. O/N = Overnight.

Table S2. Preliminary Catalyst Screening in H_2O at 180 °C by Erin Hirt



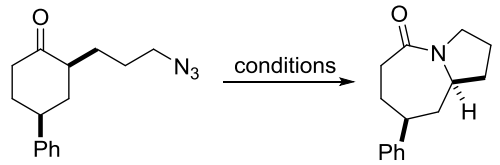
n = 1, **1a**
n = 2, **1c**

n = 1, **2a**
n = 2, **2c**

entry	n	conditions	product conversion (%)[a]
1	2	5 mol % $Sc(OTf)_3$, H_2O, 180 °C, 4 h	50
2	2	10 mol % $Sc(OTf)_3$, H_2O, 180 °C, 4 h	>95 (73)
3	2	25 mol % $LiClO_4$, toluene, 180 °C, 4 h	<20
4	2	25 mol % $LiClO_4$, H_2O, 180 °C, 4 h	<20
5	2	25 mol % AuCl, H_2O, 180 °C, 4 h	>95
6	2	25 mol % $Yb(OTf)_3$, H_2O, 180 °C, 4 h	46
7	2	25 mol % $Eu(OTf)_3$, H_2O, 180 °C, 4 h	<10
8	2	25 mol % $Ho(OTf)_3$, H_2O, 180 °C, 4 h	26
9	2	25 mol % $Gd(OTf)_3$, H_2O, 180 °C, 4 h	<15
10	2	25 mol % $Dy(OTf)_3$, H_2O, 180 °C, 4 h	37
11	1	10 mol % $Sc(OTf)_3$, H_2O, 180 °C, 4 h	NR
12	1	25 mol % $Sc(OTf)_3$, H_2O, 180 °C, 4 h	NR
13	2	25 mol % $Yb(OTf)_3$, 10 mol % *n*-Bu_4NOH, H_2O, 180 °C, 4 h	38
14	2	25 mol % $Eu(OTf)_3$, 10 mol % *n*-Bu_4NOH, H_2O, 180 °C, 4 h	<10
15	2	25 mol % $Ho(OTf)_3$, 10 mol % *n*-Bu_4NOH, H_2O, 180 °C, 4 h	31
16	2	25 mol % $Sc(OTf)_3$, 10 mol % *n*-Bu_4NOH, H_2O, 180 °C, 4 h	>95
17	2	38 mol % HCl, 10 mol % *n*-Bu_4NOH, H_2O, 180 °C, 4 h	<10
18	2	10 mol % *n*-Bu_4NOH, H_2O, μW, 180 °C, 4 h	<5
19	1	25 mol % $Sc(OTf)_3$, 10 mol % *n*-Bu_4NOH, H_2O, μW, 180 °C, 4 h	>95 (54)

[a]Product conversion was determined by ^1H NMR. [b]Yield in parentheses represents isolated yield. NR = No reaction.

Table S3. Preliminary Catalyst Screening in CH_3CN at 200 °C by Charlie Fehl



1e **2e**

entry	conditions	product conversion (%)[a]
1	25 mol % $Sc(OTf)_3$, CH_3CN, rt, 18 h	25
2	25 mol % $TiCl_4$, CH_3CN, rt, 18 h	25
3	30 mol % CF_3SO_3H, CH_3CN, rt, 18 h	40
4	25 mol % $Sc(OTf)_3$, CH_3CN, μW, 200 °C, 30 min	>95
5	10 mol % $Sc(OTf)_3$, CH_3CN, μW, 200 °C, 2 h	70
6	5 mol % $Sc(OTf)_3$, CH_3CN, μW, 200 °C, 2 h	30
7	25 mol % $TiCl_4$, CH_3CN, μW, 200 °C, 30 min	60
8	25 mol % $BF_3{\cdot}OEt_2$, CH_3CN, μW, 200 °C, 30 min	70
9	25 mol % $Yb(OTf)_3$, CH_3CN, μW, 200 °C, 30 min	80
10	25 mol % CF_3CO_2H, CH_3CN, μW, 200 °C, 30 min	25

[a]Product conversion was determined either by ^1H NMR or by UPLC.

List of Additives Screened with or without $Sc(OTf)_3$

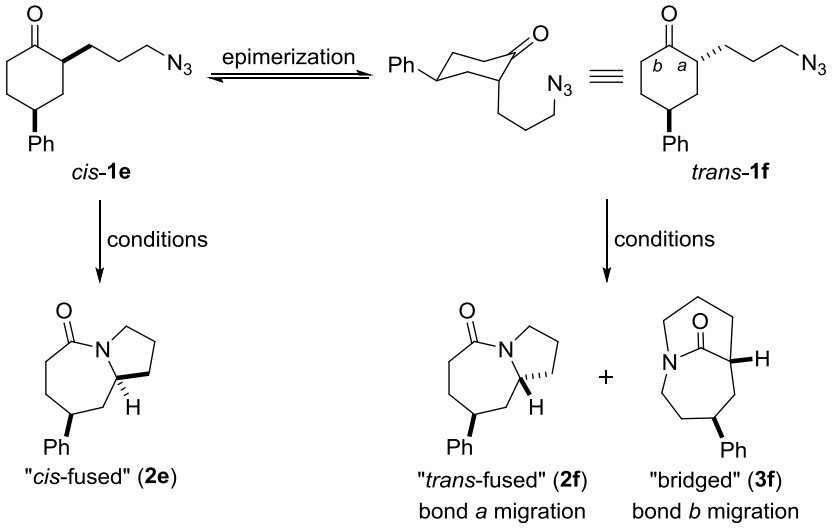
(1) Salts: NaOAc, NaOPh, Na_2CO_3, NaOTs, NaBr, NaCl, KCl, KF, and AgOTf.

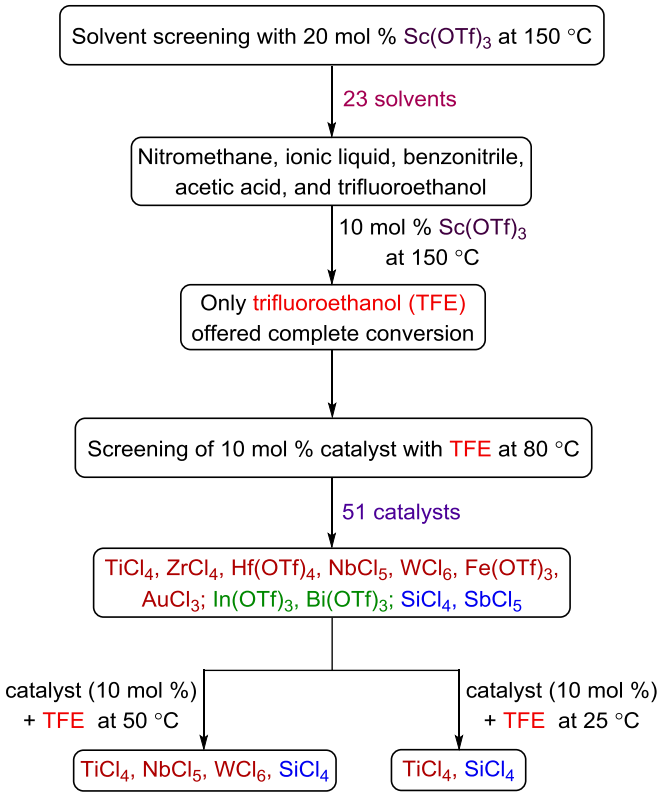
(2) Amines: $(Me)_2NNH_2$, $(Me)_2NH$, Et_3N, DABCO, DMAP, DMF, DMA, and TMANO.

(3) Ligands: (*R*)-BINOL, 1,3-di-*o*-tolyl-2-thiourea, and PYBOX such as 2,6-bis[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine.

(4) Phosphines: PPh_3, PBu_3, tri(*o*-tolyl)phosphine, and tri(2-furyl)phosphine.

In-Depth Screening of Reaction Conditions for the Intramolecular Schmidt Reaction Based on the Screening Flowchart (Scheme 10 and Figure 4)





Solvent Screening

General Procedure for Solvent Screening. To a mixture of trans azido ketone **1f** (25.7 mg, 0.100 mmol, 1.0 equiv) and $Sc(OTf)_3$ (9.84 mg, 0.0200 mmol, 0.20 equiv) in a microwave vial at rt was added a solvent (0.5 mL). The vial was capped and the reaction mixture was stirred at 150 °C for 16 h under conventional heating using a pie-block. After 16 h, the reaction mixture was allowed to cool to rt over 2 h. The cap was removed and the reaction mixture was analyzed by ultra performance liquid chromatography (UPLC) using 1-benzyl-2-pyrrolidinone as an internal standard (IS). 1-Benzyl-2-pyrrolidinone was chosen as the IS because it is a lactam and has a chromophore for UPLC analysis.

Analysis of Reaction Mixture by UPLC. After cooling, the reaction mixture was diluted with CH_2Cl_2 to a final volume of 1.0 mL (differences in initial volumes were observed for some reactions due to solvent loss). To the vial was added 1-benzyl-2-pyrrolidinone (16.0 μL, 0.100 mmol) using a microsyringe and the resulting mixture was mixed well to ensure homogeneity. An aliquot (10 μL) of the reaction mixture was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC.

Samples for UPLC analysis for the solvent screening were run on two instruments: (1) Waters Acquity System (Waters LCT premier with ESI and PDA detector). Waters Acquity BEH C18 column (2.1 x 50 mm, 1.7 μm) was employed with a basic method using a linear gradient elution of 95:5 (water:ACN, pH 9.8) to 0:100 (water:ACN) at a flow rate of 0.6 mL/min over 2.7 minutes. (2) Waters Acquity System (Waters Acquity SQ detector with ESI and Acquity TUV detector). Waters Acquity BEH Shield C18 column (2.1 x 50 mm, 1.7 μm) was employed with a basic method using a linear gradient elution of 90:10 (water:ACN, pH 9.8) to 40:60 (water:ACN) at a flow rate of 0.6 mL/min over 5.7 minutes followed by a flush with 100% ACN for 0.1 min.

Calibration was carried out each time with the IS before analyzing a batch of reaction mixture to determine a normalization factor (NF) for substrate **1f** and products **2f** and **2e** in order to correct for the differences in extinction coefficients between the IS and substrate **1f** and products **2f** and **2e**.

For the calculation of $NF_{substrate}$, 1-benzyl-2-pyrrolidinone (4.00 μL, 0.0250 mmol) and substrate **1f** (6.43 mg, 0.0250 mmol) were dissolved in CH_2Cl_2 (125 μL) to give a concentration of 0.2 M. A drop of this 0.2 M solution was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC. A retention time (t_R) in min for various peaks was obtained from a chromatogram (t_R for IS and **1f** = 1.24 and 2.15 mins, respectively for the first UPLC instrument and t_R for IS, **1f**, and **1e** = 1.92, 5.15, and 5.38 mins, respectively for the second UPLC instrument).

For the calculation of $NF_{products}$, 1-benzyl-2-pyrrolidinone (4.00 μL, 0.0250 mmol) and mixture of products **2f** and **2e** (5.73 mg, 0.0250 mmol) were dissolved in CH_2Cl_2 (125 μL) to give a concentration of 0.2 M. A drop of this 0.2 M solution was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC. A retention time (t_R) in min for various peaks was obtained from a chromatogram (t_R for IS, **2f**, and **2e** = 1.24, 1.56, and 1.60 mins, respectively for the first UPLC instrument and t_R for IS, **2f**, and **2e** = 1.92, 3.11, and 3.23 mins, respectively for the second UPLC instrument). AUC = Area under the curve.

$$\mathrm{NF_{substrate}} = \mathrm{AUC_{substrate}}/\mathrm{AUC_{IS}}$$

$$\mathrm{NF_{products}} = \mathrm{AUC_{products}}/\mathrm{AUC_{IS}}$$

Products (**2f** and **2e**) conversion (%) was calculated as:

$$\%\ \text{products conversion} = (100 * \mathrm{AUC_{products}})/(\mathrm{AUC_{IS}} * \mathrm{NF_{products}})$$

Unreacted substrate **1f** and its epimer **1e** recoveries (in %) were calculated as:

$$\%\ \text{substrate recovery} = (100 * \text{AUC}_{\text{substrate}})/(\text{AUC}_{\text{IS}} * \text{NF}_{\text{substrate}})$$

Ratio of products (**2f**:**2e**) was determined by UPLC for product conversion and by ^{1}H NMR when products were isolated.

Purification of Products (2f and 2e) by Preparative TLC. Reaction mixture was applied on a preparative TLC plate and developed twice with 2% MeOH/CH_2Cl_2. The band corresponding to the products was scraped and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of elution under reduced pressure gave a mixture of products (**2f** and **2e**) as a colorless oil, which was further dried under vacuum.

Table S4. Solvent Screening with 20 mol % Sc(OTf)$_3$[a]

entry	solvent	unreacted substrate		product conversion (**2f**:**2e**)	other byproducts observed
		1f	**1e**		
1	Neat	ND	7%	73% (~1:2.5)	≥1
2	Acetone	ND	ND	57% (~1:4)	≥3
3	Ethyl acetate	ND	11%	76% (~1:6)	≥2
4	Dioxane	trace	19%	64% (~1:3)	≥2
5	Dimethoxyethane	ND	10%	67% (~1:6)	ND
6	Tetrahydrofuran	ND	26%	53% (~1:6)	≥3
7	Dichloroethane	trace	23%	67% (~1:1)	≥3
8	Toluene	ND	25%	65% (~1:1)	≥1
9	Cyclohexane	trace	27%	62% (~1:1.5)	≥3
10	Fluorobenzene	trace	25%	66% (~1:1)[b]	≥2
11	Nitrobenzene	ND	5%	69% (~1:1)	≥1
12	*N*-Methylpyrrolidinone	15%	65%	0%	≥3
13	Diethyl Carbonate	ND	trace	49% (~1:3)	≥4
14	Water	3%	13%	55% (~1:5)	≥3
15	Acetic acid	ND	ND	94% (~1:1)	≥1
16	Formic acid	ND	ND	67% (~2.5:1)[c]	ND

entry	solvent	unreacted substrate		product conversion (**2f**:**2e**)	other byproducts observed
		1f	**1e**		
17	Nitromethane	ND	5%	84% (~1:1.5)	≥1
18	Acetonitrile	trace	11%	72% (~1:1)	≥2
19	Benzonitrile	ND	8%	~91% (~1:2)[d]	ND
20	Butyronitrile	ND	14%	75% (~1:2.5)	≥1
21	Pentafluorobenzonitrile	ND	ND	89% (~1:3.5)	≥1
22	$BMIMBF_4$	ND	ND	98% (~1:1)	≥1
23	Trifluoroethanol	ND	ND	87% (~2:1)	≥2
24	Isopropanol	ND	ND	22% (~1:4)	≥3

[a]All reactions were run with 20 mol % $Sc(OTf)_3$ at 150 °C for 16 h. [b]Solvent peak overlaps with product **2e** peak. [c]Isolated yield was 55% after preparative TLC purification. [d]Solvent peak overlaps with IS peak. ND = Not detected.

Table S5. Solvent Screening with 10 mol % $Sc(OTf)_3$[a]

entry	solvent	catalyst	unreacted substrate		product conversion (**2f**:**2e**)	other byproducts observed
			1f	**1e**		
1	Nitromethane	CH_3CO_2H (1 equiv)	50%	32%	trace	≥5
2	Formic acid	–	trace	trace	46% (~2:1)	≥5
3	Nitromethane	$Sc(OTf)_3$	trace	12%	69% (~1:1.4)	≥3
4	$BMIMBF_4$	–	13%	34%	trace	≥2
5	$BMIMBF_4$	$Sc(OTf)_3$	ND	trace	66% (~1:2)	≥3
6	Trifluoroethanol	$Sc(OTf)_3$	ND	trace	89% (~1:1)[b]	≥2
7	Acetic acid	–	11%	39%	21% (~1:10)	≥3
8	Benzonitrile	$Sc(OTf)_3$	ND	~32%	~61% (~1:2)[c]	≥2

[a]All reactions were run with 10 mol % $Sc(OTf)_3$ at 150 °C for 16 h. [b]Isolated yield was 74% after preparative TLC purification. [c]Solvent peak overlaps with IS peak. ND = Not detected. $BMIMBF_4$ = 1-Butyl-3-methylimidazolium tetrafluoroborate. Acetic acid (AcOH) = CH_3CO_2H.

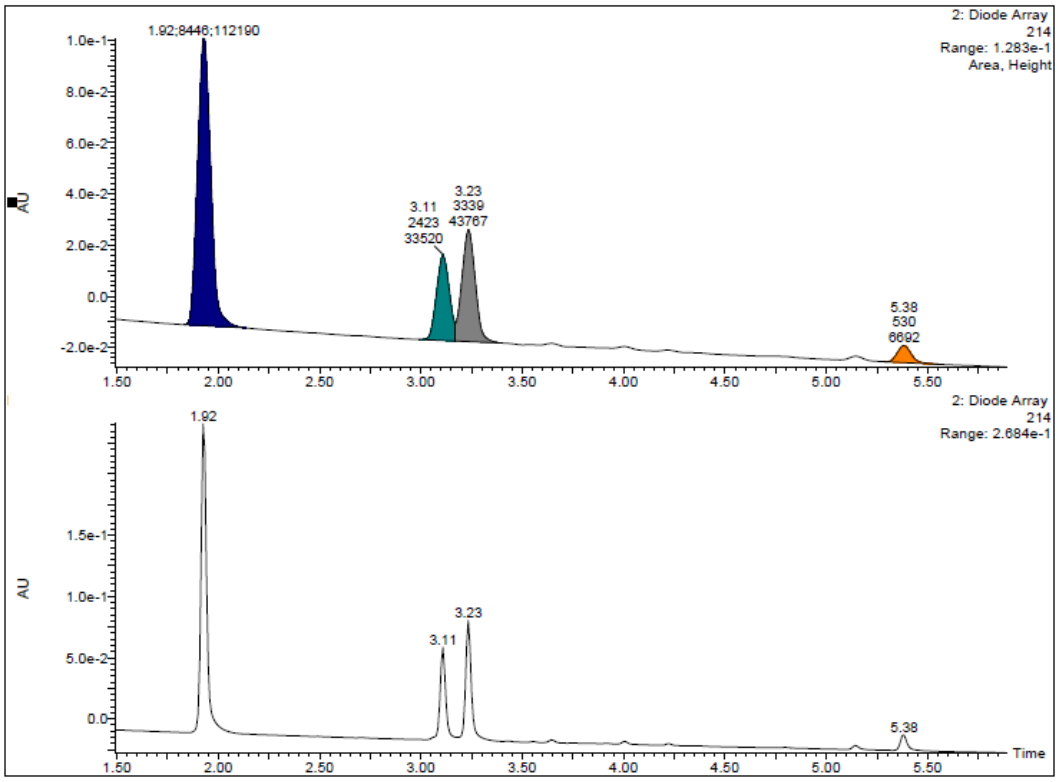


Figure S1. Representative UPLC chromatogram for entry 3, Table S5 (retention time (t_R) for IS, **2f**, **2e**, and **1e** = 1.92, 3.11, 3.23, and 5.38 mins, respectively).

Catalyst Screening

General Procedure for Catalyst Screening. To a mixture of trans azido ketone **1f** (25.7 mg, 0.100 mmol, 1.0 equiv) and catalyst (0.0100 mmol, 0.10 equiv or 0.00500 mmol, 0.050 equiv) in a microwave vial at rt was added TFE (0.5 mL). The vial was capped and the reaction mixture was stirred at 80 °C, 50 °C, or 25 °C for 16 h under conventional heating using a pie-block. The reaction mixture was allowed to cool to rt over 15 min. The cap was removed and the reaction mixture was analyzed by UPLC using 1-benzyl-2-pyrrolidinone as the IS. Catalysts were weighed or measured either in the argon glove box or under nitrogen blanket created with the help of wide mouth funnels connected to in-house nitrogen gas through Tygon® tubing.

Analysis of Reaction Mixture by UPLC. To the vial was added 1-benzyl-2-pyrrolidinone (16.0 μL, 0.100 mmol) using a microsyringe and the resulting mixture was mixed well to ensure homogeneity. An aliquot (10 μL) of the reaction mixture was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC.

Samples for UPLC analysis for the catalyst screening were run on Waters Acquity System (Waters Acquity SQ detector with ESI and Acquity TUV detector). Waters Acquity BEH Shield C18 column (2.1 x 50 mm, 1.7 μm) was employed with a basic method using a linear gradient elution of 90:10 (water:ACN, pH 9.8) to 40:60 (water:ACN) at a flow rate of 0.6 mL/min over 5.7 minutes followed by a flush with 100% ACN for 0.1 min.

Calibration was carried out each time with the IS before analyzing a batch of reaction mixture to determine the normalization factor (NF) for substrate **1f** and products **2f** and **2e** in a similar way as described before in the section for solvent screening.

For calculation of $NF_{substrate}$ and $NF_{products}$, 1-benzyl-2-pyrrolidinone (4.00 μL, 0.0250 mmol), substrate **1f** (6.43 mg, 0.0250 mmol), and mixture of products **2f** and **2e** (5.73 mg, 0.0250 mmol) were dissolved in CH_2Cl_2 (125 μL) to give a concentration of 0.2 M. A drop of this 0.2 M solution was diluted with 1.0 mL of CH_3OH in a sample vial and analyzed by UPLC. A retention time (t_R) in min for various peaks was obtained from a chromatogram (t_R for IS, **1f**, **2f**, **1e**, and **2e** were 1.92, 5.15, 3.11, 5.38 and 3.23 mins, respectively).

$$\mathrm{NF_{substrate}} = \mathrm{AUC_{substrate}}/\mathrm{AUC_{IS}}$$

$$\mathrm{NF_{products}} = \mathrm{AUC_{products}}/\mathrm{AUC_{IS}}$$

Products (**2f** and **2e**) conversion (%) was calculated as:

$$\%\ \text{products conversion} = (100 * \mathrm{AUC_{products}})/(\mathrm{AUC_{IS}} * \mathrm{NF_{products}})$$

Unreacted substrate **1f** and its epimer **1e** recoveries (in %) were calculated as:

$$\%\ \text{substrate recovery} = (100 * \mathrm{AUC_{substrate}})/(\mathrm{AUC_{IS}} * \mathrm{NF_{substrate}})$$

Purification of Products (2f and 2e) by Preparative TLC. Reaction mixture was applied on a preparative TLC plate and developed twice with 2% MeOH/CH_2Cl_2. The band corresponding to the products was scraped and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of elution under reduced pressure gave a mixture of products (**2f** and **2e**) as a colorless oil, which was further dried under vacuum.

Table S6. Transition Metal Lewis Acid Catalyst Screening with TFE[a]

entry	catalyst (10 mol %)	unreacted substrate		product conversion (**2f**:**2e**)	other byproducts observed[b]
		1f	**1e**		
1	$Sc(OTf)_3$	10%	15%	65% (~2:1)	≥1
2	$Sc(NTf_2)_3$	10%	15%	63% (~2.5:1)	≥1
3	$ScCl_3 \cdot xH_2O$	26%	17%	46% (~2:1)	≥2
4	$TiCl_4$[c]	ND	ND	94% (~1.6:1)	≥2
5	$TiCl(O^iPr)_3$[d]	16%	10%	61% (~2:1)	≥3
6	$CrCl_2$	36%	8%	39% (~3:1)	≥3
7	$Mn(OTf)_2$	66%	trace	20% (~7:1)	≥2
8	$Fe(OTf)_3$	ND	ND	84% (~7:1)	≥1
9	$Fe(OTf)_2$	15%	trace	61% (~9:1)	≥4
10	$FeCl_3$	42%	3%	10%	≥6
11	$Fe(ClO_4)_3 \cdot xH_2O$	18%	trace	66% (~7.5:1)	≥3
12	Ferrocenium PF_6	71%	3%	15% (~6.5:1)	≥3
13	$Co(ClO_4)_2 \cdot 6H_2O$	14%	trace	69% (~6:1)	≥2
14	$Ni(OTf)_3$	53%	3%	38% (~6:1)	≥2
15	$Cu(OTf)_2$	trace	trace	43% (~9:1)	≥6
16	$Zn(OTf)_2$	21%	11%	58% (~3:1)	≥1
17	$Y(OTf)_3$	17%	31%	44% (~2:1)	≥2
18	$ZrCl_4$	ND	ND	98% (~1:2.5)	≥2
19	$NbCl_5$	ND	ND	92% (~1.3:1)	≥3
20	$RuCl_3$	89%	5%	ND	≥3
21	$RhCl_3 \cdot xH_2O$	55%	3%	10%	≥3
22	$PdCl_2$	ND	ND	2%	≥6

entry	catalyst (10 mol %)	unreacted substrate		product conversion (**2f**:**2e**)	other byproducts observed[b]
		1f	**1e**		
23	AgOTf	73%	3%	18% (~7:1)	≥1
24	$CdCl_2$	96%	4%	ND	≥1
25	$Hf(OTf)_4$ hydrate	ND	ND	86% (~5.5:1)	≥3
26	$HfCl_4$	4%	3%	81% (~1.4:1)	≥2
27	WCl_6	ND	ND	84% (~2:1)	≥3
28	$AuCl_3$	ND	ND	81% (~2:1)	≥4
29	$HgCl_2$	92%	4%	ND	≥1

[a]All reactions were run at 80 °C for 16 h in TFE. [b]In most cases one of the byproducts observed was bridged lactam **3f** with a t_R of 3.43 min. [c]A 1.0 M solution in CH_2Cl_2 was used. [d]A 1.0 M solution in hexanes was used. ND = Not detected.

Table S7. Post-Transition Metal, Metalloid, and Lanthanoid Lewis Acid Catalyst Screening with TFE[a]

entry	catalyst (10 mol %)	unreacted substrate		product conversion (**2f**:**2e**)	other byproducts observed[b]
		1f	**1e**		
1	$Al(OTf)_3$	3%	trace	81% (~6:1)	≥1
2	$EtAlCl_2$[c]	19%	7%	62% (~2:1)	≥4
3	$In(OTf)_3$	ND	ND	85% (~6:1)	≥1
4	$InCl_3$	55%	3%	34% (~7:1)	≥2
5	$Sn(OTf)_2$	21%	trace	53% (~3:1)	≥1
6	$SnCl_4$[d]	trace	trace	77% (~3:1)	≥4
7	$Bi(OTf)_3$	ND	ND	85% (~4:1)	≥1
8	$BiCl_3$	3%	trace	80% (~2:1)	≥3
9	TlOTf	85%	17%	ND	≥1
10	$BF_3{\cdot}OEt_2$[e]	38%	trace	50% (~7:1)	≥3
11	CBS catalyst[f]	52%	47%	ND	≥3
12	$SiCl_4$[d]	ND	ND	93% (~1.2:1)	≥2
13	$Yb(OTf)_3$	17%	23%	49% (~2.4:1)	≥3

[a]All reactions were run at 80 °C for 16 h in TFE. [b]In most cases one of the byproducts observed was bridged lactam **3f** with a t_R of 3.43 min. [c]1.0 M solution in hexanes was used. [d]A 1.0 M solution in CH_2Cl_2 was used. [e]A stock solution of catalyst in TFE was prepared and used. [f]CBS catalyst (Corey–Bakshi–Shibata catalyst) = (*R*)-(+)-*o*-Tolyl-CBS-oxazaborolidine solution (0.5 M in toluene). ND = Not detected.

Table S8. Alkali and Alkaline Earth Metal Lewis Acid and Brønsted Acid Catalyst Screening with TFE[a]

entry	catalyst (10 mol %)	unreacted substrate		product conversion (**2f**:**2e**)	other byproducts observed[b]
		1f	**1e**		
1	LiOTf	88%	6%	ND	≥1
2	$Mg(OTf)_2$	90%	5%	~2%	≥1
3	$Ba(OTf)_2$	93%	5%	ND	≥1
4	CF_3CO_2H[c]	21%	11%	60% (~1.7:1)	≥3
5	HCl[d]	17%	6%	66% (~1:1)	≥3
6	BNDHP	11%	15%	71% (~1:1)	≥2
7	Armstrong's acid	4%	trace	82% (~3:1)	≥2
8	*p*-TsOH	41%	4%	48% (~5:1)	≥2
9	CF_3SO_3H[c]	31%	trace	57% (~7:1)	≥3

[a]All reactions were run at 80 °C for 16 h in TFE. [b]In most cases one of the byproducts observed was bridged lactam **3f** with a t_R of 3.43 min. [c]A stock solution of catalyst in TFE was prepared and used. [d]A 2.0 M solution in Et_2O was used. ND = Not detected.

Table S9. Catalyst Screening with 5 mol % $Sc(OTf)_3$ and 20 mol % HCl[a]

entry	catalyst	catalyst (mol %)	additive	unreacted substrate		product conversion (**2f**:**2e**)[b]
				1f	**1e**	
1	$Sc(OTf)_3$	5	–	28%	20%	40% (~2.5:1)
2	$Sc(OTf)_3$	5	CH_3CO_2H (1 equiv)	28%	5%	53% (~5:1)
3	HCl[c]	20	–	ND	ND	~100% (~1:3.5)

[a]All reactions were run at 80 °C for 16 h in TFE. [b]Byproducts (≥2) were observed in all cases and one of the byproducts was bridged lactam **3f**. [c]A 2.0 M solution in ether was used. ND = Not detected.

Table S10. Catalyst Screening at 50 °C with TFE[a]

entry	catalyst (10 mol %)	unreacted substrate		product yield[b,c] (**2f**:**2e**)
		1f	**1e**	
1	$SiCl_4$[d]	ND	ND	90% (~1:1)
2	$TiCl_4$[d]	ND	ND	93% (~1.7:1)
3	$Hf(OTf)_4$ hydrate	obs	trace	73% (~7:1)
4	$Bi(OTf)_3$	trace	trace	77% (~6.2:1)
5	$Fe(OTf)_3$	trace	ND	68% (~6.7:1)
6	$ZrCl_4$	obs	obs	73% (~1.7:1)
7	WCl_6	ND	ND	80% (~2.3:1)
8	$AuCl_3$	obs	obs	64% (~4.5:1)
9	$NbCl_5$	ND	ND	89% (~1.1:1)

[a]All reactions were run at 50 °C for 16 h in TFE. [b]Represents isolated yield after preparative TLC purification. [c]The ratio of products (**2f**:**2e**) was determined by ^{1}H NMR. [d]A 1.0 M solution in CH_2Cl_2 was used. ND = Not detected. obs = Substrate peak was observed by UPLC.

Table S11. Catalyst Screening at 25 °C with TFE[a]

entry	catalyst	catalysts (mol %)	unreacted substrate		product conversion (**2f**:**2e**)[b]
			1f	**1e**	
1	$SiCl_4$[c]	10	9%	3%	79% (1.4:1)
2	$SiCl_4$[c]	5	29%	5%	55% (1.7:1)
3	$TiCl_4$[c]	10	5%	2%	80% (3:1)
4	$TiCl_4$[c]	5	18%	3%	61% (4.2:1)
5	WCl_6	10	ND	ND	57%[d] (5.2:1)
6	$NbCl_5$	10	4%	2%	74% (3:1)

[a]All reactions were run at 25 °C for 8 h in TFE. [b]The ratio of products (**2f**:**2e**) was determined by UPLC except for entry 5. [c]A 1.0 M solution in CH_2Cl_2 was used. [d]Represents isolated yield after preparative TLC purification and the ratio of products (**2f**:**2e**) was determined by ^1H NMR. ND = Not determined.

Table S12. Catalyst Screening at 20 °C[a]

entry	catalyst (10 mol %)	solvent	unreacted substrate		product conversion (**2f**:**2e**)[b]
			1f	**1e**	
A	$Bi(OTf)_3$	Trifluoroethanol	19%	trace	61% (~3.5:1)
B	$Fe(OTf)_3$	Trifluoroethanol	19%	trace	62% (~7:1)
C	$In(OTf)_3$	Trifluoroethanol	27%	trace	56% (~7:1)
D	$Al(OTf)_3$	Trifluoroethanol	37%	trace	43% (~5.5:1)
E	$ZrCl_4$	Trifluoroethanol	4%	28%	61% (~1:12)
F	Armstrong's acid	Trifluoroethanol	30%	trace	50% (~6:1)
G	$Fe(OTf)_3$	Nitromethane	25%	trace	33% (~6:1)
H	$ZrCl_4$	Nitromethane	trace	69%	14%

[a]All reactions were run at 20 °C for 16 h (extending the reaction period to 24 h had minimal effect in increasing the product conversion). [b]Byproducts (≥2) were observed in all cases and one of the byproducts was bridged lactam **3f**.

Table S13. Catalyst Screening at 25 °C with HFIP[a]

entry	catalyst (10 mol %)	product yield[b,c] (**2f**:**2e**)	bridged lactam[b] (**3f**)
A	$TiCl_4$[d]	85% (9:1)	~4%
B	$SiCl_4$[d]	84% (4.7:1)	~4%

[a]All reactions were run at 25 °C for 4 h in HFIP. [b]Represents isolated yield after preparative TLC purification. [c]The ratio of products (**2f**:**2e**) was determined by ^{1}H NMR. [d]A 1.0 M solution in CH_2Cl_2 was used.

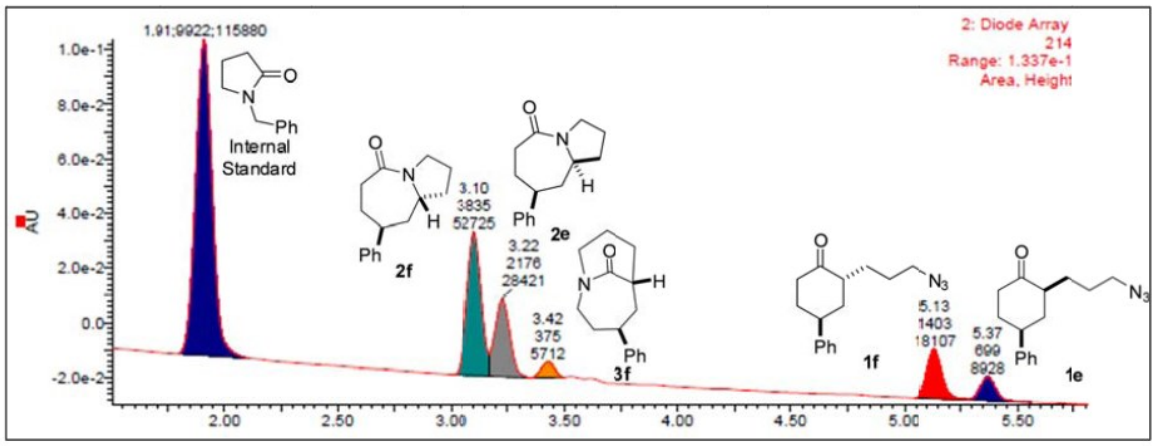
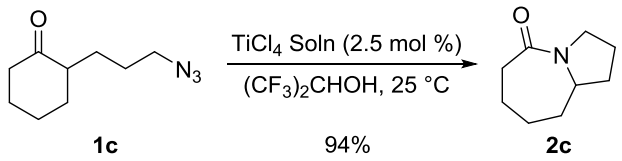


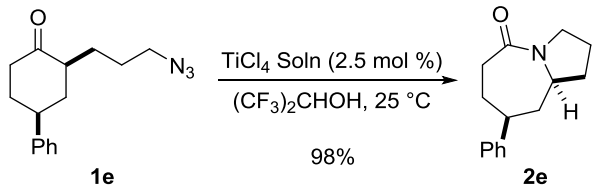
Figure S2. Representative UPLC chromatogram showing AUC for the possible outcomes of an incomplete intramolecular Schmidt reaction for one of the entries during catalyst screening.

General Procedure for Reaction Conditions Optimization (Table 1). To a solution of trans azido ketone **1f** (0.0257 g, 0.100 mmol, 1.0 equiv) in solvent (0.50 mL) at rt was added catalyst (5–20 mol %) and/or an additive under nitrogen or argon atmosphere in a one dram vial. The vial was capped and the reaction mixture was stirred at 25 or 37 °C for 12–38 h. The reaction progress was monitored by UPLC. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and applied on a preparative TLC plate. Preparative TLC plate was either developed once or twice with 100 % CH_2Cl_2 or 2% MeOH/CH_2Cl_2. Bands corresponding to substrates (**1f** and **1e**), products (**2f** and **2e**), and bridged lactam (**3f**) were scraped and eluted with 100% CH_2Cl_2 or 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of elution under reduced pressure provided recovered substrates (trans azido ketone **1f** and cis azido ketone **1e**), products (trans fused lactam **2f** and cis fused lactam **2e**), and bridged lactam **3f**, respectively. Ratios of **1f**:**1e** and **2f**:**2e** were determined by ^{1}H NMR or UPLC.

General Procedure A for the Catalytic Intramolecular Schmidt Reaction using $TiCl_4$ (Tables 3 and 4). To a solution of azido ketone in HFIP in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (2.5–35 mol %). The vial was capped and the reaction mixture was stirred at 25 °C for 18–62 h (gas evolution was observed upon addition of $TiCl_4$). The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g normal phase silica flash column on a CombiFlash Rf system with a gradient elution of 0–5% MeOH/CH_2Cl_2 afforded the corresponding lactam products after concentration of appropriate fractions.

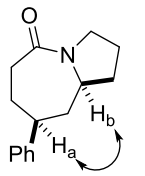


Hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2c). To a solution of 2-(3′-azidopropyl)cyclohexanone **1c** (0.0725 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (10.0 μL, 0.0100 mmol, 0.025 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded lactam **2c** as a pale yellow oil in 94% yield (0.0575 g, 0.375 mmol).



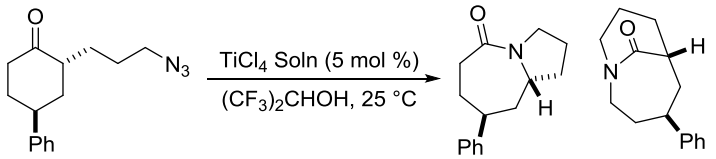
(8*S*,9a*S*)-*rel*-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*cis*-2e). To a solution of (2*S*,4*S*)-*rel*-2-(3′-azidopropyl)-4-phenylcyclohexanone **1e** (0.103 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (10.0 μL, 0.0100 mmol, 0.025 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded **2e** as a pale yellow oil in 98% yield (0.0901 g, 0.393 mmol). Lactam (*cis*-**2e**): R_f = 0.31 (2% MeOH/CH_2Cl_2); IR (neat) 1626, 1450,

1425 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59–1.79 (m, 4H), 1.81–1.88 (m, 1H), 1.90–1.97 (m, 2H), 2.18–2.26 (m, 1H), 2.50–2.64 (m, 2H), 2.75 (tt, J = 12.2, 3.3 Hz, 1H), 3.37–3.44 (m, 1H), 3.69 (m, 1H), 3.79–3.85 (m, 1H), 7.11–7.18 (m, 3H), 7.24–7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 30.6, 34.9, 37.4, 43.5, 46.9, 48.1, 57.9, 126.5, 126.6, 128.6, 146.4, 173.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M + H]^+$ 230.1545, found 230.1555; Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.08; H, 8.28; N 5.98; Cl, 0.43 (the presence of chlorine in the sample could be from the residual CH_2Cl_2 used for transferring the sample or from a trace amount of HCl complexed with the lactam).



"*cis*-fused" (**2e**)

The cis configuration for lactam **2e** was determined by NOESY experiment.

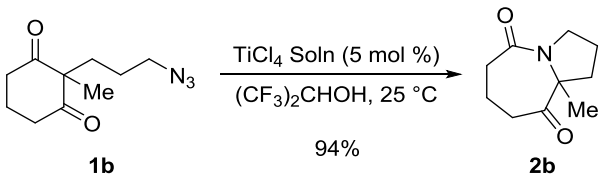


1f **2f** (87%) **3f** (2%)

(8*S*,9a*R*)-*rel*-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*trans*-2f) and (4*R*,6*R*)-*rel*-4-Phenyl-1-azabicyclo[4.3.1]decan-10-one (3f). To a solution of (2*R*,4*S*)-*rel*-2-(3′-azidopropyl)-4-phenylcyclohexanone **1f** (0.103 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 38 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and applied on a preparative TLC plate. Preparative TLC plate was developed twice with 2% MeOH/CH_2Cl_2. Bands

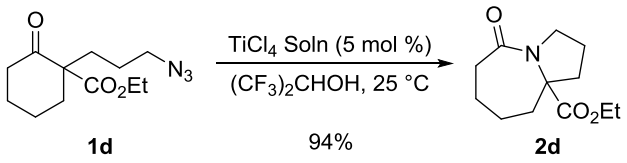
corresponding to fused lactam **2f** and bridged lactam **3f** were scraped and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of elution under reduced pressure afforded **2f** as a pale yellow oil in 87% yield (0.0796 g, 0.347 mmol) and **3f** as a colorless oil in ca. 2% yield (0.00220 g, 0.00959 mmol). Fused lactam (*trans*-**2f**): R_f = 0.18 (2% MeOH/CH_2Cl_2); IR (neat) 1628, 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61–1.70 (m, 1H), 1.72–1.81 (m, 1H), 1.84–1.96 (m, 2H), 2.01 (m, 1H), 2.09–2.20 (m, 3H), 2.46–2.53 (m, 1H), 2.71 (m, 1H), 3.02 (m, 1H), 3.48–3.60 (m, 2H), 3.98 (m, 1H), 7.19–7.23 (m, 3H), 7.29–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 27.6, 34.2, 34.6, 39.5, 39.6, 46.8, 54.7, 126.4, 127.3, 128.8, 144.6, 172.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M + H]^+$ 230.1545, found 230.1545.

Bridged lactam **3f**: R_f = 0.25 (2% MeOH/CH_2Cl_2); IR (neat) 1675, 1492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56–1.65 (m, 1H), 1.67–1.76 (m, 1H), 1.77–1.93 (complex, 4H), 2.24 (m, 1H), 2.42 (dtd, *J* = 14.5, 11.2, 7.4 Hz, 1H), 2.75 (ddd, *J* = 13.8, 11.2, 6.4 Hz, 1H), 3.00 (td, *J* = 11.8, 2.0 Hz, 1H), 3.08 (dtd, *J* = 10.2, 5.1, 2.0 Hz, 1H), 3.39 (td, *J* = 11.4, 3.1 Hz, 1H), 3.60–3.64 (m, 1H), 3.89 (dd, *J* = 13.8, 7.3 Hz, 1H), 7.11–7.13 (m, 2H), 7.17–7.20 (m, 1H), 7.26–7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 28.3, 32.5, 39.9, 45.2, 46.0, 49.1, 54.3, 126.4, 126.7, 128.8, 148.0, 184.9; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M + H]^+$ 230.1545, found 230.1566. Bridged lactam **3f** seemed to be unstable.



9a-Methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione (2b). To a solution of 2-(3′-azidopropyl)-2-methylcyclohexane-1,3-dione **1b** (0.0837 g, 0.400 mmol,

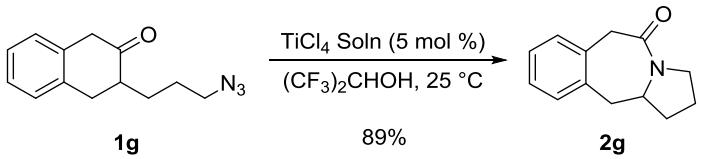
1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded lactam **2b** as a cream-yellow solid in 94% yield (0.0681 g, 0.376 mmol).



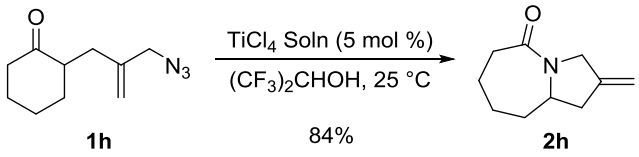
1d 94% **2d**

Ethyl 5-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepine-9a-carboxylate (2d). To a solution of ethyl 1-(3′-azidopropyl)-2-oxocyclohexanecarboxylate **1d** (0.101 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 40 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 30 min) afforded lactam **2d** as a white solid in 94% yield (0.0850 g, 0.377 mmol).

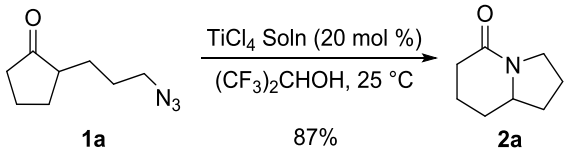
The reaction of **1d** (0.101 g, 0.400 mmol, 1.0 equiv) with 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (40 μL, 0.0400 mmol, 0.10 equiv) for 18 h in a similar way as described above afforded **2d** in 95% yield (0.0856 g, 0.380 mmol).



2,3,11,11a-Tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2g). To a solution of 3-(3′-azidopropyl)-3,4-dihydronaphthalen-2(1*H*)-one **1g** (0.0917 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded lactam **2g** as a pale orange solid in 89% yield (0.0720 g, 0.358 mmol).



2-Methylenehexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2h). To a solution of 2-(2′-(azidomethyl)allyl)cyclohexanone **1h** (0.0773 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 35 min) afforded lactam **2h** as a pale orange oil in 84% yield (0.0554 g, 0.335 mmol).

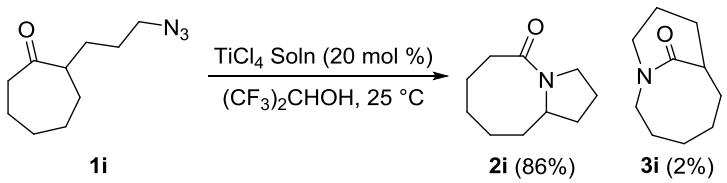


1a 2a

Hexahydroindolizin-5(1*H*)-one (2a). To a solution of 2-(3′-azidopropyl)-cyclopentanone **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 30 min) afforded lactam **2a** as a pale yellow oil in 87% yield (0.0485 g, 0.348 mmol).

The reaction of **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) with 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (60.0 μL, 0.0600 mmol, 0.15 equiv) for 44 h in a similar way as described above afforded **2a** in 79% yield (0.0440 g, 0.316 mmol).

The reaction of **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv) for 44 h in a similar way as described above afforded **2a** in 60% yield (0.0333 g, 0.239 mmol; 78% brsm). Azido ketone **1a** was recovered in 23% yield (0.0157 g, 0.0939 mmol).

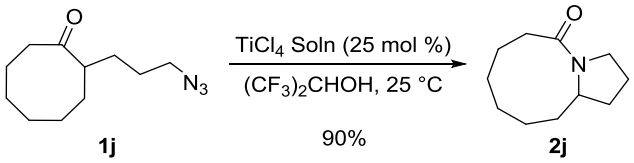


1i 2i (86%) 3i (2%)

Octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one (2i) and 1-Azabicyclo[5.3.1]undecan-11-one (3i). To a solution of 2-(3′-azidopropyl)cycloheptanone **1i** (0.0781 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M

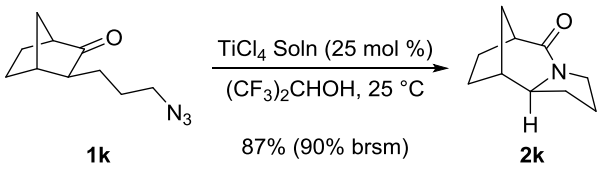
solution of $TiCl_4$ in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 48 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded fused lactam **2i** as a colorless oil in 86% yield (0.0573 g, 0.343 mmol) and **3i** as a colorless oil in ca. 2% yield (0.00170 g, 0.0102 mmol). Bridged lactam **3i**: R_f = 0.22 (2% MeOH/CH_2Cl_2); IR (neat) 1643, 1445, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44–1.54 (m, 3H), 1.60–1.76 (m, 3H), 1.77–1.88 (m, 3H), 1.96 (m, 1H), 2.06 (m, 1H), 2.17–2.24 (m, 1H), 2.72 (dd, J = 13.6, 4.7 Hz, 1H), 2.74–2.79 (m, 1H), 3.20 (ddd, J = 11.4, 6.5, 2.7 Hz, 1H), 3.64 (td, J = 11.7, 3.0 Hz, 1H), 4.58 (td, J = 13.3, 4.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 23.7, 25.5, 26.6, 32.4, 42.0, 42.1, 48.1, 49.8, 181.3; HRMS (ESI) *m/z* calcd for $C_{10}H_{18}NO$ $[M + H]^+$ 168.1388, found 168.1392.

The reaction of **1i** (0.0781 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.050 equiv) for 62 h in a similar way as described above afforded **2i** in 34% yield (0.0228 g, 0.136 mmol; 85% brsm). Azido ketone **1i** was recovered in 60% yield (0.0469 g, 0.240 mmol).



Octahydro-1*H*-pyrrolo[1,2-*a*]azonin-5(6*H*)-one (2j). To a solution of 2-(3′-azidopropyl)cyclooctanone **1j** (0.0837 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (100 μL, 0.100 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C

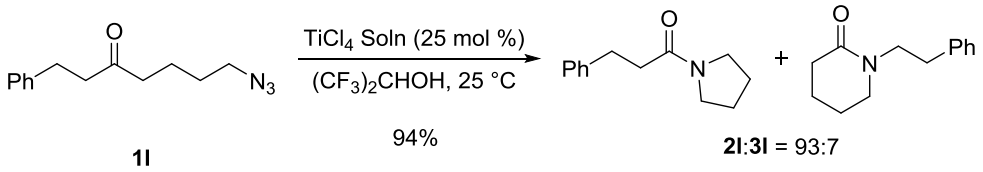
for 62 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 35 min) afforded lactam **2j** as a colorless oil in 90% yield (0.0651 g, 0.359 mmol).



1k **2k**

(6*S*,9*R*,9a*S*)-*rel*-Hexahydro-1*H*-6,9-methanopyrrolo[1,2-*a*]azepin-5(6*H*)-one (2k). To a solution of (1*S*,3*S*,4*R*)-*rel*-3-(3′-azidopropyl)bicyclo[2.2.1]heptan-2-one **1k** (0.0773 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (100 μL, 0.100 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 62 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 35 min) afforded **2k** as a colorless oil in 87% yield (0.0574 g, 0.347 mmol; 90% brsm). Azido ketone **1k** was recovered in 3% yield (0.00250 g, 0.0129 mmol). Lactam **2k**: R_f = 0.19 (2% MeOH/CH_2Cl_2); IR (neat) 1641, 1432, 1129 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30–1.39 (m, 1H), 1.45 (dt, J = 11.8, 4.3 Hz, 1H), 1.56–1.61 (m, 1H), 1.65 (d, J = 11.8 Hz, 1H), 1.68–1.90 (complex, 6H), 2.40 (m, 1H), 2.70 (m, 1H), 3.00 (m, 1H), 3.08 (dd, J = 11.7, 4.7 Hz, 1H), 3.80 (ddd, J = 11.9, 8.9, 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 28.4, 29.5, 30.4, 32.1, 36.3, 43.0, 43.6, 65.6, 175.2; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}NO$ $[M + H]^+$ 166.1232, found 166.1226.

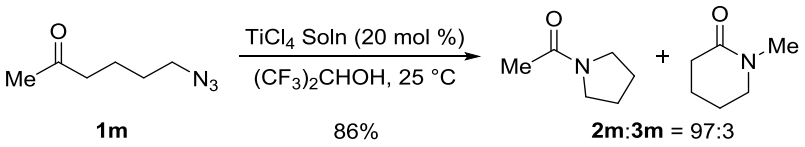
The reaction of **1k** (0.0773 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv) for 62 h in a similar way as described above afforded **2k** in 43% yield (0.0285 g, 0.172 mmol; 78% brsm). Azido ketone **1k** was recovered in 45% yield (0.0346 g, 0.179 mmol).



1l **2l**:**3l** = 93:7

3-Phenyl-1-(pyrrolidin-1-yl)propan-1-one (2l) and 1-Phenethylpiperidin-2-one (3l). To a solution of 7-azido-1-phenylheptan-3-one **1l** (0.0925 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (100 μL, 0.100 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 32 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded a mixture of amide **2l** and lactam **3l** as a colorless oil in 94% yield (0.0763 g, 0.375 mmol; **2l**:**3l** = 93:7 by ^{1}H NMR).

The reaction of **1l** (0.0925 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv) for 24 h in a similar way as described above afforded a mixture of **2l** and **3l** as a pale yellow oil in 79% yield (0.0640 g, 0.315 mmol, 96% brsm; **2l**:**3l** = 93:7 by ^{1}H NMR). Azido ketone **1l** was recovered in 18% yield (0.0165 g, 0.0713 mmol).

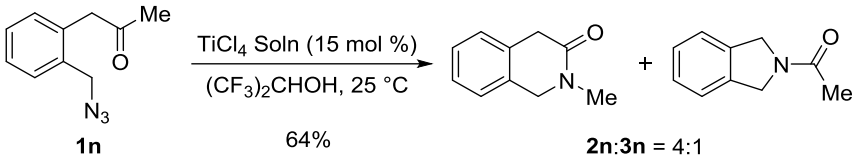


1m 86% **2m**:**3m** = 97:3

1-(Pyrrolidin-1-yl)ethanone (2m) and *N*-Methyl-2-piperidone (3m). To a solution of 6-azidohexan-2-one **1m** (0.0564 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded a mixture of amide **2m** and lactam **3m** as a colorless oil in 86% yield (0.0390 g, 0.345 mmol; **2m**:**3m** = 97:3 by ^{1}H NMR).

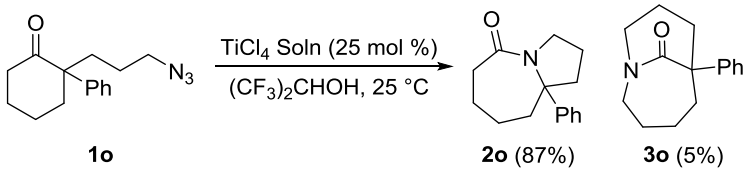
The reaction of **1m** (0.0564 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (60.0 μL, 0.0600 mmol, 0.15 equiv) for 24 h in a similar way as described above afforded a mixture of **2m** and **3m** as a colorless oil in 77% yield (0.0350 g, 0.309 mmol, 81% brsm; **2m**:**3m** = 97:3 by ^{1}H NMR). Azido ketone **1m** was recovered in 4% yield (0.00250 g, 0.0177 mmol).

The reaction of **1m** (0.0564 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv) for 36 h in a similar way as described above afforded a mixture of **2m** and **3m** as a colorless oil in 73% yield (0.0331 g, 0.292 mmol; **2m**:**3m** = 97:3 by ^{1}H NMR).



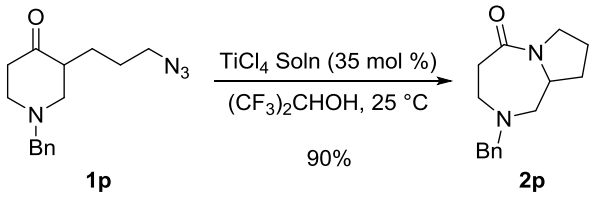
2-Methyl-1,2-dihydroisoquinolin-3(4*H*)-one (2n) and 1-(Isoindolin-2-yl)ethanone (3n). To a solution of 1-(2′-(azidomethyl)phenyl)propan-2-one **1n** (0.0757 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (60.0 μL, 0.0600 mmol, 0.15 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded a mixture of lactam **2n** and amide **3n** as a yellow oil in 64% yield (0.0411 g, 0.255 mmol; **2n**:**3n** = 79:21 (ca. 4:1) by ^{1}H NMR).

The reaction of **1n** (0.0757 g, 0.400 mmol, 1.0 equiv) with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv) for 24 h in a similar way as described above afforded a mixture of **2n** and **3n** as a yellow oil in 58% yield (0.0376 g, 0.233 mmol, 64% brsm; **2n**:**3n** = 77:23 by ^{1}H NMR). Azido ketone **1n** was recovered in 9% yield (0.00700 g, 0.0370 mmol).



9a-Phenyloctahydro-5*H*-pyrrolo[1,2-*a*]azepin-5-one (2o) and 6-Phenyl-1-azabicyclo[4.3.1]decan-10-one (3o). To a solution of 2-(3′-azidopropyl)-2-phenyl-cyclohexan-1-one **1o** (0.103 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (100 μL, 0.100

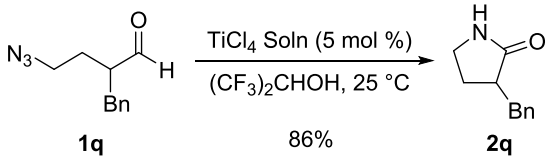
mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 48 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 (1.0 mL), quenched with Et_3N (0.10 mL), and reconcentrated. A solution of the resulting residue in CH_2Cl_2 was loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded **3o** (eluted between 0.8–1.2% MeOH/CH_2Cl_2) as a pale yellow waxy solid in 5% yield (0.0050 g, 0.022 mmol) and fused lactam **2o** (eluted between 1.3–1.7% MeOH/CH_2Cl_2) as a pale orange solid in 87% yield (0.0802 g, 0.350 mmol). Bridged lactam **3o**: R_f = 0.39 (2% MeOH/CH_2Cl_2); IR (neat) 1664, 1177 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.78–1.87 (complex, 3H), 1.88–1.96 (complex, 2H), 1.97–2.04 (complex, 3H), 2.09–2.13 (m, 1H), 2.25 (m, 1H), 2.65–2.70 (m, 1H), 3.42 (m, 1H), 3.60 (m, 1H), 3.92 (m, 1H), 7.19–7.22 (m, 1H), 7.29–7.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 22.7, 24.9, 38.0, 41.1, 49.1, 53.0, 56.7, 126.4, 126.5, 128.6, 147.1, 183.9; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ $[M + H]^+$ 230.1545, found 230.1538.



2-Benzylhexahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-5(2*H*)-one (2p). To a solution of 3-(3′-azidopropyl)-1-benzylpiperidin-4-one **1p** (0.109 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (140 μL, 0.140 mmol, 0.35 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2, neutralized with saturated aqueous $NaHCO_3$

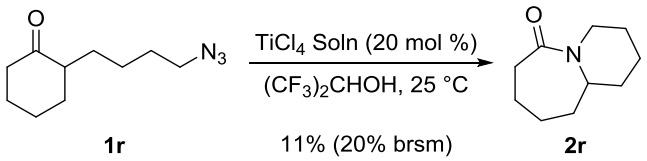
solution (0.6 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The orange residue obtained was re-dissolved in CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 35 min) afforded lactam **2p** as a colorless oil in 90% yield (0.0876 g, 0.359 mmol).

During the initial addition of $TiCl_4$ solution up to 25 mol %, a formation of yellow solid was observed (presumably, the HCl salt of amine). Work-up with aqueous $NaHCO_3$ was necessary to neutralize the amine salt into free amine base for purification and TLC monitoring.



1q **2q**

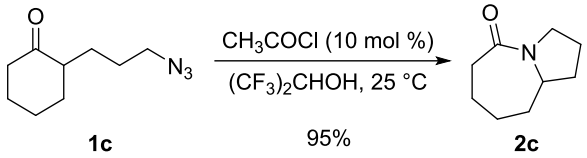
3-Benzylpyrrolidin-2-one (**2q**)**.** To a solution of 4-azido-2-benzylbutanal **1q** (0.0813 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (20.0 μL, 0.0200 mmol, 0.05 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 35 min) afforded lactam **2q** as a pale blue crystalline solid in 86% yield (0.0604 g, 0.345 mmol).



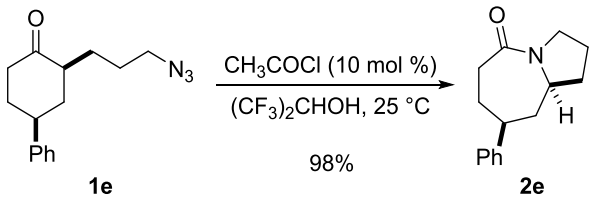
Octahydropyrido[1,2-*a*]azepin-6(2*H*)-one (2r). To a solution of 2-(4′-azidobutyl)cyclohexanone **1r** (0.0781 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (80.0 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 60 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded lactam **2r** as a pale yellow oil in 11% yield (0.00720 g, 0.0431 mmol; 20% brsm). Azido ketone **1r** was recovered in 47% yield (0.0370 g, 0.190 mmol).

General Procedure for Reaction Conditions Optimization (Table 5). To a solution of 2-(3′-azidopropyl)cyclopentanone **1a** (0.0167 g, 0.100 mmol, 1.0 equiv) in HFIP (0.50 mL) at rt was added catalyst (5–40 mol %) and/or additive (5–80 mol %) under nitrogen atmosphere in a one dram vial. The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with 5% MeOH/CH_2Cl_2 and eluted through a phase separator tabless containing a short bed of silica gel. Evaporation of elution under reduced pressure provided a mixture of **1a** and hexahydroindolizin-5(1*H*)-one **2a**, whose ratios were determined by ^{1}H NMR.

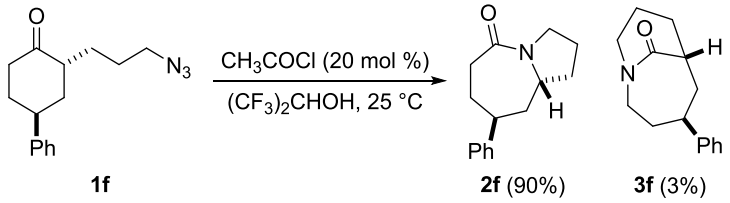
General Procedure B for the Catalytic Intramolecular Schmidt Reaction using AcCl (Table 6). To a solution of azido ketone in HFIP in a nitrogen-flushed four dram vial was added AcCl (10–100 mol %). The vial was capped and the reaction mixture was stirred at 25 °C for 20–62 h (gas evolution was observed upon addition of AcCl). The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g normal phase silica flash column on a CombiFlash Rf system with a gradient elution of 0–5% MeOH/CH_2Cl_2 afforded the corresponding lactam products after concentration of appropriate fractions.



Hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2c). To a solution of 2-(3′-azidopropyl)cyclohexanone **1c** (0.0725 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (2.84 μL, 0.0400 mmol, 0.10 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded lactam **2c** as a pale yellow oil in 95% yield (0.0582 g, 0.380 mmol).

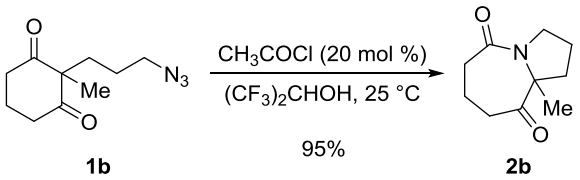


(8*S*,9a*S*)-*rel*-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*cis*-2e). To a solution of (2*S*,4*S*)-*rel*-2-(3′-azidopropyl)-4-phenylcyclohexanone **1e** (0.103 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (2.84 μL, 0.0400 mmol, 0.10 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 20 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded cis fused lactam **2e** as a colorless oil in 98% yield (0.0897 g, 0.391 mmol).

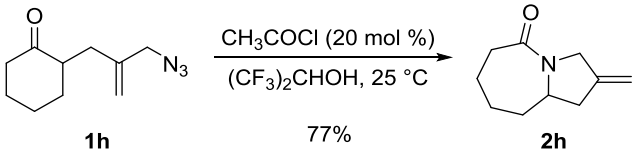


(8*S*,9a*R*)-*rel*-8-Phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (*trans*-2f) and (4*R*,6*R*)-*rel*-4-Phenyl-1-azabicyclo[4.3.1]decan-10-one (3f). To a solution of (2*R*,4*S*)-*rel*-2-(3′-azidopropyl)-4-phenylcyclohexanone **1f** (0.0257 g, 0.100 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (1.42 μL, 0.0200 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 38 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and applied on a preparative TLC plate. Preparative TLC plate was developed twice with 2% MeOH/CH_2Cl_2. Bands corresponding to trans fused lactam **2f** and

bridged lactam **3f** were scraped and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of elution under reduced pressure afforded **2f** as a colorless oil in 90% yield (0.0206 g, 0.0898 mmol) and **3f** as a colorless oil in ca. 3% yield (0.000600 g, 0.00261 mmol).

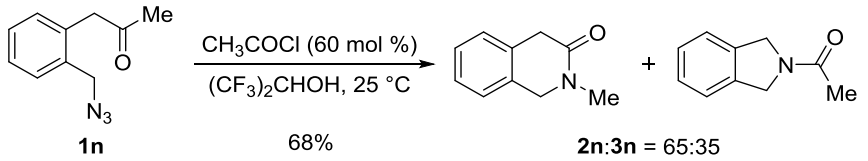


9a-Methyltetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9a*H*)-dione (2b). To a solution of 2-(3′-azidopropyl)-2-methylcyclohexane-1,3-dione **1b** (0.0837 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (5.70 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded lactam **2b** as a cream-yellow solid in 95% yield (0.0692 g, 0.382 mmol).



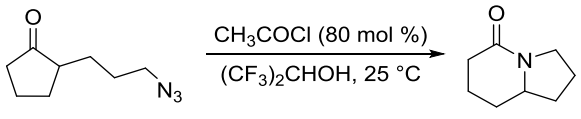
2-Methylenehexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2h). To a solution of 2-(2′-(azidomethyl)allyl)cyclohexanone **1h** (0.0773 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (5.70 μL, 0.0800 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The

reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded lactam **2h** as a pale orange oil in 77% yield (0.0508 g, 0.307 mmol).



1n **2n**:**3n** = 65:35

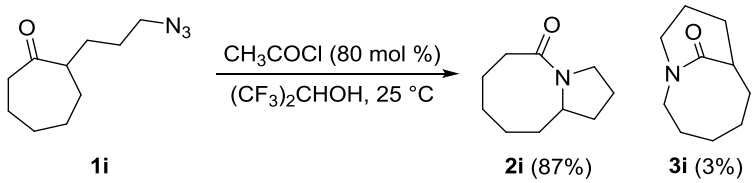
2-Methyl-1,2-dihydroisoquinolin-3(4*H*)-one (2n) and 1-(Isoindolin-2-yl)ethanone (3n). To a solution of 1-(2′-(azidomethyl)phenyl)propan-2-one **1n** (0.0757 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (17.1 μL, 0.240 mmol, 0.60 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded a mixture of lactam **2n** and amide **3n** as a yellow oil in 68% yield (0.0437 g, 0.271 mmol; **2n**:**3n** = 65:35 by ^{1}H NMR).



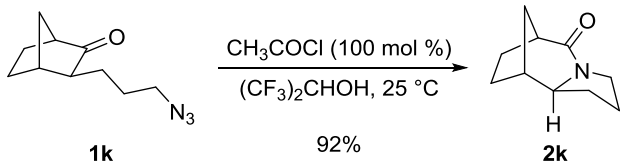
1a **2a**

Hexahydroindolizin-5(1*H*)-one (2a). To a solution of 2-(3′-azidopropyl)-cyclopentanone **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (22.8 μL, 0.320 mmol, 0.80 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was

concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded lactam **2a** as a pale yellow oil in 90% yield (0.0503 g, 0.361 mmol).

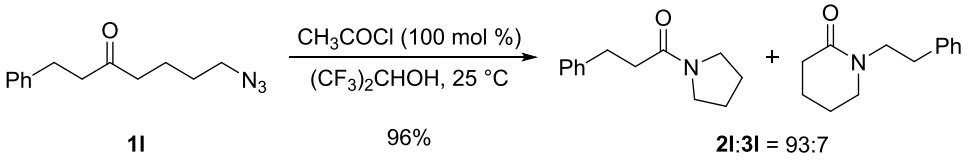


Octahydropyrrolo[1,2-*a*]azocin-5(1*H*)-one (2i) and 1-Azabicyclo[5.3.1]undecan-11-one (3i). To a solution of 2-(3′-azidopropyl)cycloheptanone **1i** (0.0781 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (22.8 μL, 0.320 mmol, 0.80 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 48 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded fused lactam **2i** as a pale yellow oil in 87% yield (0.0583 g, 0.349 mmol) and bridged lactam **3i** as a pale yellow oil in ca. 3% yield (0.00220 g, 0.0132 mmol).



(6*S*,9*R*,9a*S*)-*rel*-Hexahydro-1*H*-6,9-methanopyrrolo[1,2-*a*]azepin-5(6*H*)-one (2k). To a solution of (1*S*,3*S*,4*R*)-*rel*-3-(3′-azidopropyl)bicyclo[2.2.1]heptan-2-one **1k** (0.0773 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (28.4 μL, 0.400 mmol, 1.0 equiv). The vial was capped and the reaction mixture was

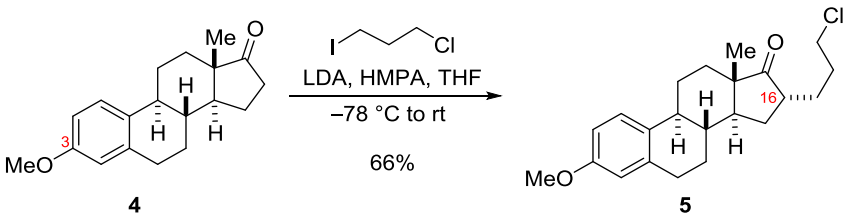
stirred at 25 °C for 62 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded lactam **2k** as a colorless oil in 92% yield (0.0610 g, 0.369 mmol).



1l

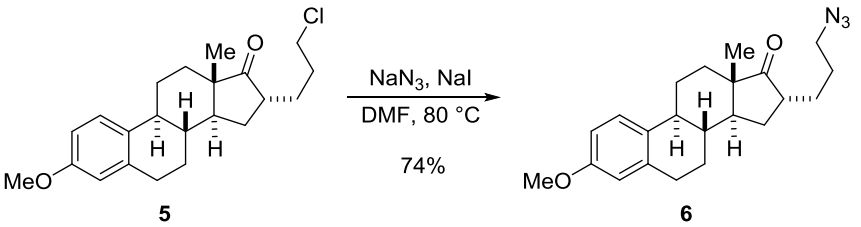
3-Phenyl-1-(pyrrolidin-1-yl)propan-1-one (2l) and 1-Phenethylpiperidin-2-one (3l). To a solution of 7-azido-1-phenylheptan-3-one **1l** (0.0925 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (28.4 μL, 0.400 mmol, 1.0 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 32 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded a mixture of amide **2l** and lactam **3l** as a pale yellow oil in 96% yield (0.0784 g, 0.386 mmol; **2l**:**3l** = 93:7 by ^{1}H NMR).

Experimental Procedure for the Synthesis of 17-Azaestrone Analogues 7 and 8 (Schemes 11 and 12)



(8*R*,9*S*,13*S*,14*S*,16*R*)-16-(3′-Chloropropyl)-3-methoxy-13-methyl-7,8,9,11,12,13, 15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one (5). To a cooled 1.0 M LDA solution (2.11 mL, 2.11 mmol, 1.2 equiv) in THF at –78 °C in a flame-dried flask under argon atmosphere was added a suspension of estrone 3-methyl ether **4** (0.500 g, 1.76 mmol, 1.0 equiv) in THF (10 mL) slowly over 10 min, and the reaction mixture was allowed to warmed to rt over 30 min. The resulting colorless solution was cooled to –78 °C and HMPA (1.5 mL) was added followed by 1-chloro-3-iodopropane (0.226 mL, 2.11 mmol, 1.2 equiv) over 5 min. The pale yellow solution was stirred at –78 °C for 1 h, warmed to rt and stirred for 1.5 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl (25 mL) and extracted with ether (3 × 30 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification using a 24 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 55 min) afforded a mixture of **5**, **4**, and some unidentified byproducts. Subsequent purification of this mixture using a 24 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 70 min) afforded a small amount of a mixture of **5**, **4**, and some unidentified byproducts along with the partial separation of **5** (C16-α diastereomer) containing a little bit of byproduct (could be a C16-β diastereomer of **5**)[44] as a colorless semisolid (0.420 g, 1.16 mmol, 66% corrected yield by ^{1}H NMR). Chloro ketone **5**: R_f = 0.47 (10% EtOAc/hexanes, run twice); IR (neat) 2930,

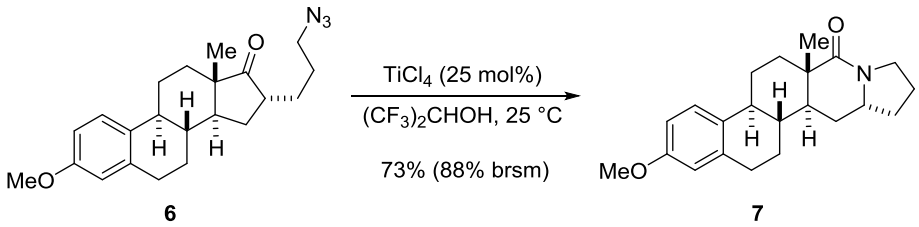
2863, 1733, 1609, 1499, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.37–1.63 (complex, 6H), 1.77 (ddd, J = 12.6, 6.3, 1.6 Hz, 1H), 1.85–2.02 (complex, 6H), 2.24 (td, J = 10.4, 4.3 Hz, 1H), 2.36–2.41 (m, 1H), 2.49 (m, 1H), 2.91 (m, 2H), 3.56 (m, 2H), 3.78 (s, 3H), 6.65 (d, J = 2.7 Hz, 1H), 6.72 (dd, J = 8.6, 2.8 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 25.9, 26.6, 27.7, 28.7, 29.7, 31.3, 31.8, 38.4, 44.1, 44.2, 44.9, 48.4, 48.8, 55.3, 111.6, 114.0, 126.4, 132.1, 137.8, 157.7, 221.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{30}ClO_2$ $[M + H]^+$ 361.1934, found 361.1972.



5 **6**

(8*R*,9*S*,13*S*,14*S*,16*R*)-16-(3′-Azidopropyl)-3-methoxy-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one (6). To a solution of (8*R*,9*S*,13*S*,14*S*,16*R*)-16-(3′-chloropropyl)-3-methoxy-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one **5** (0.352 g, 0.975 mmol, 1.0 equiv) in anhydrous DMF (5.0 mL) at rt under nitrogen atmosphere was added sodium iodide (0.175 g, 1.17 mmol, 1.2 equiv) followed by sodium azide (0.127 g, 1.95 mmol, 2.0 equiv), and the resulting pale yellow suspension was stirred at 80 °C for 1 h. The reaction mixture was cooled to rt, diluted with water (40 mL), and extracted with ether (3 × 30 mL). The combined organic extracts were washed with water (3 × 40 mL), brine (1 × 40 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification using a 24 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 75 min) afforded a mixture of **6** and an unidentified byproduct (could be a C16-β diastereomer of **6**) along with the partial separation of **6** as a colorless waxy solid (0.267 g, 0.727 mmol, 74% corrected

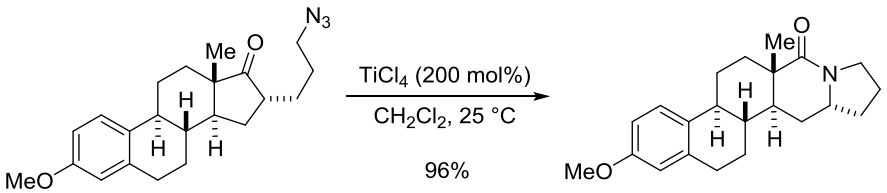
yield by ^{1}H NMR). Azido ketone **6**: R_f = 0.42 (10% EtOAc/hexanes, run twice); IR (neat) 2930, 2861, 2093, 1735, 1609, 1499, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.32–1.63 (complex, 6H), 1.66–2.02 (complex, 7H), 2.24 (td, J = 10.4, 4.1 Hz, 1H), 2.36–2.41 (m, 1H), 2.48 (m, 1H), 2.91 (m, 2H), 3.31 (m, 2H), 3.78 (s, 3H), 6.65 (d, J = 2.6 Hz, 1H), 6.72 (dd, J = 8.5, 2.7 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 25.9, 26.6, 27.64, 27.67, 28.4, 29.7, 31.8, 38.4, 44.0, 44.4, 48.3, 48.7, 51.4, 55.2, 111.6, 113.9, 126.4, 132.0, 137.8, 157.7, 221.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{30}NO_2$ $[M + H - N_2]^+$ 340.2277, found 340.2301.



6 **7**

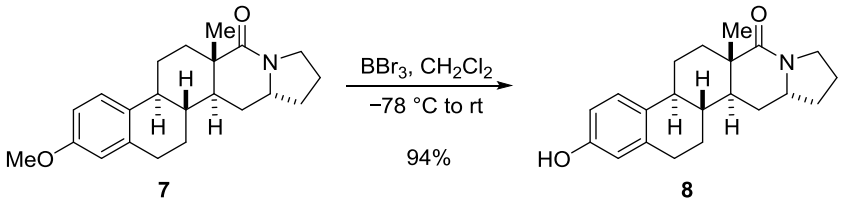
(4b*S*,6a*S*,11a*R*,12a*S*,12b*R*)-2-Methoxy-6a-methyl-4b,5,6,6a,9,10,11,11a,12,12a, 13,14-dodecahydronaphtho[2,1-*f*]pyrrolo[1,2-*b*]isoquinolin-7(12b*H*)-one (7). To a solution of (8*R*,9*S*,13*S*,14*S*,16*R*)-16-(3′-azidopropyl)-3-methoxy-13-methyl-7,8,9,11,12,13, 15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one **6** (0.0735 g, 0.200 mmol, 1.0 equiv) in HFIP (1.0 mL) in a nitrogen-flushed two dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (50.0 μL, 0.0500 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 48 h (gas evolution was observed upon addition of $TiCl_4$). The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded **7** (eluted between 1.5–2.1% MeOH/CH_2Cl_2) as an off-white solid in 73% yield (0.0495 g, 0.146 mmol; 88% brsm). Starting azido ketone **6** was also recovered during this

purification in 17% yield (0.0125 g, 0.0340 mmol). Methoxy lactam **7**: R_f = 0.17 (2% MeOH in CH_2Cl_2); mp 134–137 °C; IR (neat) 2939, 2863, 1640, 1501, 1442, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.23–1.37 (complex, 2H), 1.37–1.57 (m, 3H), 1.67–1.80 (complex, 3H), 1.88–1.95 (m, 1H), 1.97–2.04 (m, 2H), 2.10–2.26 (m, 3H), 2.36 (dq, J = 13.3, 3.6 Hz, 1H), 2.84 (m, 2H), 3.39 (ddd, J = 12.0, 9.7, 2.3 Hz, 1H), 3.55–3.64 (m, 2H), 3.76 (s, 3H), 6.61 (d, J = 2.7 Hz, 1H), 6.71 (dd, J = 8.6, 2.7 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 22.1, 26.0, 26.6, 28.4, 30.2, 33.8, 35.6, 40.3, 40.7, 42.0, 42.7, 44.6, 53.8, 55.3, 111.7, 113.6, 126.6, 132.3, 137.6, 157.6, 176.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{30}NO_2$ $[M + H]^+$ 340.2277, found 340.2299.



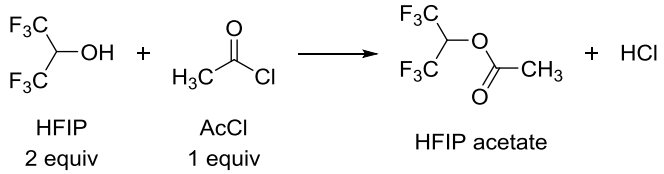
6 **7**

To a solution of (8*R*,9*S*,13*S*,14*S*,16*R*)-16-(3′-azidopropyl)-3-methoxy-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one **6** (0.0368 g, 0.100 mmol, 1.0 equiv) in CH_2Cl_2 (0.30 mL) in a nitrogen-flushed one dram vial was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.200 mL, 0.200 mmol, 2.0 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 1.5 h. The reaction mixture was quenched with five drops of Et_3N and concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded methoxy lactam **7** (eluted between 1.5–1.9% MeOH/CH_2Cl_2) as a creamish solid in 96% yield (0.0325 g, 0.0957 mmol).



(4b*S*,6a*S*,11a*R*,12a*S*,12b*R*)-2-Hydroxy-6a-methyl-4b,5,6,6a,9,10,11,11a,12,12a, 13,14-dodecahydronaphtho[2,1-*f*]pyrrolo[1,2-*b*]isoquinolin-7(12b*H*)-one (8). To a solution of (4b*S*,6a*S*,11a*R*,12a*S*,12b*R*)-2-methoxy-6a-methyl-4b,5,6,6a,9,10,11,11a,12,12a, 13,14-dodecahydronaphtho[2,1-*f*]pyrrolo[1,2-*b*]isoquinolin-7(12b*H*)-one **7** (0.0339 g, 0.100 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2.5 mL) at –78 °C under nitrogen atmosphere was added a 1.0 M solution of boron tribromide (BBr_3) in CH_2Cl_2 (0.800 mL, 0.800 mmol, 8.0 equiv) over 5 min. The reaction mixture was stirred at –78 °C for 1 h, warmed to rt over 4 h, and continued stirring at rt for 1 h (pinkish-orange suspension). The reaction mixture was quenched with two drops of water and the residue was dissolved in CH_2Cl_2–MeOH mixture and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded **8** as a colorless solid in 94% yield (0.0306 g, 0.0940 mmol). Hydroxy lactam **8**: R_f = 0.15 (2% MeOH/CH_2Cl_2, run twice); mp >250 °C, dec.; IR (neat) 3294, 2931, 2865, 1621, 1605, 1505, 1447, 1326, 1224, 921 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2 + $(CF_3)_2CDOD$) δ 1.15 (s, 3H), 1.33–1.46 (complex, 2H), 1.50–1.58 (m, 2H), 1.59–1.75 (m, 2H), 1.81–1.93 (complex, 2H), 2.00–2.15 (complex, 4H), 2.24–2.32 (m, 2H), 2.42–2.46 (m, 1H), 2.88–2.90 (m, 2H), 3.53 (m, 2H), 3.72 (m, 1H), 6.66 (d, J = 2.6 Hz, 1H), 6.72 (dd, J = 8.4, 2.7 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2 + $(CF_3)_2CDOD$) δ 15.1, 22.8, 26.7, 27.4, 28.8, 30.8, 34.8, 35.9, 41.8, 42.1, 43.1, 43.9, 46.7, 56.5, 114.0, 116.3, 128.4, 135.4, 140.5, 153.2, 181.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{28}NO_2$ $[M + H]^+$ 326.2120, found 326.2132. Since **8** was insoluble in most commonly used organic solvents, $(CF_3)_2CDOD$) was used to dissolve

8 for its characterization. Hydrogen bonding between lactam **8** and $(CF_3)_2CDOD$) may have changed the actual chemical shifts of **8**. For $(C^1F_3)_2C^2D^1OD^2$): ^{1}H NMR (400 MHz) δ 4.13 (br s, D^2), 4.46 (m, D^1); ^{13}C NMR (125 MHz) δ 69.9–71.3 (C^2), 119.5–126.3 (C^1). Residual CH_2Cl_2 was observed at δ 5.33 as a singlet.



Experimental Procedure for the Reaction of AcCl with HFIP to Probe the In Situ Generation of HCl Through the Formation of HFIP Acetate. In a nitrogen-flushed vial at rt was added HFIP (0.500 mL, 4.80 mmol, 2.0 equiv) followed by AcCl (0.170 mL, 2.40 mmol, 1.0 equiv), and the solution was mixed gently (white fumes of HCl were observed). Aliquots (35 μL) were withdrawn at different time intervals and diluted with 0.45 mL of $CDCl_3$ in NMR tubes. ^{1}H NMR integrations were used to determine the conversion ratio (see Figure 5 for ^{1}H NMR spectra). The graph was plotted using Microsoft Excel 2010.

time (min)	% conversion to HFIP acetate	% remaining of AcCl
0	0	100
1	19	81
6	47	53
10	55	45
20	67	33
30	74	26
60	84	16
120	91	9
160	93	7
240	96	4
480	99	1

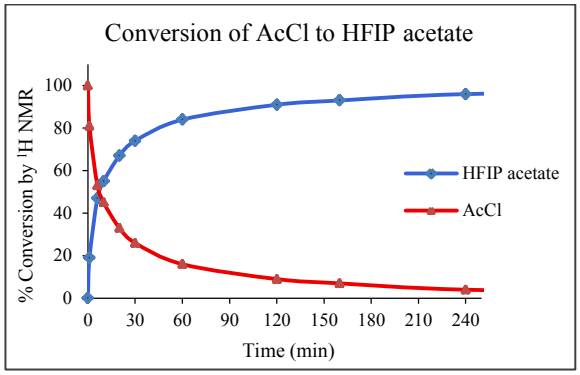
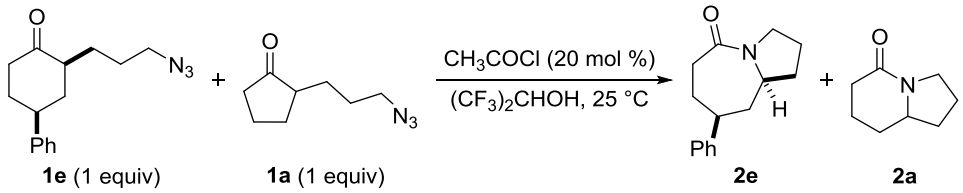


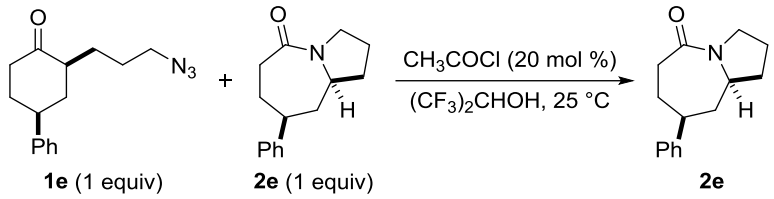
Figure S3. Reaction rate for the conversion of AcCl to HFIP acetate.

Procedure for the Competition and Product Inhibition Experiments (Scheme 15 and Figure 7)

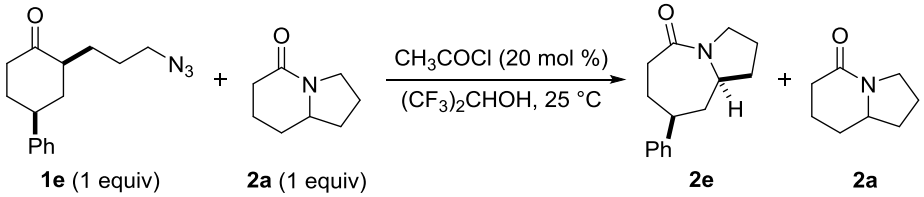
Nonlinear regression (curve fit) analysis was performed using GraphPad Prism 5 software.



(a) Competition Experiment Between Azido Ketones 1e and 1a. To a solution of (2*R*,4*S*)-*rel*-2-(3′-azidopropyl)-4-phenylcyclohexanone **1e** (0.0257 g, 0.100 mmol, 1.0 equiv) and 2-(3′-azidopropyl)cyclopentanone **1a** (0.0167 g, 0.100 mmol, 1.0 equiv) in HFIP (0.50 mL) at rt was added AcCl (1.42 μL, 0.0200 mmol, 0.20 equiv) under nitrogen atmosphere in a 1 dram vial. The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Aliquots (50 μL) were withdrawn using a micropipette at different time points (0 min, 20 min, 3 h, 6 h, 12 h, and 24 h) into sample vials and concentrated under nitrogen gas. The residues were diluted with 0.50 mL of $CDCl_3$ and transferred into NMR tubes and ^{1}H NMR integrations were used to determine the conversion ratio.



(b) Product Inhibition Experiment of 1e with Added Lactam 2e at the Outset of the Reaction. To a solution of cis azido ketone **1e** (0.0257 g, 0.100 mmol, 1.0 equiv) and (8*S*,9a*S*)-*rel*-8-phenylhexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one **2e** (0.0229 g, 0.100 mmol, 1.0 equiv) in HFIP (0.50 mL) at rt was added AcCl (1.42 μL, 0.0200 mmol, 0.20 equiv) under nitrogen atmosphere in a one dram vial. The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Aliquots (50 μL) were withdrawn using a micropipette at different time points into sample vials and concentrated under nitrogen gas. The residues were diluted with 0.50 mL of $CDCl_3$ and transferred into NMR tubes and ^{1}H NMR integrations were used to determine the conversion ratio. Since complete conversion was observed within 12 h, reaction graph was plotted only up to 12 h.



(c) Product Inhibition Experiment of 1e with Added Lactam 2a at the Outset of the Reaction. To a solution of cis azido ketone **1e** (0.0257 g, 0.100 mmol, 1.0 equiv) and hexahydroindolizin-5(1*H*)-one **2a** (0.0139 g, 0.100 mmol, 1.0 equiv) in HFIP (0.50 mL) at rt was added AcCl (1.42 μL, 0.0200 mmol, 0.20 equiv) under nitrogen atmosphere in a one dram vial. The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. Aliquots (50 μL) were withdrawn using a micropipette at different time points into sample vials and concentrated under nitrogen gas. The residues were diluted with 0.50 mL of

$CDCl_3$ and transferred into NMR tubes and ^1H NMR integrations were used to determine the conversion ratio.

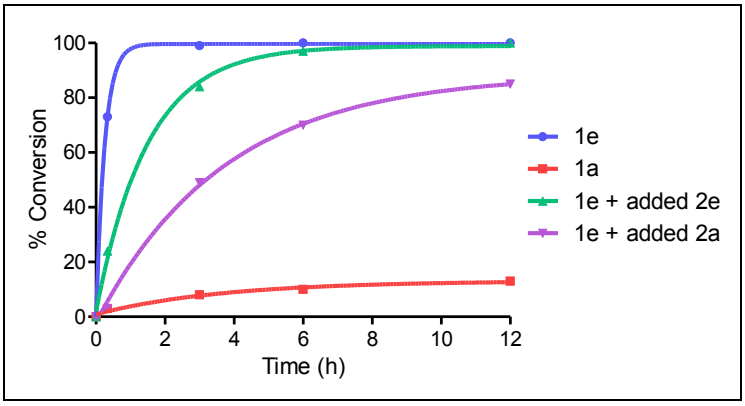
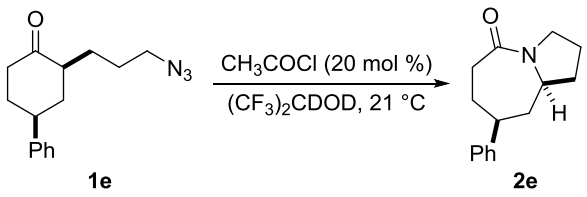


Figure 7. Nonlinear regression analysis for relative reaction rates for **1e** and **1a** (competition experiment), **1e** with 1 equiv of **2e** added at the outset of the reaction (product inhibition experiment with added **2e**), and **1e** with 1 equiv of **2a** added at the outset of the reaction (product inhibition experiment with added **2a**). The curve fitting for the competiton experiment (shown in blue line) gives the impression that the complete conversion of **1e** to **2e** occurred in 1 h, since no data were collected at time points between 20 min and 3 h. However, complete conversion may have occurred in ca. 3 h (cf. Figure 8).



Experimental Procedure for the Determination of the Reaction Rate for 1e in HFIP-d_2 (Figure 8). A solution of cis azido ketone **1e** (0.0257 mg, 0.100 mmol, 1.0 equiv) in HFIP-d_2 (0.50 mL) in a nitrogen-flushed vial at rt was added AcCl (1.4 μL, 0.020 mmol, 0.20 equiv) and the pale yellow solution was transferred to the NMR tube after 2 min. ^1H

NMR data were collected at different time points (The cap of the NMR tube was opened after every NMR experiment to release the nitrogen gas). ^{1}H NMR integrations were used to determine the conversion ratio. The graph was plotted using Microsoft Excel 2010 software.

time (h)	% conversion to **2e**	% remaining of **1e**
0	0	100
0.17	58	42
0.5	76	24
1	88	12
2	95	5
4	>98	<2
6	>99	<1

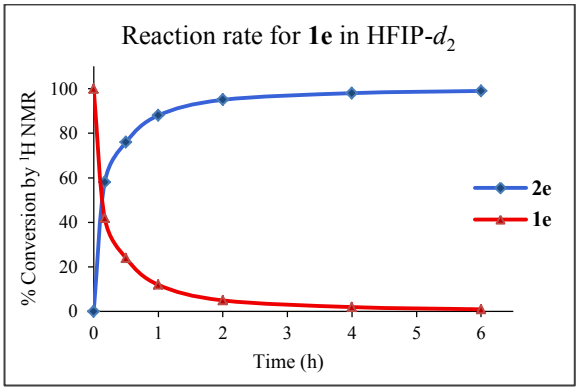
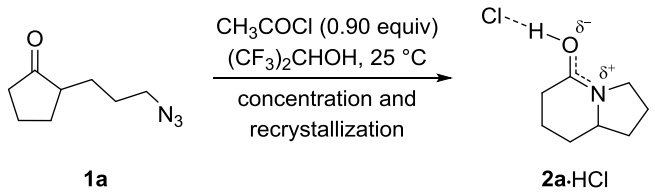
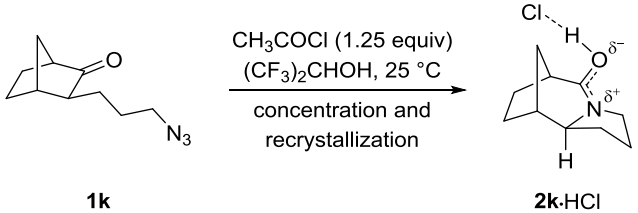


Figure 8. Reaction rate for **1e** in HFIP-d_2 (blue line represents the % conversion to **2e** and red line represents the % remaining of **1e**).



1a **2a**·HCl

HCl salt of Hexahydroindolizin-5(1*H*)-one (2a·HCl; Scheme 16). To a solution of 2-(3′-azidopropyl)cyclopentanone **1a** (0.0669 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0 mL) in a nitrogen-flushed four dram vial was added AcCl (25.6 μL, 0.360 mmol, 0.90 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas and the pale yellow oily residue obtained was dried under vacuum. Initial recrystallization attempts from CH_2Cl_2–Et_2O mixture failed to give diffractable crystals. Therefore, the sample was concentrated and the resulting solid residue was suspended in EtOAc. The suspension was warmed gently and CH_2Cl_2 was added drop wise to obtain a clear solution. The vial was sealed with a septum and pierced with a hollow needle for slow evaporation of solvents at rt. After 24 h, colorless plate-like crystals obtained were used for single-crystal X-ray analysis (see Table S14). For **2a**·HCl: Crude ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 1H), 1.46 (qd, J = 12.2, 7.2 Hz, 1H), 1.70 (m, 1H), 1.80 (m, 1H), 1.91–2.02 (m, 2H), 2.12–2.20 (m, 2H), 2.47 (m, 1H), 2.68 (dd, J = 19.0, 6.4 Hz, 1H), 3.46–3.56 (complex, 3H), 10.67 (br s, 1H).



1k **2k**·HCl

HCl salt of (6*S*,9*R*,9a*S*)-*rel*-Hexahydro-1*H*-6,9-methanopyrrolo[1,2-*a*]azepin-5(6*H*)-one (2k·HCl; Scheme 16). To a solution of (1*S*,3*S*,4*R*)-*rel*-3-(3′-azidopropyl)bicyclo[2.2.1]heptan-2-one **1k** (0.0773 g, 0.400 mmol, 1.0 equiv) in HFIP (2.0

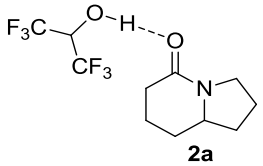
mL) in a nitrogen-flushed four dram vial was added AcCl (35.6 μL, 0.500 mmol, 1.25 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 32 h. The reaction mixture was concentrated under nitrogen gas and the pale yellow oily residue obtained was dried under vacuum. The resulting solid residue was suspended in EtOAc, followed by a drop wise addition of CH_2Cl_2 to obtain a clear solution upon warming. The solution was left open to the atmosphere at rt for slow evaporation of solvents. After 24 h, colorless plate-like crystals obtained were used for single-crystal X-ray analysis (see Table S14). For **2k**·HCl: Crude ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (m, 1H), 1.54 (m, 1H), 1.58–1.64 (m, 2H), 1.79–2.00 (complex, 6H), 2.48 (apparent t, J = 4.5 Hz, 1H), 3.05 (apparent dd, J = 7.0, 4.2 Hz, 1H), 3.15 (m, 1H), 3.23 (apparent dd, J = 12.2, 4.9 Hz, 1H), 3.73 (m, 1H), 10.11 (br s, 1H); crude ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 28.6, 29.0, 29.6, 31.6, 35.6, 40.5, 44.2, 66.9, 177.8.

Table S14. Selected Crystallographic and Refinement Parameters for Lactam Salts

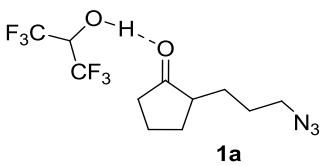
Lactam	**2a**·HCl	**2k**·HCl
Empirical formula	$C_8H_{13}ClNO$	$C_{10}H_{15}ClNO$
Formula wt.	174.64	200.68
Temperature	100(2) K	100(2) K
Crystal system	Triclinic	Orthorhombic
Crystal size (mm^3)	0.10 × 0.03 × 0.01	0.22 × 0.15 × 0.12
Space group	P1	Pna2(1)
a [Å]	7.1423(6)	9.7402(4)
b [Å]	7.1462(7)	14.2950(5)
c [Å]	10.0804(8)	7.3235(3)
α [deg]	95.684(6)	90
β [deg]	97.147(6)	90
γ [deg]	117.026(5)	90
Z	2	4

Lactam	**2a**·HCl	**2k**·HCl
Volume [Å^3]	447.66(7)	1019.70(7)
D*calc* [Mg/m^3]	1.296	1.307
F (000)	186	428
Absorption coefficient μ [mm^{-1}]	3.326	2.991
Theta range for data collection	4.49 to 58.56°	4.54 to 69.62°
Range h	–7<=h<=7	–11<=h<=11
Range k	–6<=k<=7	–13<=k<=16
Range l	–11<=l<=11	–7<=l<=8
Reflections collected	1711	8615
Independent reflections	1101	1633
R_{int}	0.0216	0.0248
Data / Restraints / Parameters	1101 / 12 / 101	1633 / 30 / 118
Final R indices [I>2σ(I)]	0.1491	0.0978
wR_2	0.3958	0.2053
Goodness-of-fit on F^2	1.017	1.014
R-factor (%)	14.91	9.78
Largest diff. peak and hole (e·Å^{-3})	1.110 and –0.585	1.411 and –0.548

Experimental Procedure for Job Plots to Determine the Stoichiometry of Binding using ^{1}H NMR (Figure 9). Commercially purchased HFIP was distilled from sodium carbonate and dried over molecular sieves before use. $CDCl_3$ was passed through basic alumina.



2a



1a

0.10 M stock solutions of HFIP (31.6 μL, 0.300 mmol, 1.0 equiv) and lactam **2a** (41.8 mg, 0.300 mmol, 1.0 equiv) were prepared in 3.0 mL of $CDCl_3$ each. The total

concentration of HFIP and **2a** was kept constant. Eleven NMR samples were prepared with a constant volume of 0.50 mL, where the mole fractions of HFIP and **2a** varied from 0.0 to 1.0 (see Table S15). The Job plot was obtained by plotting the mole fraction multiplied by the change in chemical shifts ($\Delta\delta$) of the hydroxyl proton of HFIP against the mole fraction of HFIP.

Table S15. Mole Fractions and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 2a Complex

HFIP (mmol)	volume of HFIP in NMR tube (mL)	**2a** (mmol)	volume of **2a** in NMR tube (mL)	mole fraction of HFIP (χHFIP)	mole fraction of **2a**	δ of hydroxyl proton	$\Delta\delta$ of hydroxyl proton	(χHFIP)$\Delta\delta$
0.050	0.500	0.000	0.000	1.000	0.000	3.07	0.00	0.000
0.045	0.450	0.005	0.050	0.900	0.100	3.82	0.75	0.675
0.040	0.400	0.010	0.100	0.800	0.200	4.56	1.49	1.192
0.035	0.350	0.015	0.150	0.700	0.300	5.34	2.27	1.589
0.030	0.300	0.020	0.200	0.600	0.400	6.12	3.05	1.830
0.025	0.250	0.025	0.250	0.500	0.500	6.84	3.77	1.885
0.020	0.200	0.030	0.300	0.400	0.600	7.35	4.28	1.712
0.015	0.150	0.035	0.350	0.300	0.700	7.65	4.58	1.374
0.010	0.100	0.040	0.400	0.200	0.800	7.86	4.79	0.958
0.005	0.050	0.045	0.450	0.100	0.900	7.99	4.92	0.492
0.000	0.000	0.050	0.500	0.000	1.000	0.00	0.00	0.000

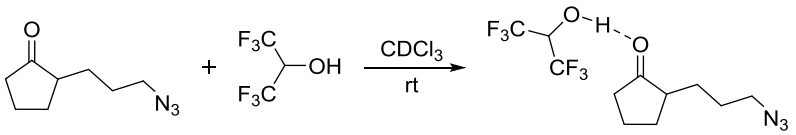
In a similar way as described above for **2a**, 0.10 M stock solutions of HFIP (31.6 μL, 0.300 mmol, 1.0 equiv) and azido ketone **1a** (50.2 mg, 0.300 mmol, 1.0 equiv) were prepared in 3.0 mL of $CDCl_3$ each and the Job plot was generated (see Table S16).

Table S16. Mole Fractions and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 1a Complex

HFIP (mmol)	volume of HFIP in NMR tube (mL)	**1a** (mmol)	volume of **1a** in NMR tube (mL)	mole fraction of HFIP (χHFIP)	mole fraction of **1a**	δ of hydroxyl proton	$\Delta\delta$ of hydroxyl proton	(χHFIP)$\Delta\delta$
0.050	0.500	0.000	0.000	1.000	0.000	3.19	0.00	0.000
0.045	0.450	0.005	0.050	0.900	0.100	3.31	0.12	0.108
0.040	0.400	0.010	0.100	0.800	0.200	3.47	0.28	0.224
0.035	0.350	0.015	0.150	0.700	0.300	3.63	0.44	0.308
0.030	0.300	0.020	0.200	0.600	0.400	3.79	0.60	0.360
0.025	0.250	0.025	0.250	0.500	0.500	3.93	0.74	0.370
0.020	0.200	0.030	0.300	0.400	0.600	4.08	0.89	0.356
0.015	0.150	0.035	0.350	0.300	0.700	4.19	1.00	0.300
0.010	0.100	0.040	0.400	0.200	0.800	4.31	1.12	0.224
0.005	0.050	0.045	0.450	0.100	0.900	4.43	1.24	0.124
0.000	0.000	0.050	0.500	0.000	1.000	0.00	0.00	0.000

General Procedure C for NMR Titration Experiments for the Determination of K_a for Hydrogen-Bonded Complexes of HFIP with Azido Ketones and Lactams (Figures 11–14 and Table 8). 21.1 μL (0.200 mmol) of HFIP (host) was diluted with 10 mL $CDCl_3$ (contains TMS as an internal standard) to give a stock solution **A** (concentration of HFIP is 20 mM or 0.020 M). A measured amount of an azido ketone or a lactam (guest) was dissolved in a specified amount of stock solution **A** to give a stock solution **B**. Depending on the experiments, 10 or 11 NMR tubes were used. The first NMR tube contained only stock solution **A** and the last NMR tube contained only stock solution **B**. Increasing amounts of stock solution **B** was added from second to penultimate NMR tubes. To maintain the HFIP concentration constant throughout the experiment, the final volume

in the NMR tube to 0.60 mL was made with stock solution **A** (0.60 mL of stock solution contained 0.012 mmol of HFIP, which is present in each NMR tube). The solution was properly mixed in the NMR tube and ^{1}H NMR was recorded. The change in the chemical shift (δ) for the hydroxyl proton of HFIP was measured for each sample. The absolute value of $\Delta\delta$, which is a measured change in chemical shift (upon addition of guest species) referenced to that of the uncomplexed host, i.e., δ value obtained for the first NMR sample containing only stock solution **A**. The absolute value of the measured chemical shift change ($\Delta\delta$) was plotted against the concentration of the guest compound using one site specific binding model in GraphPad Prism. The value of dissociation constant (K_d) was obtained from which the values of association constant (K_a) and hydrogen-bond basicity constant (pK_{HB} or pK_a which is equal to $\log_{10}K_a$) were calculated.



1a **1a**–HFIP complex

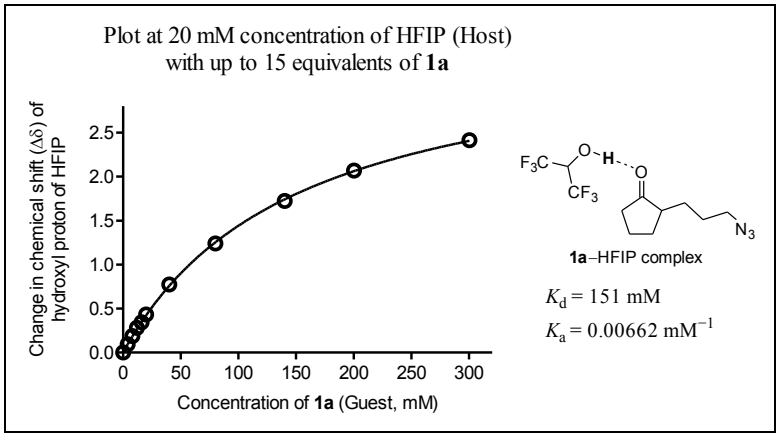
NMR Titration of HFIP at 20 mM Concentration with Azido Ketone 1a (11 Titration Points). Following the general procedure **C**, 21.1 μL (0.200 mmol) of HFIP was diluted with 10 mL $CDCl_3$ to give a stock solution **A** (concentration of HFIP is 20 mM or 0.020 M). 82.4 mg (0.493 mmol) of **1a** was dissolved in 1.64 mL (no volume was accounted for 82.4 mg of **1a**) of stock solution **A** to give a corresponding stock solution **B** (concentration of **1a** is 300 mM or 0.300 M). The titration was carried out by preparing a series of 11 different concentrations (see Table S17 below), where increasing amounts of **1a** as stock solution **B** was added up to 15 equiv in to individual NMR tubes. The final volume was maintained at 0.60 mL with stock solution **A** (0.60 mL of stock solution

contained 0.012 mmol of HFIP). ^{1}H NMR were recorded and a titration curve was obtained from GraphPad Prism.

Table S17. Concentrations, Dilution Volumes, and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 1a Complex (11 Dilutions)

NMR tube	dilution factor (equiv of **1a**)*	**1a** (mmol)	amount of **1a** (mg)	volume of stock **B** (μL)	dilution volume of stock **A** (μL)	concn of **1a** (mM)	δ of hydroxyl proton	$\Delta\delta$
1 (stock **A**)	0.00	0.00	0.00	0.00	600	0.000	2.959	0.000
2	0.20	0.0024	0.400	8.00	592	4.004	3.053	0.0940
3	0.40	0.0048	0.800	16.0	584	8.008	3.146	0.187
4	0.60	0.0072	1.21	24.0	576	12.01	3.241	0.282
5	0.80	0.0096	1.61	32.0	568	16.02	3.304	0.345
6	1.0	0.012	2.01	40.0	560	20.02	3.391	0.432
7	2.0	0.024	4.02	80.0	520	40.04	3.732	0.773
8	4.0	0.048	8.03	160	440	80.09	4.200	1.241
9	7.0	0.084	14.1	280	320	140.2	4.682	1.723
10	10	0.12	20.1	400	200	200.2	5.027	2.068
11 (stock **B**)	15	0.18	30.1	600	0.00	300.3	5.372	2.413

*Dilution factor is the number of equiv of **1a** to 1 equiv of HFIP (0.012 mmol of HFIP is present in 0.60 mL).

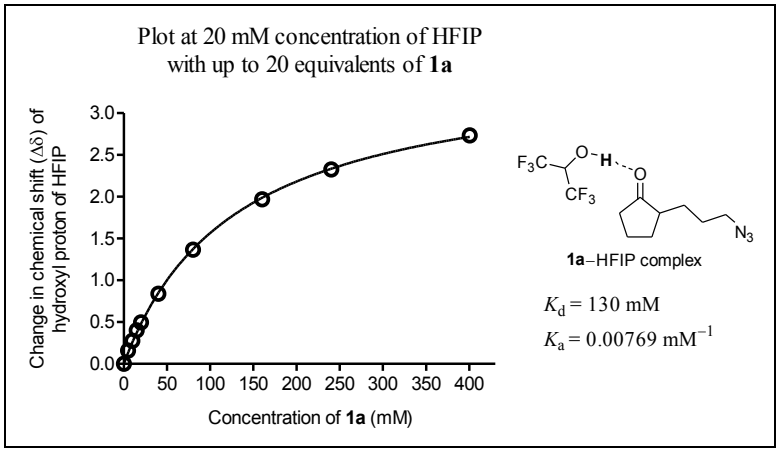


One site – Specific binding	
Best-fit values	
B_{max}	3.616
K_d	151 mM (0.151 M)
K_a	0.00662 mM^{-1} (6.62 M^{-1})
pK_a	0.821
Standard error	
B_{max}	0.03491
K_d	3.030 mM
95% Confidence intervals	
B_{max}	3.537 to 3.695
K_d	144.0 to 157.7 mM
Goodness of fit	
Degrees of freedom	9
R^2	0.9998
Absolute sum of squares	0.001120
Number of points	
Analyzed	11

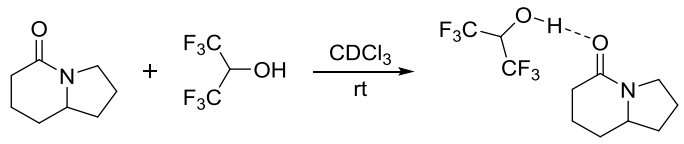
NMR Titration of HFIP at 20 mM Concentration with Azido Ketone 1a (10 Titration Points). Following the general procedure **C**, 21.1 μL (0.200 mmol) of HFIP was diluted with 10 mL $CDCl_3$ to give a stock solution **A** (concentration of HFIP is 20 mM or 0.020 M). 97.4 mg (0.583 mmol) of **1a** was dissolved in 1.375 mL of stock solution **A** to give 1.455 mL (ca. 80 μL was accounted for 97.4 mg of **1a** since density was unknown) of a corresponding stock solution **B** (concentration of **1a** is 400 mM or 0.400 M). The titration was carried out by preparing a series of 10 different concentrations (see Table S18 below), where increasing amounts of **1a** as stock solution **B** was added up to 20 equiv in to individual NMR tubes. The final volume was maintained at 0.60 mL with stock solution **A**. ^{1}H NMR were recorded and a titration curve was obtained from GraphPad Prism.

Table S18. Concentrations, Dilution Volumes, and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 1a Complex (10 Dilutions)

NMR tube	dilution factor (equiv of **1a**)	**1a** (mmol)	amount of **1a** (mg)	volume of stock **B** (μL)	dilution volume of stock **A** (μL)	concn of **1a** (mM)	δ of hydroxyl proton	$\Delta\delta$
1 (stock **A**)	0.00	0.00	0.00	0.00	600	0.000	2.888	0.000
2	0.25	0.0030	0.500	7.50	592.5	5.005	3.047	0.159
3	0.50	0.0060	1.00	15.0	585	10.01	3.165	0.277
4	0.75	0.0090	1.51	22.5	577.5	15.02	3.289	0.401
5	1.0	0.012	2.01	30.0	570	20.02	3.384	0.496
6	2.0	0.024	4.02	60.0	540	40.04	3.727	0.839
7	4.0	0.048	8.03	120	480	80.09	4.254	1.366
8	8.0	0.096	16.1	240	360	160.2	4.856	1.968
9	12	0.14	24.1	360	240	240.3	5.215	2.327
10 (stock **B**)	20	0.24	40.2	600	0.00	400.4	5.622	2.734



One site – Specific binding	
Best-fit values	
B_{max}	3.596
K_d	130 mM (0.130 M)
K_a	0.00769 mM^{-1} (7.69 M^{-1})
pK_a	0.886
Standard error	
B_{max}	0.04059
K_d	3.536
95% Confidence intervals	
B_{max}	3.503 to 3.690
K_d	121.6 to 137.9
Goodness of fit	
Degrees of freedom	8
R^2	0.9997
Absolute sum of squares	0.002903
Number of points	
Analyzed	10



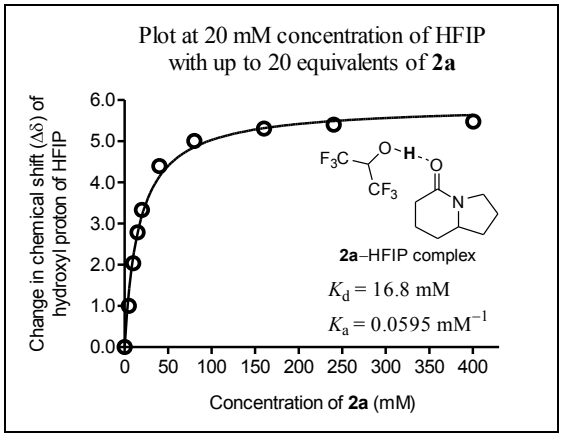
2a **2a**–HFIP complex

NMR Titration of HFIP at 20 mM Concentration with Lactam 2a (10 Titration Points). Following the general procedure **C**, 21.1 μL (0.200 mmol) of HFIP was diluted with 10 mL $CDCl_3$ to give a stock solution **A** (concentration of HFIP is 20 mM or 0.020 M). 81.1 mg (0.583 mmol) of **2a** was dissolved in 1.375 mL of stock solution **A** to give 1.455 mL (ca. 80 μL was accounted for 81.1 mg of **2a** since density was unknown) of a corresponding stock solution **B** (concentration of **2a** is 400 mM or 0.400 M). The titration was carried out by preparing a series of 10 different concentrations (see Table S19 below), where increasing amounts of **2a** as stock solution **B** was added up to 20 equiv in to

individual NMR tubes. The final volume was maintained at 0.60 mL with stock solution **A**. ^{1}H NMR were recorded and a titration curve was obtained from GraphPad Prism.

Table S19. Concentrations, Dilution Volumes, and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 2a Complex (10 Dilutions)

NMR tube	dilution factor (equiv of **2a**)	**2a** (mmol)	amount of **2a** (mg)	volume of stock **B** (μL)	dilution volume of stock **A** (μL)	concn of **2a** (mM)	δ of hydroxyl proton	$\Delta\delta$
1 (stock **A**)	0.00	0.00	0.00	0.00	600	0.000	2.899	0.000
2	0.25	0.0030	0.420	7.50	592.5	5.005	3.900	1.001
3	0.50	0.0060	0.840	15.0	585	10.01	4.937	2.038
4	0.75	0.0090	1.25	22.5	577.5	15.02	5.684	2.785
5	1.0	0.012	1.67	30.0	570	20.02	6.231	3.332
6	2.0	0.024	3.34	60.0	540	40.04	7.296	4.397
7	4.0	0.048	6.69	120	480	80.09	7.908	5.009
8	8.0	0.096	13.4	240	360	160.2	8.205	5.306
9	12	0.14	20.1	360	240	240.3	8.301	5.402
10 (stock **B**)	20	0.24	33.4	600	0.00	400.4	8.378	5.479

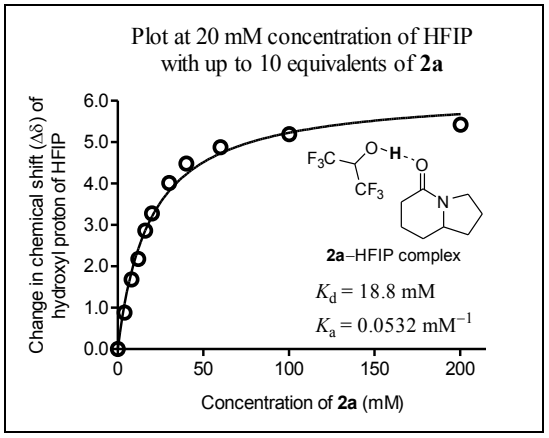


One site – Specific binding	
Best-fit values	
B_{max}	5.874
K_d	16.8 mM (0.0168 M)
K_a	0.0595 mM^{-1} (59.5 M^{-1})
pK_a	1.77
Standard error	
B_{max}	0.1287
K_d	1.458
95% Confidence intervals	
B_{max}	5.577 to 6.171
K_d	13.41 to 20.13
Goodness of fit	
Degrees of freedom	8
R^2	0.9918
Absolute sum of squares	0.2876
Number of points	
Analyzed	10

NMR Titration of HFIP at 20 mM Concentration with Lactam 2a (11 Titration Points). Following the general procedure **C**, 21.1 μL (0.200 mmol) of HFIP was diluted with 10 mL $CDCl_3$ to give a stock solution **A** (concentration of HFIP is 20 mM or 0.020 M). 41.0 mg (0.294 mmol) of **2a** was dissolved in 1.430 mL of stock solution **A** to give 1.470 mL (ca. 40 μL was accounted for 41.0 mg of **2a**) of a corresponding stock solution **B** (concentration of **2a** is 200 mM or 0.200 M). The titration was carried out by preparing a series of 11 different concentrations (see Table S20 below), where increasing amounts of **2a** as stock solution **B** was added up to 10 equiv in to individual NMR tubes. The final volume was maintained at 0.60 mL with stock solution **A**. ^1H NMR were recorded and a titration curve was obtained from GraphPad Prism.

Table S20. Concentrations, Dilution Volumes, and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 2a Complex (11 Dilutions)

NMR tube	dilution factor (equiv of **2a**)	**2a** (mmol)	amount of **2a** (mg)	volume of stock **B** (μL)	dilution volume of stock **A** (μL)	concn of **2a** (mM)	δ of hydroxyl proton	$\Delta\delta$
1 (stock **A**)	0.00	0.00	0.00	0.00	600	0.000	2.850	0.000
2	0.20	0.0024	0.330	12.0	588	4.004	3.733	0.8830
3	0.40	0.0048	0.670	24.0	576	8.008	4.534	1.684
4	0.60	0.0072	1.00	36.0	564	12.01	5.027	2.177
5	0.80	0.0096	1.34	48.0	552	16.02	5.713	2.863
6	1.0	0.012	1.67	60.0	540	20.02	6.128	3.278
7	1.5	0.018	2.51	90.0	510	30.03	6.865	4.015
8	2.0	0.024	3.34	120	480	40.04	7.331	4.481
9	3.0	0.036	5.02	180	420	60.06	7.726	4.876
10	5.0	0.060	8.36	300	300	100.1	8.041	5.191
11 (stock **B**)	10	0.12	16.7	600	0.00	200.2	8.271	5.421



One site – Specific binding	
Best-fit values	
B_{max}	6.210
K_d	18.8 mM (0.0188 M)
K_a	0.0532 mM^{-1} (53.2 M^{-1})
pK_a	1.73
Standard error	
B_{max}	0.1865
K_d	1.709
95% Confidence intervals	
B_{max}	5.788 to 6.632
K_d	14.93 to 22.66
Goodness of fit	
Degrees of freedom	9
R^2	0.9900
Absolute sum of squares	0.3293
Number of points	
Analyzed	11

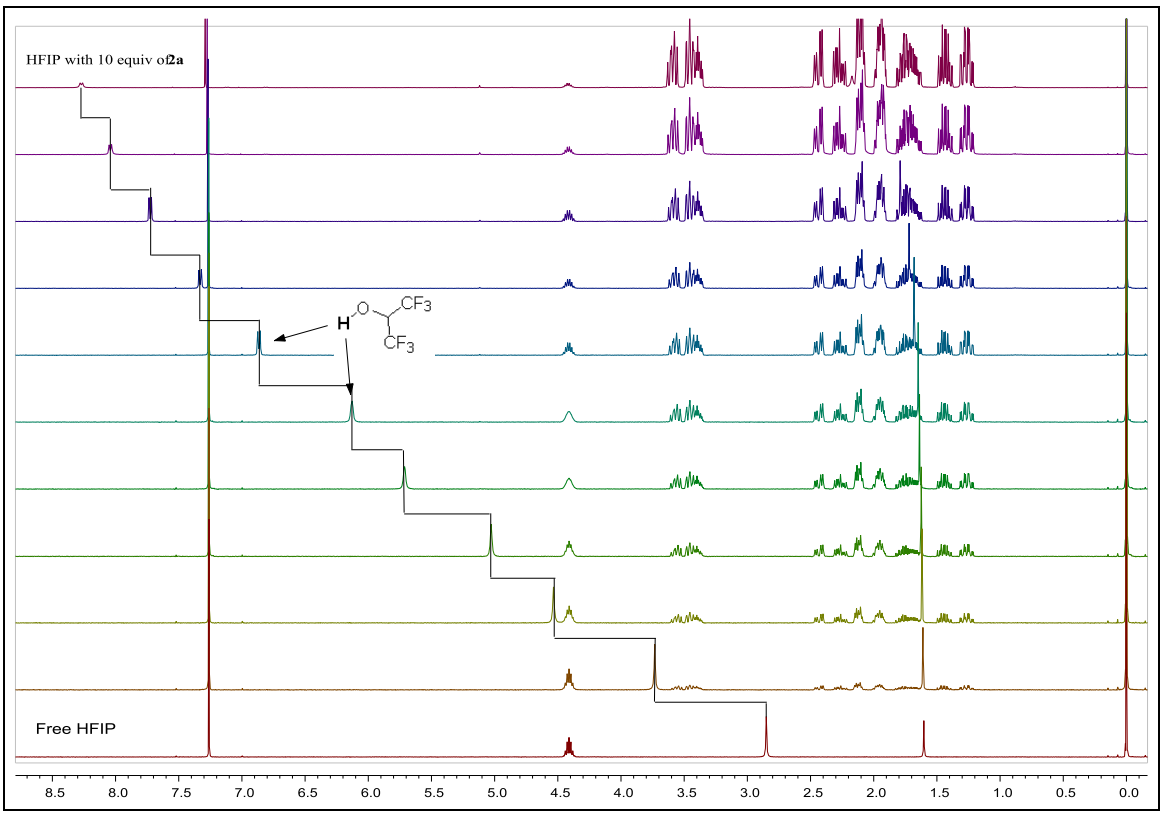
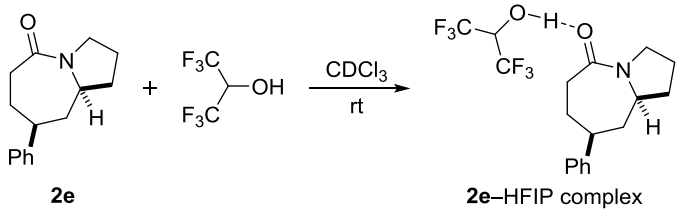


Figure S4. Representative stacked ^{1}H NMR spectra displaying a change in the chemical shift for the hydroxyl proton of HFIP upon titration of HFIP with increasing amounts of lactam **2a**.



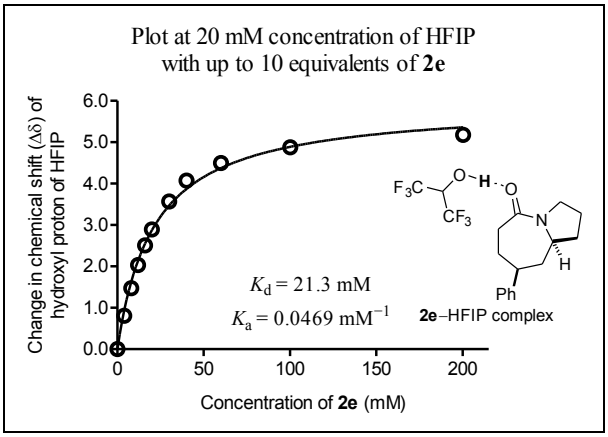
2e **2e**–HFIP complex

NMR Titration of HFIP at 20 mM Concentration with Lactam 2e (11 Titration Points). Following the general procedure **C**, 21.1 μL (0.200 mmol) of HFIP was diluted with 10 mL $CDCl_3$ to give a stock solution **A** (concentration of HFIP is 20 mM or 0.020 M). 67.5 mg (0.294 mmol) of **2e** was dissolved in 1.403 mL of stock solution **A** to give 1.470 mL (ca. 67 μL was accounted for 67.5 mg of **2e**) of a corresponding stock solution **B**

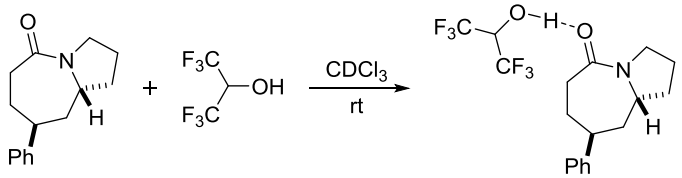
(concentration of **2e** is 200 mM or 0.200 M). The titration was carried out by preparing a series of 11 different concentrations (see Table S21 below), where increasing amounts of **2e** as stock solution **B** was added up to 10 equiv in to individual NMR tubes. The final volume was maintained at 0.60 mL with stock solution **A**. ^{1}H NMR were recorded and a titration curve was obtained from GraphPad Prism.

Table S21. Concentrations, Dilution Volumes, and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 2e Complex

NMR tube	dilution factor (equiv of **2e**)	**2e** (mmol)	amount of **2e** (mg)	volume of stock **B** (μL)	dilution volume of stock **A** (μL)	concn of **2e** (mM)	δ of hydroxyl proton	$\Delta\delta$
1 (stock **A**)	0.00	0.00	0.00	0.00	600	0.000	2.868	0.000
2	0.20	0.0024	0.550	12.0	588	4.004	3.674	0.8060
3	0.40	0.0048	1.10	24.0	576	8.008	4.341	1.473
4	0.60	0.0072	1.65	36.0	564	12.01	4.900	2.032
5	0.80	0.0096	2.20	48.0	552	16.02	5.373	2.505
6	1.0	0.012	2.75	60.0	540	20.02	5.761	2.893
7	1.5	0.018	4.13	90.0	510	30.03	6.436	3.568
8	2.0	0.024	5.51	120	480	40.04	6.941	4.073
9	3.0	0.036	8.26	180	420	60.06	7.367	4.499
10	5.0	0.060	13.8	300	300	100.1	7.744	4.876
11 (stock **B**)	10	0.12	27.6	600	0.00	200.2	8.047	5.179



One site – Specific binding	
Best-fit values	
B_{max}	5.929
K_d	21.3 mM (0.0213 M)
K_a	0.0469 mM^{-1} (46.9 M^{-1})
pK_a	1.67
Standard error	
B_{max}	0.1336
K_d	1.396
95% Confidence intervals	
B_{max}	5.627 to 6.231
K_d	18.14 to 24.46
Goodness of fit	
Degrees of freedom	9
R^2	0.9948
Absolute sum of squares	0.1507
Number of points	
Analyzed	11



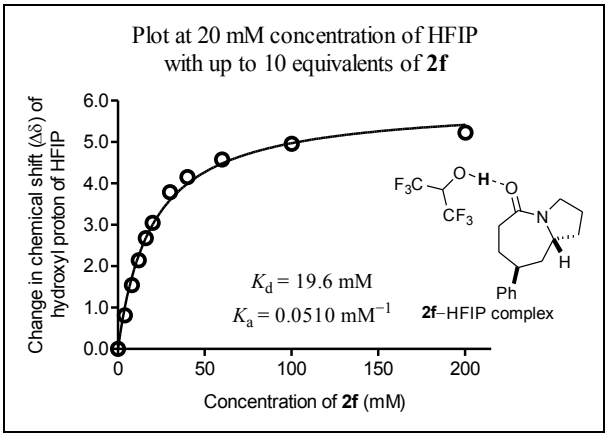
2f **2f**–HFIP complex

NMR Titration of HFIP at 20 mM Concentration with Lactam 2f (11 Titration Points). Following the general procedure **C**, 21.1 μL (0.200 mmol) of HFIP was diluted with 10 mL $CDCl_3$ to give a stock solution **A** (concentration of HFIP is 20 mM or 0.020 M). 67.5 mg (0.294 mmol) of **2f** was dissolved in 1.403 mL of stock solution **A** to give 1.470 mL (ca. 67 μL was accounted for 67.5 mg of **2f**) of a corresponding stock solution **B** (concentration of **2f** is 200 mM or 0.200 M). The titration was carried out by preparing a series of 11 different concentrations (see Table S22 below), where increasing amounts of **2f**

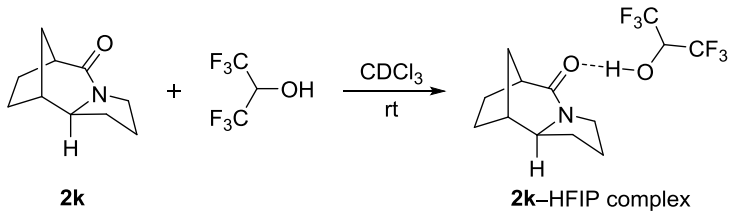
as stock solution **B** was added up to 10 equiv in to individual NMR tubes. The final volume was maintained at 0.60 mL with stock solution **A**. ^{1}H NMR were recorded and a titration curve was obtained from GraphPad Prism.

Table S22. Concentrations, Dilution Volumes, and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 2f Complex

NMR tube	dilution factor (equiv of **2f**)	**2f** (mmol)	amount of **2f** (mg)	volume of stock **B** (μL)	dilution volume of stock **A** (μL)	concn of **2f** (mM)	δ of hydroxyl proton	$\Delta\delta$
1 (stock **A**)	0.00	0.00	0.00	0.00	600	0.000	2.855	0.000
2	0.20	0.0024	0.550	12.0	588	4.004	3.668	0.8130
3	0.40	0.0048	1.10	24.0	576	8.008	4.400	1.545
4	0.60	0.0072	1.65	36.0	564	12.01	5.000	2.145
5	0.80	0.0096	2.20	48.0	552	16.02	5.532	2.677
6	1.0	0.012	2.75	60.0	540	20.02	5.904	3.049
7	1.5	0.018	4.13	90.0	510	30.03	6.643	3.788
8	2.0	0.024	5.51	120	480	40.04	7.005	4.150
9	3.0	0.036	8.26	180	420	60.06	7.433	4.578
10	5.0	0.060	13.8	300	300	100.1	7.811	4.956
11 (stock **B**)	10	0.12	27.6	600	0.00	200.2	8.081	5.226



One site – Specific binding	
Best-fit values	
B_{max}	5.946
K_d	19.6 mM (0.0196 M)
K_a	0.0510 mM^{-1} (51.0 M^{-1})
pK_a	1.71
Standard error	
B_{max}	0.1451
K_d	1.428
95% Confidence intervals	
B_{max}	5.618 to 6.274
K_d	16.36 to 22.82
Goodness of fit	
Degrees of freedom	9
R^2	0.9936
Absolute sum of squares	0.1921
Number of points	
Analyzed	11



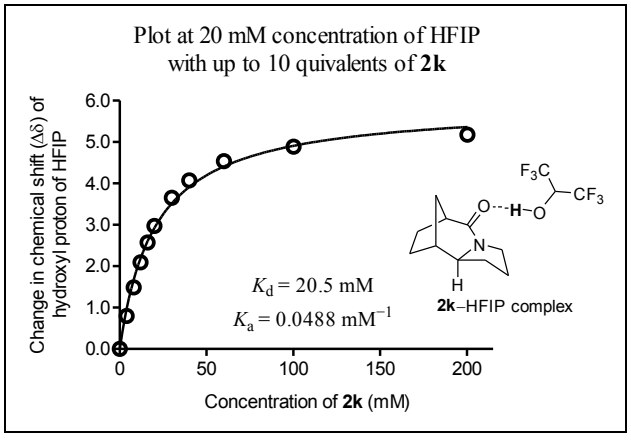
2k **2k**–HFIP complex

NMR Titration of HFIP at 20 mM Concentration with Lactam 2k (11 Titration Points). Following the general procedure **C**, 21.1 μL (0.200 mmol) of HFIP was diluted with 10 mL $CDCl_3$ to give a stock solution **A** (concentration of HFIP is 20 mM or 0.020 M). 48.6 mg (0.294 mmol) of **2k** was dissolved in 1.422 mL of stock solution **A** to give 1.470 mL (ca. 48 μL was accounted for 48.6 mg of **2k**) of a corresponding stock solution **B** (concentration of **2k** is 200 mM or 0.200 M). The titration was carried out by preparing a series of 11 different concentrations (see Table S23 below), where increasing amounts of

2k as stock solution **B** was added up to 10 equiv in to individual NMR tubes. The final volume was maintained at 0.60 mL with stock solution **A**. ^{1}H NMR were recorded and a titration curve was obtained from GraphPad Prism.

Table S23. Concentrations, Dilution Volumes, and Measured Chemical Shift Change ($\Delta\delta$) for HFIP and 2k Complex

NMR tube	dilution factor (equiv of **2k**)	**2k** (mmol)	amount of **2k** (mg)	volume of stock **B** (μL)	dilution volume of stock **A** (μL)	concn of **2k** (mM)	δ of hydroxyl proton	$\Delta\delta$
1 (stock **A**)	0.00	0.00	0.00	0.00	600	0.000	2.877	0.000
2	0.20	0.0024	0.400	12.0	588	4.004	3.673	0.7960
3	0.40	0.0048	0.790	24.0	576	8.008	4.364	1.487
4	0.60	0.0072	1.19	36.0	564	12.01	4.968	2.091
5	0.80	0.0096	1.59	48.0	552	16.02	5.448	2.571
6	1.0	0.012	1.98	60.0	540	20.02	5.851	2.974
7	1.5	0.018	2.98	90.0	510	30.03	6.531	3.654
8	2.0	0.024	3.97	120	480	40.04	6.951	4.074
9	3.0	0.036	5.95	180	420	60.06	7.413	4.536
10	5.0	0.060	9.92	300	300	100.1	7.766	4.889
11 (stock **B**)	10	0.12	19.9	600	0.00	200.2	8.055	5.178



One site – Specific binding	
Best-fit values	
B_{max}	5.911
K_d	20.5 mM (0.0205 M)
K_a	0.0488 mM^{-1} (48.8 M^{-1})
pK_a	1.69
Standard error	
B_{max}	0.1386
K_d	1.413
95% Confidence intervals	
B_{max}	5.598 to 6.225
K_d	17.26 to 23.65
Goodness of fit	
Degrees of freedom	9
R^2	0.9943
Absolute sum of squares	0.1686
Number of points	
Analyzed	11

Experimental Procedures for Section 1.3

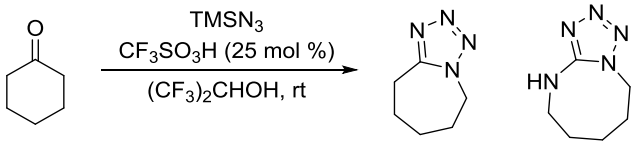
General Procedure for the Optimization of Reaction Conditions for Tetrazole Synthesis (Table 9)

Procedure for Reactions Carried out under Heating at 55 °C. Either to a neat suspension of cyclohexanone **12a** (39.3 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (138 mg, 1.20 mmol, 3.0 equiv) or to a solution of **12a** (0.400 mmol) and $TMSN_3$ (1.20 mmol) in HFIP (1.0 mL) in a nitrogen-flushed microwave reaction vial (2–5 mL capacity) was added catalyst (5–10 mol %). The vial was sealed and the reaction mixture was allowed to stir at 55 °C for 16 h (effervescence due to nitrogen gas evolution was observed upon addition of a catalyst). Reaction mixture was cooled to room temperature, concentrated under nitrogen using a sample concentrator. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification was carried out using a 4 g normal phase silica flash column on a CombiFlash Rf MPLC system with a gradient elution from 0–5% MeOH/CH_2Cl_2 over 50 min. Concentration of appropriate fractions afforded tetrazole **13a**.

Procedure for Reactions Carried out at Room Temperature. Either to a neat suspension of 4-phenylcyclohexanone **12b** (34.9mg, 0.200 mmol, 1.0 equiv) and $TMSN_3$ (57.6mg, 0.500 mmol, 2.5 equiv) or to a solution of **12b** (0.200 mmol) and $TMSN_3$ (1.5–3.0 equiv) in HFIP (0.5 mL) in a nitrogen-flushed two dram vial was added catalyst (10–25 mol %) unless otherwise noted (see Table 9 footnotes). The vial was capped and the reaction mixture was allowed to stir at room temperature for 1–22 h (slight exotherm and effervescence due to nitrogen gas evolution was immediately observed upon addition of a catalyst for a successful reaction). Reaction mixture was concentrated under nitrogen. The residue obtained was diluted with CH_2Cl_2 and loaded on silica gel in a 5 g sample cartridge. Purification was carried out using a 4 g normal phase silica flash column on a CombiFlash

Rf MPLC system with a gradient elution from 0–5% MeOH/CH_2Cl_2 over 30–50 min. Concentration of appropriate fractions afforded products **13b**, **14b**, and **15b**.

General Procedure D for the Synthesis of Tetrazoles from Ketones (Table 10). To a solution of ketone (0.400 mmol, 1.0 equiv) and $TMSN_3$ (1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) in a nitrogen-flushed two dram vial was added TfOH (0.100–0.400 mmol, 0.25–1.0 equiv). The vial was capped and the reaction mixture was allowed to stir at room temperature for 2–22 h (exotherm and brisk effervescence due to nitrogen gas evolution was immediately observed upon addition of TfOH). The reaction mixture was concentrated under nitrogen. The residue obtained was diluted with CH_2Cl_2 (unless otherwise noted) and loaded on a silica gel in a 5 g sample cartridge. Purification was carried out using a 4 or 12 g normal phase silica flash column on a CombiFlash Rf MPLC system with a gradient elution from 0–5% MeOH/CH_2Cl_2 over 50 min (unless otherwise noted). Concentration of appropriate fractions afforded products. In most cases, recrystallization of products from solvents afforded after solvent evaporation, plate-like crystals or crystalline solids, which were utilized for determining melting point, and in two cases for acquiring single-crystal X-ray diffraction data. Unreacted starting materials (ketones) were not recovered in few cases where reaction did not go to completion.

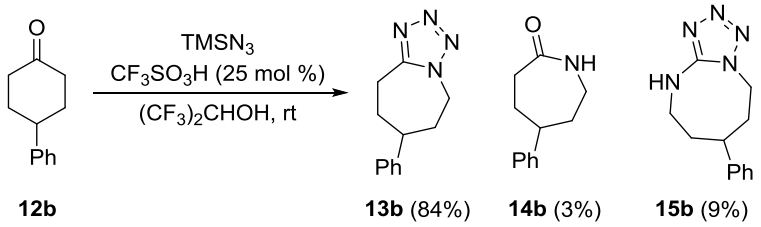


12a **13a** (91%) **15a** (4%)

6,7,8,9-Tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine (13a)[127] **and 4,5,6,7,8,9-Hexahydrotetrazolo[1,5-*a*][1,3]diazocine (15a).** Following the general procedure **D**, a solution of cyclohexanone **12a** (39.3 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg,

1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (8.90 μL, 0.100 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded tetrazole **13a** (eluted between 1.2–2.7% MeOH/CH_2Cl_2) as a colorless partially crystalline semisolid (50.3 mg, 0.364 mmol, 91% yield) and aminotetrazole **15a** (eluted between 3.4–3.5% MeOH/CH_2Cl_2) as a colorless waxy solid (2.5 mg, 0.016 mmol, 4% yield). Recrystallization of **13a** from EtOAc–hexanes mixture under cold conditions afforded after solvent evaporation, colorless plate-like crystals. Tetrazole **13a**: R_f = 0.53 (2% MeOH/CH_2Cl_2, run twice); mp 57–59.5 °C (lit.[77b] mp 57–58 °C and lit.[77g] mp 59 °C).

Aminotetrazole **15a**: R_f = 0.14 (2% MeOH/CH_2Cl_2, run twice); IR (neat) 3263, 1601, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–1.65 (m, 2H), 1.87 (m, 2H), 2.04 (p, J = 6.4 Hz, 2H), 3.57 (q, J = 6.1 Hz, 2H), 4.58 (t, J = 6.5 Hz, 2H), 6.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 28.7, 30.2, 42.2, 46.5, 157.0; HRMS (ESI) *m/z* calcd for $C_6H_{12}N_5$ $[M + H]^+$ 154.1093, found 154.1086.



12b **13b** (84%) **14b** (3%) **15b** (9%)

7-Phenyl-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine (13b), 5-Phenylazepan-2-one (14b),[128] and 7-Phenyl-4,5,6,7,8,9-hexahydrotetrazolo[1,5-*a*][1,3]diazocine (15b). Following the general procedure **D**, a solution of 4-phenylcyclohexanone **12b** (69.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (8.90 μL, 0.100 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on a CombiFlash Rf system

(0–5% MeOH/CH_2Cl_2 over 50 min) afforded tetrazole **13b** (eluted between 1.3–2.6% MeOH/CH_2Cl_2) as a colorless solid (71.7 mg, 0.335 mmol, 84% yield) and an impure mixture of lactam **14b** and aminotetrazole **15b** (eluted between 3.3–3.5% MeOH/CH_2Cl_2) as a colorless solid. The impure mixture of **14b** and **15b** was purified by preparative TLC developing two times with 2% MeOH/CH_2Cl_2 and one time with 60% EtOAc/hexanes. Bands corresponding to **15b** (top band) and **14b** (bottom band) were scraped from the plate and eluted separately with 2% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded **14b** as a colorless solid (2.4 mg, 0.013 mmol, 3% yield) and **15b** as a colorless solid (8.6 mg, 0.038 mmol, 9% yield). Recrystallization of **15b** from CH_2Cl_2–EtOH mixture through slow solvent evaporation afforded colorless fine crystals, which were used for X-ray diffraction analysis (see Table S24). Tetrazole **13b**: R_f = 0.53 (2% MeOH/CH_2Cl_2, run twice); mp 128–130 °C; IR (neat) 1602, 1531, 1244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71 (m, 1H), 1.89 (m, 1H), 2.19–2.28 (m, 2H), 2.84 (ddd, J = 15.5, 12.9, 2.3 Hz, 1H), 2.96 (tt, J = 11.8, 2.4 Hz, 1H), 3.61 (ddd, J = 15.7, 5.8, 1.9 Hz, 1H), 4.20 (m, 1H), 5.01 (ddd, J = 14.6, 5.1, 2.3 Hz, 1H), 7.15 (m, 2H), 7.23 (m, 1H), 7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 32.2, 34.5, 48.2, 48.4, 126.6, 127.1, 129.1, 145.8, 156.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_4$ $[M + H]^+$ 215.1297, found 215.1275.

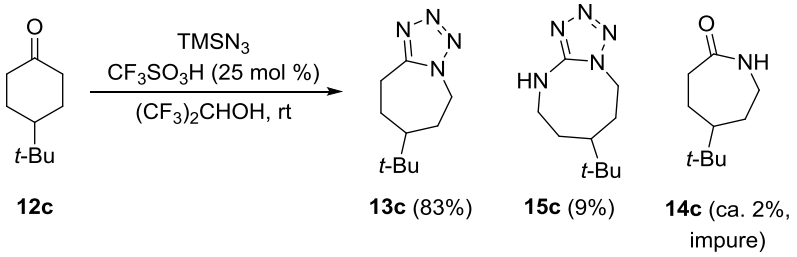
Lactam **14b**: R_f = 0.18 (80% EtOAc/hexanes); mp 193–195 °C (lit.[128] mp 199–200 °C); IR (neat) 3194, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68–1.85 (m, 2H), 1.98–2.04 (m, 2H), 2.53–2.67 (m, 2H), 2.76 (tt, J = 12.1, 3.4 Hz, 1H), 3.26–3.42 (m, 2H), 6.72 (br s, 1H), 7.16–7.23 (m, 3H), 7.29–7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 36.1, 37.6, 42.3, 49.0, 126.7, 126.8, 128.8, 146.5, 178.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}NO$ $[M + H]^+$ 190.1232, found 190.1238.

Aminotetrazole **15b**: R_f = 0.32 (80% EtOAc/hexanes); mp 190–192 °C; IR (neat) 3245, 1624, 1605, 1491 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.02 (ddt, J = 15.5, 12.1, 3.7 Hz, 1H), 2.11 (ddt, J = 16.3, 12.6, 3.8 Hz, 1H), 2.17–2.23 (m, 1H), 2.32–2.40 (m, 1H), 2.86 (tt, J = 12.2, 3.3 Hz, 1H), 3.51 (dtd, J = 15.6, 6.3, 3.5 Hz, 1H), 3.87 (m, 1H), 4.62 (ddd, J = 15.3, 6.0, 3.5 Hz, 1H), 4.75 (m, 1H), 6.65 (t, J = 6.3 Hz, 1H), 7.12 (d, J = 7.3 Hz, 2H), 7.18 (m, 1H), 7.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.7, 38.3, 40.1, 41.6, 46.0, 127.0, 127.1, 129.0, 145.4, 156.8; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}N_5$ $[M + H]^+$ 230.1400, found 230.1391.

Table S24. Selected Crystallographic and Refinement Parameters for 15b

Compound	Aminotetrazole **15b**
Empirical formula	$C_{12}H_{15}N_5$
Formula wt.	229.29
Temperature	100(2) K
Crystal system	Monoclinic
Crystal size (mm^3)	0.28 × 0.17 × 0.01
Space group	$P2_1/c$
a [Å]	5.9910(6)
b [Å]	28.946(3)
c [Å]	7.1474(7)
α [deg]	90
β [deg]	111.950(6)
γ [deg]	90
Z	4
Volume [$Å^3$]	1149.62(19)
D*calc* [Mg/m^3]	1.325
F (000)	488
Absorption coefficient μ [mm^{-1}]	0.680
Theta range for data collection	3.05 to 69.84°
Range h	–6<=h<=7

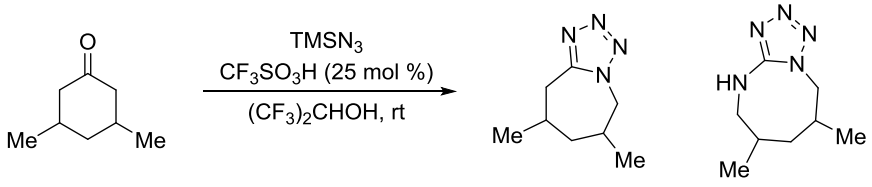
Compound	Aminotetrazole **15b**
Range k	–34<=k<=34
Range l	–8<=l<=8
Reflections collected	8327
Independent reflections	2031
R_{int}	0.0353
Data / Restraints / Parameters	2031 / 62 / 309
Final R indices [I>2σ(I)]	0.0651
wR_2	0.1880
Goodness-of-fit on F^2	1.063
R-factor (%)	6.51
Largest diff. peak and hole (e·Å^{-3})	0.253 and –0.219



7-(*tert*-Butyl)-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine (13c) and 7-(*tert*-Butyl)-4,5,6,7,8,9-hexahydrotetrazolo[1,5-*a*][1,3]diazocine (15c). Following the general procedure **D**, a solution of 4-*tert*-butylcyclohexanone **12c** (61.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (8.9 μL, 0.100 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded tetrazole **13c** (eluted between 1.0–2.4% MeOH/CH_2Cl_2) as a colorless crystalline solid (64.5 mg, 0.332 mmol, 83% yield) and aminotetrazole **15c** (eluted between 2.8–3.0% MeOH/CH_2Cl_2) as a colorless solid (7.6 mg, 0.036 mmol, 9% yield). Recrystallization of **13c** from EtOAc–CH_2Cl_2 mixture afforded colorless, long plate-

like crystals. A small amount (ca. 2%) of impure lactam **14c**[129] was also obtained during this purification but was not completely characterized. Tetrazole **13c**: R_f = 0.39 (2% MeOH/CH_2Cl_2); mp 131–132 °C (lit.[130] mp 132.5–133 °C); IR (neat) 1537, 1476 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.10 (m, 1H), 1.23–1.38 (m, 2H), 2.14–2.24 (m, 2H), 2.58 (ddd, J = 15.4, 12.6, 2.4 Hz, 1H), 3.46 (ddd, J = 15.8, 6.3, 1.9 Hz, 1H), 3.92–3.99 (m, 1H), 4.88 (ddd, J = 14.4, 5.6, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 25.8, 27.7, 28.4, 33.9, 48.5, 52.2, 156.4; HRMS (ESI) *m/z* calcd for $C_{10}H_{19}N_4$ $[M + H]^+$ 195.1610, found 195.1607.

Aminotetrazole **15c**: R_f = 0.12 (2% MeOH/CH_2Cl_2); mp 164–165 °C; IR (neat) 3264 (br), 3071, 1621, 1604, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.22 (m, 1H), 1.44 (m, 1H), 1.60 (m, 1H), 2.09 (m, 1H), 2.29 (m, 1H), 3.33 (m, 1H), 3.71 (m, 1H), 4.50–4.61 (m, 2H), 5.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 30.0, 30.8, 33.6, 43.4, 44.1, 45.8, 157.2; HRMS (ESI) *m/z* calcd for $C_{10}H_{20}N_5$ $[M + H]^+$ 210.1719, found 210.1704.



12d

13d (83% corrected yield)

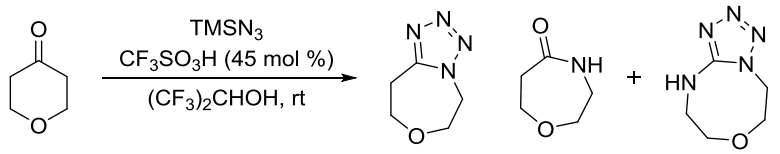
15d (ca. 3%, slightly impure)

6,8-Dimethyl-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine (13d) and 6,8-Dimethyl-4,5,6,7,8,9-hexahydrotetrazolo[1,5-*a*][1,3]diazocine (15d). Following the general procedure **D**, a solution of 3,5-dimethylcyclohexanone **12d**, mixture of isomers, ca. 95% major isomer (50.5 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (8.9 μL, 0.100 mmol, 0.25 equiv). The

reaction mixture was stirred at room temperature for 1.5 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded a mixture of tetrazole isomers, ca. 97% of major isomer **13d** (eluted between 1.0–2.2% MeOH/CH_2Cl_2) as a colorless solid and an impure aminotetrazole **15d** (eluted between 3.0–3.1% MeOH/CH_2Cl_2). Further purification of tetrazole isomers using a 4 g flash column on a CombiFlash Rf system (0–3% MeOH/CH_2Cl_2 over 45 min) afforded a partial separation of major tetrazole isomer **13d** as a colorless crystalline solid and remaining as a mixture of tetrazole isomers (ca. 97% of **13d**) as a colorless solid (**13d**: 55.0 mg, 0.331 mmol, 83% corrected yield). Recrystallization of **13d** from EtOAc afforded large, colorless, rectangular plate-like crystals. Impure aminotetrazole **15d** was purified by preparative TLC developing two times with 3% MeOH/CH_2Cl_2. The band corresponding to **15d** was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded a slightly impure sample of **15d** as a colorless waxy solid film (2.2 mg, 0.012 mmol, ca. 3% yield). Recrystallization of **15d** from EtOAc–CH_2Cl_2 mixture afforded partial recrystallization into colorless, tiny plate-like crystals and an off-white solid film (quantity of **15d** was not sufficient for determining the melting point). Tetrazole **13d**: R_f = 0.38 (2% MeOH/CH_2Cl_2); mp 152–155 °C (lit.[130] mp 156 °C); IR (neat) 1525, 1455, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (dd, J = 8.3, 6.8 Hz, 6H), 1.30 (m, 1H), 1.65–1.76 (m, 1H), 1.77–1.89 (m, 1H), 1.96 (dp, J = 14.2, 2.2 Hz, 1H), 2.48 (dd, J = 15.3, 11.7 Hz, 1H), 3.34 (dt, J = 15.3, 2.0 Hz, 1H), 3.78 (dd, J = 14.2, 11.0 Hz, 1H), 4.72 (dt, J = 14.2, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 24.1, 31.5, 31.7, 33.3, 47.9, 54.7, 155.3; HRMS (ESI) *m/z* calcd for $C_8H_{15}N_4$ $[M + H]^+$ 167.1297, found 167.1306.

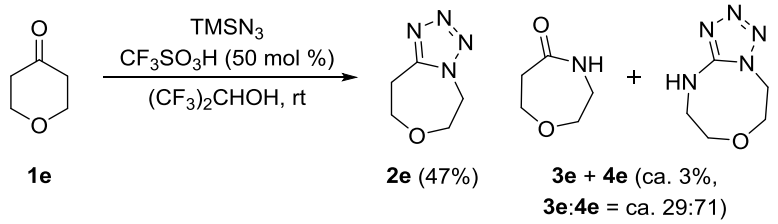
Aminotetrazole **15d**: R_f = 0.10 (2% MeOH/CH_2Cl_2); IR (neat) 3259, 1599, 1385 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, J = 6.6 Hz, 6H), 1.04–1.11 (m, 1H), 1.54 (dt, J =

15.2, 3.6 Hz, 1H), 2.00 (m, 1H), 2.20 (m, 1H), 3.10 (d, J = 15.6 Hz, 1H), 3.91 (dd, J = 15.6, 3.6 Hz, 1H), 4.36 (dd, J = 15.2, 1.6 Hz, 1H), 4.70 (dd, J = 15.2, 4.8 Hz, 1H), 5.79 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.1, 34.3, 34.8, 37.7, 47.5, 51.9 (peak for a quaternary carbon of tetrazole ring was not observed); HRMS (ESI) *m/z* calcd for $C_8H_{16}N_5$ $[M + H]^+$ 182.1406, found 182.1399.



12e **13e** (53%) **14e** + **15e** (ca. 10%, **14e**:**15e** = ca. 66:34; slightly impure)

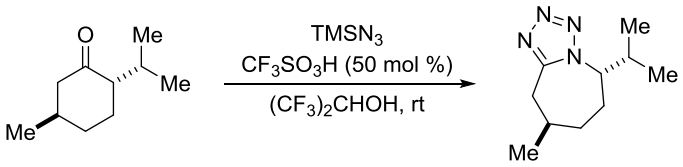
5,6,8,9-Tetrahydrotetrazolo[1,5-*d*][1,4]oxazepine (13e), 1,4-Oxazepan-5-one (14e),[66d] and (5,6,8,9-Tetrahydro-4*H*-tetrazolo[1,5-*d*][1,4,6]oxadiazocine (15e). Following the general procedure **D**, a solution of tetrahydro-4*H*-pyran-4-one **12e** (40.1 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (15.9 μL, 0.180 mmol, 0.45 equiv). The reaction mixture was stirred at room temperature for 2.5 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded tetrazole **13e** (eluted between 1.1–3.1% MeOH/CH_2Cl_2) as a colorless solid (30.0 mg, 0.214 mmol, 53% yield) and a slightly impure mixture of lactam **14e** and aminotetrazole **15e** (eluted between 3.9–4.3% MeOH/CH_2Cl_2) as a colorless solid (for **14e**: ca. 3.4 mg, 0.30 mmol, 7% corrected yield and for **15e**: ca. 1.8 mg, 0.012 mmol, 3% corrected yield; ratio of **14e**:**15e** = ca. 66:34 by ^{1}H NMR).



Similarly, the solution of **12e** (40.1 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (17.7 μL, 0.200 mmol, 0.50 equiv) at room temperature for 1 h. Concentration, followed by quenching with triethylamine (Et_3N) (ca. 0.10 mL), and purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded tetrazole **13e** (eluted between 2.4–2.7% MeOH/CH_2Cl_2) as a colorless solid (26.5 mg, 0.189 mmol, 47% yield) and a mixture of lactam **14e** and aminotetrazole **15e** (eluted between 3.6–3.7% MeOH/CH_2Cl_2, pure fractions only) as a colorless solid (for **14e**: ca. 0.50 mg, 0.0043 mmol, 1% corrected yield and for **15e**: ca. 1.3 mg, 0.0084 mmol, 2% corrected yield; ratio of **14e**:**15e** = ca. 29:71 by ^{1}H NMR). Tetrazole **13e**: R_f = 0.36 (2% MeOH/CH_2Cl_2); mp 157–159 °C; IR (neat) 1530, 1468, 1143 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30 (m, 2H), 3.90 (m, 2H), 3.96 (m, 2H), 4.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 51.4, 68.3, 69.4, 155.5; HRMS (ESI) *m/z* calcd for $C_5H_9N_4O$ $[M + H]^+$ 141.0776, found 141.0787.

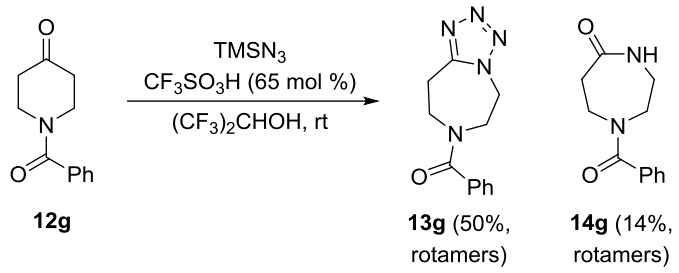
Mixture of lactam **14e** and aminotetrazole **15e** (**14e**:**15e** = ca. 29:71): R_f = 0.31 (4% MeOH/CH_2Cl_2); IR (neat) 3261, 3130, 3074, 1665 (lactam), 1633 (aminotetrazole), 1547 cm^{-1}. For lactam **14e** in a mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72 (m, 2H), 3.35 (m, 2H), 3.77 (m, 2H), 3.81 (m, 2H), 6.14 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.1, 45.0, 65.7, 71.8, 177.5; HRMS (ESI) *m/z* calcd for $C_5H_{10}NO_2$ $[M + H]^+$ 116.0712, found 116.0711. For aminotetrazole **15e** in a mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54 (apparent q, J = 5.2 Hz, 2H), 3.90 (apparent t, J = 5.0 Hz, 2H), 3.98 (t, J = 5.5 Hz, 2H),

4.61 (t, J = 5.5 Hz, 2H), 5.61 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.3, 47.5, 68.3, 71.2, 157.6; HRMS (ESI) *m/z* calcd for $C_5H_{10}N_5O$ $[M + H]^+$ 156.0885, found 156.0896.



12f **13f** (87%)

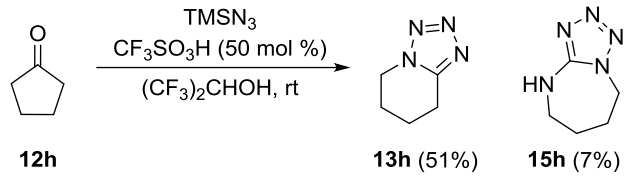
(5*S*,8*R*)-5-Isopropyl-8-methyl-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine (13f).[130-131] Following the general procedure **D**, a solution of purified L-menthone **12f** (61.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (17.7 μL, 0.200 mmol, 0.50 equiv). The reaction mixture was stirred at room temperature for 6 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded a single tetrazole regioisomer **13f** (eluted between 1.1–2.0% MeOH/CH_2Cl_2) as a colorless oil (67.6 mg, 0.348 mmol, 87% yield). Tetrazole **13f**: R_f = 0.50 (2% MeOH/CH_2Cl_2); IR (neat) 2962, 1520, 1459, 1429 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 1.58 (m, 1H), 1.79–1.87 (m, 1H), 1.91–1.99 (m, 1H), 2.05–2.13 (complex, 2H), 2.40 (m, 1H), 3.03 (d, J = 4.1 Hz, 2H), 4.33 (ddd, J = 9.0, 6.1, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 18.9, 19.9, 23.9, 28.6, 28.9, 30.2, 31.6, 65.8, 154.1; HRMS (ESI) *m/z* calcd for $C_{10}H_{19}N_4$ $[M + H]^+$ 195.1610, found 195.1620.



Phenyl(5,6,8,9-tetrahydro-7*H*-tetrazolo[1,5-*d*][1,4]diazepin-7-yl)methanone (13g) (mixture of rotamers) and 1-Benzoyl-1,4-diazepan-5-one (14g)[132] (mixture of rotamers). Following the general procedure **D**, a solution of 1-benzoyl-4-piperidone **12g** (81.3 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (23.0 μL, 0.260 mmol, 0.65 equiv). The reaction mixture was stirred at room temperature for 2.5 h. Purification using a 12 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 45 min) afforded impure tetrazole **13g** as a mixture of rotamers (eluted between 3.5–3.7% MeOH/CH_2Cl_2) and impure lactam **14g** as a mixture of rotamers (eluted between 4.5–4.9% MeOH/CH_2Cl_2). The impure tetrazole **13g** was purified by preparative TLC developing four times with 2% MeOH/CH_2Cl_2. The band corresponding to **13g** was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded **13g** (mixture of rotamers) as a colorless crystalline solid (49.0 mg, 0.201 mmol, 50% yield; ratio of rotamers = 70:30). Recrystallization of **13g** with CH_2Cl_2–MeOH mixture afforded almost colorless, large plate-like crystals. Similarly, the impure lactam **14g** was purified twice by preparative TLC developing three times each with 3% MeOH/CH_2Cl_2. The band corresponding to **14g** was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded **14g** (mixture of rotamers) as a colorless amorphous solid (12.5 mg, 0.0573 mmol, 14% yield; ratio of rotamers = 65:35). Recrystallization of **14g** with CH_2Cl_2 afforded colorless small plate-like crystals.

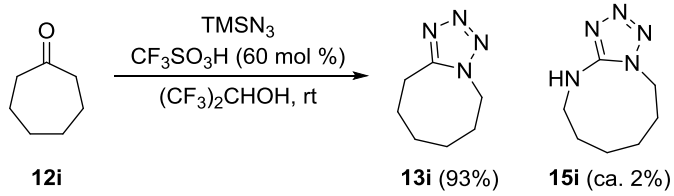
Tetrazole **13g**: R_f = 0.37 (3% MeOH/CH_2Cl_2, run twice); mp 197–199 °C; IR (neat) 1631, 1423, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 3.17 and 3.41 (br s, 2H, rotamers), 3.72 and 3.94 (br s, 2H, rotamers), 3.85 and 4.08 (br s, 2H, rotamers), 4.49 and 4.75 (br s, 2H, rotamers), 7.41–7.43(m, 2H), 7.46–7.51 (complex, 3H); ^1H NMR (major rotamer, diagnostic peaks only) δ 3.17 (br s, 1.4 H), 3.72 (br s, 1.4 H), 4.08 (br s, 1.4 H), 4.75 (br s, 1.4 H); ^1H NMR (minor rotamer, diagnostic peaks only) δ 3.41 (br s, 0.6 H), 3.85 (br s, 0.6 H), 3.94 (br s, 0.6 H), 4.49 (br s, 0.6 H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 25.4, 27.0, 43.4, 45.3, 47.6, 49.3, 49.9, 50.8, 126.8, 129.2, 130.6, 135.1, 154.6, 155.5, 171.9; ^{13}C NMR (major rotamer, diagnostic peaks only) δ 27.0, 45.3, 47.6, 49.9, 154.6; ^{13}C NMR (minor rotamer, diagnostic peaks only) δ 25.4, 43.4, 49.3, 50.8, 155.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_5O$ $[M + H]^+$ 244.1198, found 244.1219.

Lactam **14g**: R_f = 0.15 (3% MeOH/CH_2Cl_2, run twice); mp 170–173 °C, melted slowly above 155 °C; IR (neat) 3280, 1659, 1626, 1433, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 2.59 and 2.75 (br s, 2H, rotamers), 3.25 and 3.42 (br s, 2H, rotamers), 3.58 (br s, 2H, rotamers), 3.91 (br s, 2H, rotamers), 6.44 (br s, 1H), 7.37–7.39 (complex, 2H), 7.41–7.45 (complex, 3H); ^1H NMR (major rotamer, diagnostic peaks only) δ 2.59 (br s, 1.3 H), 3.42 (br s, 1.3 H); ^1H NMR (minor rotamer, diagnostic peaks only) δ 2.75 (br s, 0.7 H), 3.25 (br s, 0.7 H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 38.5, 39.4, 40.4, 43.2, 44.1, 45.4, 46.9, 52.1, 127.0, 129.0, 130.2, 135.7, 171.4, 176.4, 177.3; ^{13}C NMR (major rotamer, diagnostic peaks only) δ 39.4, 43.2, 45.4, 46.9, 176.4; ^{13}C NMR (minor rotamer, diagnostic peaks only) δ 38.5, 40.4, 44.1, 52.1, 177.3; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_2O_2$ $[M + H]^+$ 219.1134, found 219.1134.



5,6,7,8-Tetrahydrotetrazolo[1,5-*a*]pyridine (13h)[77g] and 5,6,7,8-Tetrahydro-4*H*-tetrazolo[1,5-*a*][1,3]diazepine (15h). Following the general procedure **D**, a solution of cyclopentanone **12h** (33.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (17.7 μL, 0.200 mmol, 0.50 equiv). The reaction mixture was stirred at room temperature for 6 h. Concentration, followed by quenching with Et_3N (ca. 0.10 mL), and purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded tetrazole **13h** (eluted between 1.9–2.8% MeOH/CH_2Cl_2) as a colorless solid (25.3 mg, 0.204 mmol, 51% yield) and aminotetrazole **15h** (eluted between 3.2–3.4% MeOH/CH_2Cl_2) as a colorless waxy solid film (3.8 mg, 0.027 mmol, 7% yield). Recrystallization of **15h** from CH_2Cl_2 afforded small, almost colorless crystals. Tetrazole **13h**: R_f = 0.32 (2% MeOH/CH_2Cl_2); mp 114–116 °C (lit.[77g] mp 116 °C and lit.[77b] mp 115–116 °C); IR (neat) 1532, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98–2.05 (m, 2H), 2.07–2.14 (m, 2H), 3.02 (t, J = 6.4 Hz, 2H), 4.35 (t, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 20.9, 22.4, 45.7, 152.1; HRMS (ESI) *m/z* calcd for $C_5H_9N_4$ $[M + H]^+$ 125.0827, found 125.0825.

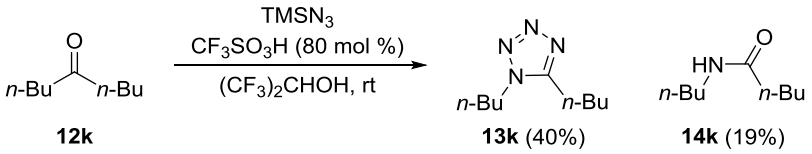
Aminotetrazole **15h**: R_f = 0.26 (4% MeOH/CH_2Cl_2); mp 100–104 °C, melted slowly above 92 °C; IR (neat) 3250, 3063, 1591, 1397 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.92–1.98 (complex, 4H), 3.23 (m, 2H), 4.32 (m, 2H), 5.58 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 29.7, 45.7, 49.0, 159.6; HRMS (ESI) *m/z* calcd for $C_5H_{10}N_5$ $[M + H]^+$ 140.0936, found 140.0940.



5,6,7,8,9,10-Hexahydrotetrazolo[1,5-*a*]azocine (13i)[77g] **and 5,6,7,8,9,10-Hexahydro-4*H*-tetrazolo[1,5-*a*][1,3]diazonine (15i).** Following the general procedure **D**, a solution of cycloheptanone **12i** (44.9 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (21.2 μL, 0.240 mmol, 0.60 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded tetrazole **13i** (eluted between 1.3–2.9% MeOH/CH_2Cl_2) as a colorless waxy solid (56.5 mg, 0.371 mmol, 93% yield) and an impure aminotetrazole **15i** (eluted between 3.2–3.5% MeOH/CH_2Cl_2), which was purified by preparative TLC developing one time with 3% MeOH/CH_2Cl_2 and one time with 60% EtOAc/hexanes. The band corresponding to **15i** was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded **15i** as a colorless solid film (1.1 mg, 0.0066 mmol, ca. 2% yield). Tetrazole **13i**: R_f = 0.34 (2% MeOH/CH_2Cl_2); mp 66.5–68.5 °C (lit.[133] mp 68 °C and lit.[77b] mp 66–67 °C); IR (neat) 1525, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28–1.36 (m, 2H), 1.38–1.46 (m, 2H), 1.84 (m, 2H), 1.91 (m, 2H), 3.01 (m, 2H), 4.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 23.7, 25.0, 29.7, 30.5, 45.8, 155.8; HRMS (ESI) *m/z* calcd for $C_7H_{13}N_4$ $[M + H]^+$ 153.1140, found 153.1140.

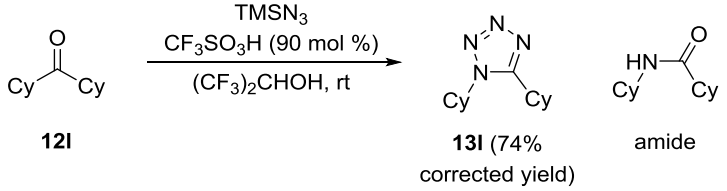
Aminotetrazole **15i**: R_f = 0.14 (2% MeOH/CH_2Cl_2); IR (neat) 3253, 3074, 1616, 1390 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (m, 2H), 1.67 (m, 4H), 1.92 (m, 2H), 3.55 (m, 2H), 4.52 (m, 2H), 5.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 24.2, 30.8, 32.3, 42.4, 47.5, 156.6; HRMS (ESI) *m/z* calcd for $C_7H_{14}N_5$ $[M + H]^+$ 168.1249, found 168.1249.

6,7,8,9,10,11-Hexahydro-5*H*-tetrazolo[1,5-*a*]azonine (13j).[77g] Following the general procedure **D**, a solution of cyclooctanone **12j** (50.5 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (21.2 μL, 0.240 mmol, 0.60 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded tetrazole **13j** (eluted between 1.2–2.7% MeOH/CH_2Cl_2) as a colorless viscous oil (57.5 mg, 0.346 mmol, 86% yield). Tetrazole **13j**: R_f = 0.38 (2% MeOH/CH_2Cl_2); IR (neat) 1520, 1474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25–1.32 (m, 2H), 1.33–1.40 (m, 2H), 1.43–1.49 (m, 2H), 1.85–1.91 (m, 2H), 1.97 (m, 2H), 3.04 (m, 2H), 4.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.5, 25.6, 25.8, 26.4, 28.5, 47.6, 156.3; HRMS (ESI) *m/z* calcd for $C_8H_{15}N_4$ $[M + H]^+$ 167.1297, found 167.1297.



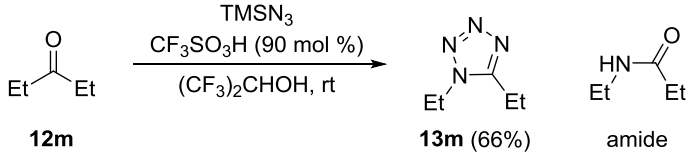
1,5-Dibutyl-1*H*-tetrazole (13k)[134] **and *N*-Butylpentanamide (14k).**[135] Following the general procedure **D**, a solution of 5-nonanone **12k** (56.9 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (28.3 μL, 0.320 mmol, 0.80 equiv). The reaction mixture was stirred at room temperature for 3 h. Purification using a 12 g flash column on a CombiFlash Rf system (0–2% MeOH/CH_2Cl_2 over 45 min) afforded tetrazole **13k** (eluted between 0.4–0.7% MeOH/CH_2Cl_2) as a pale yellow oil and a mixture of **13k** and amide **14k** (eluted between 0.7–1.0% MeOH/CH_2Cl_2;

ca. 41:59 ratio of **13k**:**14k** by ^{1}H NMR) as a pale yellow oil (for **13k**: 29.4 mg, 0.161 mmol, 40% corrected yield and for **14k**: 11.8 mg, 0.0750 mmol, 19% corrected yield). The unreacted 5-nonanone was not isolated during this purification. For amide **14k** in a mixture of **13k** and **14k** (**13k**:**14k** = ca. 41:59 by ^{1}H NMR): R_f = 0.36 (2% MeOH/CH_2Cl_2); IR (neat) 3303, 1648 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, amide **14k**) δ 0.89 (td, J = 7.3, 3.9 Hz, 6H), 1.28–1.38 (complex, 4H, partially obscured by peaks of **13k**), 1.39–1.49 (complex, 2H, partially obscured by peaks of **13k**), 1.59 (m, 2H), 2.14 (t, J = 7.7 Hz, 2H), 3.22 (m, 2H), 5.57 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, amide **14k**) δ 13.9, 14.0, 20.2, 22.6, 28.1, 31.9, 36.8, 39.4, 173.3; HRMS (ESI) *m/z* calcd for $C_9H_{20}NO$ $[M + H]^+$ 158.1545, found 158.1561.



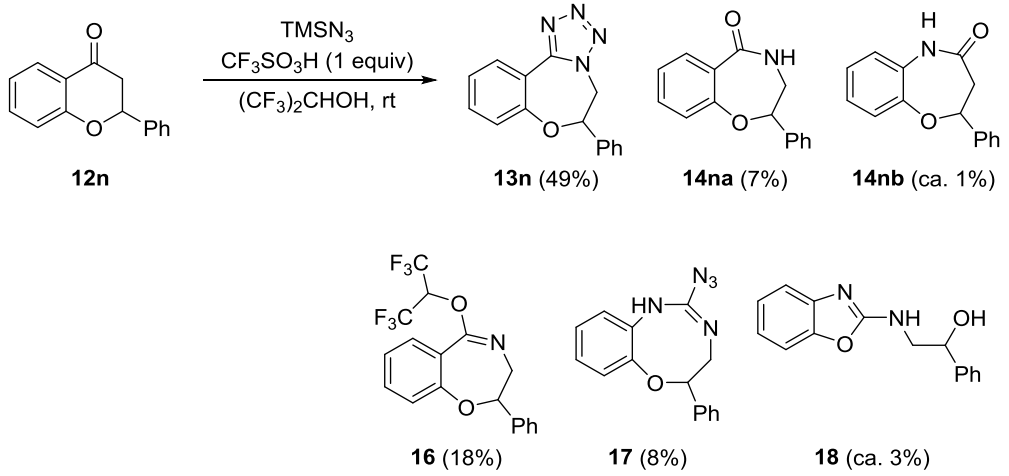
1,5-Dicyclohexyl-1*H*-tetrazole (13l).[136] Following the general procedure **D**, a solution of dicyclohexylketone **12l** (77.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (31.9 μL, 0.360 mmol, 0.90 equiv). The reaction mixture was stirred at room temperature for 6 h. Concentration, followed by quenching with Et_3N (ca. 0.050 mL), and purification using a 12 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 55 min) afforded tetrazole **13l** (eluted between 1.0–1.2% MeOH/CH_2Cl_2) as a colorless crystalline solid, followed by a mixture of **13l** and an unidentified byproduct (eluted between 1.2–1.9% MeOH/CH_2Cl_2; ca. 88:12 ratio of **13l**:byproduct by ^{1}H NMR), and an impure mixture of **13l** and byproduct (eluted between 1.9–2.6% MeOH/CH_2Cl_2). Further purification of the impure mixture of

13l and byproduct using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 25 min) afforded **13l** with a trace amount of byproduct (eluted between 2.4–3.2% MeOH/CH_2Cl_2) as a colorless solid (for **13l**: 69.8 mg, 0.298 mmol, 74% corrected overall yield) and an impure mixture of byproduct with a little bit of **13l** (eluted between 3.2–3.4% MeOH/CH_2Cl_2). Subsequent purification of the impure mixture in order to obtain an analytically pure sample of byproduct for characterization was unsuccessful. HRMS of a mixture of **13l** and byproduct showed molecular ion peaks $[M + H]^+$ for both **13l** and amide (for amide: HRMS (ESI) *m/z* calcd for $C_{13}H_{24}NO$ $[M + H]^+$ 210.1858, found 210.1828). The byproduct could not be confirmed as amide due to lack of complete spectroscopic data. The unreacted dicyclohexylketone was not isolated during this purification. Tetrazole **13l**: R_f = 0.56 (2% MeOH/CH_2Cl_2); mp 173–177 °C (lit.[136] mp 179.5–180 °C); IR (neat) 2928, 1501, 1450, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 1.27–1.48 (complex, 6H), 1.70–1.80 (complex, 4H), 1.85–2.08 (complex, 10H), 2.75 (tt, J = 11.6, 3.5 Hz, 1H), 4.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.57, 25.63, 26.1, 31.6, 33.4, 33.7, 57.5, 157.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{23}N_4$ $[M + H]^+$ 235.1923, found 235.1904.



1,5-Diethyl-1*H*-tetrazole (13m).[77b,137] Following the general procedure **D**, a solution of 3-pentanone **12m** (34.5 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (31.9 μL, 0.360 mmol, 0.90 equiv). The reaction mixture was stirred at room temperature for 6 h. Concentration, followed by quenching with Et_3N (ca. 0.050 mL), and purification using a 12 g flash column on a

CombiFlash Rf system (0–10% MeOH/CH_2Cl_2 over 55 min) afforded tetrazole **13m** (eluted between 1.1–1.9% MeOH/CH_2Cl_2) as a pale yellow oily solid (33.6 mg, 0.266 mmol, 66% yield). Tetrazole **13m**: R_f = 0.50 (2% MeOH/CH_2Cl_2); IR (neat) 2985, 1521, 1456, 1426, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.6 Hz, 3H), 1.51 (t, J = 7.3 Hz, 3H), 2.84 (q, J = 7.6 Hz, 2H), 4.28 (q, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 15.1, 16.9, 42.2, 155.5; HRMS (ESI) *m/z* calcd for $C_5H_{11}N_4$ $[M + H]^+$ 127.0984, found 127.0961. A small amount of impure amide was also obtained during this purification.



6-Phenyl-5,6-dihydrobenzo[*f*]tetrazolo[1,5-*d*][1,4]oxazepine (13n),[91a] 2-Phenyl-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (14na),[91a] 2-Phenyl-2,3-dihydrobenzo-[*b*][1,4]oxazepin-4(5*H*)-one (14nb),[91a] 5-((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)-2-phenyl-2,3-dihydrobenzo[*f*][1,4]oxazepine (16), (*E*)-2-Azido-5-phenyl-4,5-dihydro-1H-benzo[*b*][1,4,6]oxadiazocine (17), and 2-(Benzo[*d*]oxazol-2-ylamino)-1-phenylethan-1-ol (18; Scheme 19). Following the general procedure **D**, a solution of flavanone **12n** (89.7 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (35.4 μL, 0.400 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under nitrogen gas; the

residue obtained was diluted with hexanes–CH_2Cl_2 mixture, and loaded on silica gel in a 5 g sample cartridge. Purification using a 12 g flash column on a CombiFlash Rf system (0–90% EtOAc/hexanes over 55 min) afforded iminoether **16** (eluted at 100% hexanes) as a colorless oil (28.1 mg, 0.0722 mmol, 18% yield), tetrazole **13n** (eluted between 3.0–5.0% EtOAc/hexanes) as a colorless amorphous solid (52.0 mg, 0.197 mmol, 49% yield), an impure mixture of guanyl azide **17** and lactam **14nb** (eluted between 15–35% EtOAc/hexanes), and an impure mixture of aminobenzoxazole **18** and lactam **14na** (eluted between 40–60% EtOAc/hexanes). The unreacted flavanone was not isolated during this purification. Recrystallization of **13n** from EtOAc afforded colorless, thick plate-like crystals. The impure mixture of guanyl azide **17** and lactam **14nb** was purified by preparative TLC developing two times with 30% EtOAc/hexanes. Bands corresponding to **17** and **14nb** were scraped from the plate and separately eluted with 1% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded **17** as a pale orange amorphous solid (8.5 mg, 0.030 mmol, 8% yield) and **14nb** as a colorless waxy solid film (1.1 mg, 0.0046 mmol, ca. 1% yield). Recrystallization of **17** from CH_2Cl_2–hexanes mixture afforded colorless, thread-like, fine crystals. Similarly, the impure mixture of aminobenzoxazole **18** and lactam **14na** was purified by preparative TLC developing two times with 40% EtOAc/hexanes. Bands corresponding to **18** and **14na** were scraped from the plate and separately eluted with 2% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded a slightly impure sample of **18** as a colorless waxy solid film (2.8 mg, 0.011 mmol, ca. 3% yield) and **14na** as colorless viscous oil (7.0 mg, 0.029 mmol, 7% yield). Recrystallization of **18** from EtOAc–hexanes mixture afforded partial recrystallization into almost colorless, thin plate-like crystals and a pale brownish residue. Crystals of **18** were utilized for acquiring a single-crystal X-ray diffraction data (see Table S25) and for determining the melting point. Recrystallization of **14na** from CH_2Cl_2

afforded partially crystalline, off-white waxy solid. Tetrazole **13n**: R_f = 0.33 (20% EtOAc/hexanes); mp 124.5–126.5 °C (lit.[77a] mp 136–137 °C and lit.[91a] mp 137–138 °C); IR (neat) 1609, 1484, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (dd, J = 14.6, 9.8 Hz, 1H), 5.12 (dd, J = 14.6, 1.5 Hz, 1H), 5.26 (dd, J = 9.8, 1.3 Hz, 1H), 7.18 (dd, J = 8.3, 1.0 Hz, 1H), 7.26 (m, 1H), 7.44–7.56 (m, 6H), 8.57 (dd, J = 8.0, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 79.1, 113.1, 121.7, 124.2, 126.2, 129.3, 129.4, 130.5, 133.4, 136.5, 152.1, 157.0; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}N_4O$ $[M + H]^+$ 265.1089, found 265.1071.

Lactam **14na**: R_f = 0.34 (50% EtOAc/hexanes); mp 122.5–125.5 °C (lit.[91a] mp 125–126 °C); IR (neat) 3222, 1654, 1603, 1459 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (dt, J = 15.4, 5.8 Hz, 1H), 3.67 (ddd, J = 15.4, 6.2, 3.5 Hz, 1H), 5.46 (dd, J = 6.1, 3.5 Hz, 1H), 6.87 (br s, 1H), 7.09 (dd, J = 8.1, 0.9 Hz, 1H), 7.22 (td, J = 7.5, 1.0 Hz, 1H), 7.34–7.42 (m, 5H), 7.48 (m, 1H), 7.87 (dd, J = 7.8, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.6, 86.0, 122.7, 124.0, 126.1, 126.5, 128.8, 128.9, 131.2, 133.6, 139.2, 154.8, 171.0; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}NO_2$ $[M + H]^+$ 240.1025, found 240.1012.

Lactam **14nb**: R_f = 0.21 (30% EtOAc/hexanes); IR (neat) 3214, 1673, 1597, 1497 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.99 (ddd, J = 14.8, 4.1, 0.8 Hz, 1H), 3.09 (dd, J = 14.8, 8.8 Hz, 1H), 5.66 (dd, J = 8.8, 4.1 Hz, 1H), 6.95–6.98 (m, 1H), 7.05–7.13 (complex, 3H), 7.34–7.44 (complex, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.1, 83.3, 122.1, 123.8, 124.6, 126.2, 126.3, 128.8, 128.9, 130.2, 140.2, 148.4, 171.1; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}NO_2$ $[M + H]^+$ 240.1025, found 240.1039.

Iminoether **16**: R_f = 0.78 (20% EtOAc/hexanes); IR (neat) 1685, 1605, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (dd, J = 15.5, 7.8 Hz, 1H), 4.05 (dd, J = 15.5, 2.2 Hz, 1H), 5.35 (dd, J = 7.8, 2.2 Hz, 1H), 6.51 (hept, J = 6.5 Hz, 1H), 7.16–7.21 (m, 2H), 7.38–7.43 (m, 1H), 7.45 (m, 4H), 7.50 (m, 1H), 7.91 (dd, J = 7.9, 1.6 Hz, 1H); ^{13}C NMR (100 MHz,

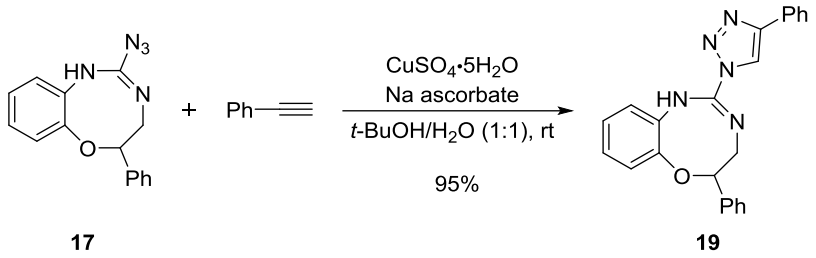
$CDCl_3$) δ 54.9, 66.9 (p, J = 135.1 Hz, 1C), 85.7, 118.2, 120.1, 121.9, 122.7, 122.9, 126.3, 128.5, 128.9, 129.8, 133.7, 139.5, 155.4, 158.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{14}F_6NO_2$ $[M + H]^+$ 390.0929, found 390.0900.

Guanyl azide **17**: R_f = 0.43 (30% EtOAc/hexanes); mp 99.5–101 °C; IR (neat) 3209, 2101, 1643, 1583, 1459 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.62 (dd, J = 14.0, 8.8 Hz, 1H), 3.81 (dd, J = 14.0, 5.1 Hz, 1H), 4.92 (dd, J = 8.8, 5.1 Hz, 1H), 5.46 (br s, 1H), 7.07 (td, J = 7.8, 1.1 Hz, 1H), 7.19 (td, J = 7.7, 1.0 Hz, 1H), 7.27 (m, 1H), 7.36–7.44 (complex, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.4, 65.2, 109.2, 116.8, 121.5, 124.3, 127.3, 129.2, 129.3, 136.7, 142.7, 148.7, 161.5; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}N_5O$ $[M + H]^+$ 280.1198, found 280.1183.

Aminobenzoxazole **18**: R_f = 0.39 (50% EtOAc/hexanes); mp 118–121 °C; IR (neat) 3255, 1647, 1585, 1461 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (dd, J = 14.1, 8.0 Hz, 1H), 3.84 (dd, J = 14.0, 3.4 Hz, 1H), 5.05 (dd, J = 7.9, 3.4 Hz, 1H), 5.45 (br s, 1H), 7.05 (td, J = 7.8, 1.1 Hz, 1H), 7.18 (td, J = 7.7, 1.0 Hz, 1H), 7.24–7.26 (m, 2H), 7.31 (m, 1H), 7.36–7.39 (complex, 3H), 7.42–7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.8, 73.7, 109.1, 116.7, 121.4, 124.3, 126.1, 128.3, 128.9, 141.6, 142.5, 148.8, 162.6; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}N_2O_2$ $[M + H]^+$ 255.1134, found 255.1136.

Table S25. Selected Crystallographic and Refinement Parameters for 18

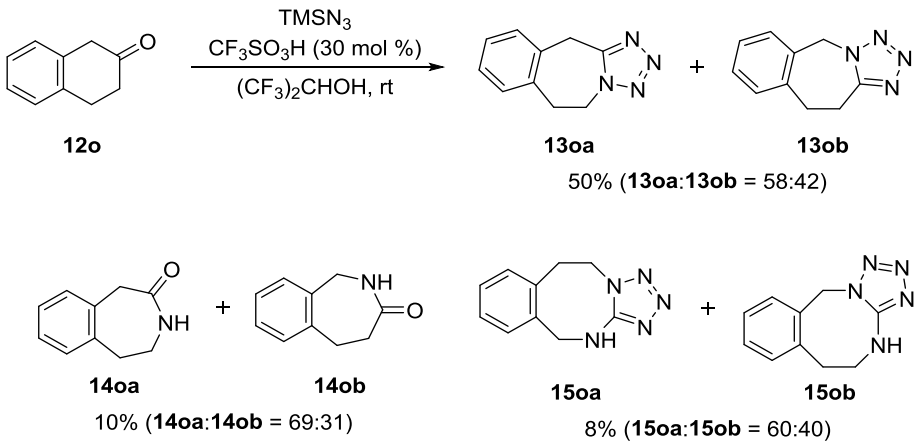
Compound	Aminobenzoxazole **18**
Empirical formula	$C_{15}H_{14}N_2O_2$
Formula wt.	254.28
Temperature	100(2) K
Crystal system	Monoclinic
Crystal size (mm^3)	0.11 × 0.08 × 0.05
Space group	$P2_1/c$
a [Å]	12.8994(7)
b [Å]	10.6296(5)
c [Å]	9.5520(5)
α [deg]	90
β [deg]	99.3230(10)
γ [deg]	90
Z	4
Volume [$Å^3$]	1292.43(11)
D*calc* [Mg/m^3]	1.307
F (000)	536
Absorption coefficient μ [mm^{-1}]	0.715
Theta range for data collection	5.42 to 68.04°
Range h	–15<=h<=15
Range k	–8<=k<=12
Range l	–10<=l<=11
Reflections collected	7865
Independent reflections	2262
R_{int}	0.0178
Data / Restraints / Parameters	2262 / 12 / 248
Final R indices [I>2σ(I)]	0.0501
wR_2	0.1214
Goodness-of-fit on F^2	1.113
R-factor (%)	5.01
Largest diff. peak and hole ($e \cdot Å^{-3}$)	0.265 and –0.162



17 19

(*E*)-5-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-4,5-dihydro-1*H*-benzo[*b*][1,4,6]-oxadiazocine (19; Scheme 21). Following a slight modification of the reported procedure,[138] in a one dram vial, to a clear colorless solution of guanyl azide **17** (4.0 mg, 0.014 mmol, 1.0 equiv) and phenyl acetylene (1.8 mg, 0.017 mmol, 1.2 equiv) in *tert*-butanol and deionized water mixture (0.6 mL, 1:1) was added copper(II) sulfate pentahydrate (3.6 mg, 0.014 mmol, 1.0 equiv) and (+)-sodium L-ascorbate (5.7 mg, 0.029 mmol, 2.0 equiv). The vial was capped and the resulting pale yellowish-blue turbid suspension was stirred at room temperature for 18 h. The reaction mixture was partially concentrated under N_2, diluted with CH_2Cl_2 (1.0 mL), and quenched with NH_4OH solution (five drops). After stirring at room temperature for 5 min, the biphasic mixture was passed through a hydrophobic phase separator tabless, which allowed the CH_2Cl_2 layer to pass through the tabless. The blue aqueous layer was further washed with CH_2Cl_2 (2 × 1 mL) and the CH_2Cl_2 layer was allowed to pass through the tabless. The combined CH_2Cl_2 layers were concentrated and the residue was purified by preparative TLC developing one time with 2% MeOH/CH_2Cl_2. The band corresponding to guanidino triazole **19** was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded **19** as a colorless amorphous solid (5.2 mg, 0.014 mmol, 95% yield). Guanidino triazole **19**: R_f = 0.18 (2% MeOH/CH_2Cl_2); mp 216.5–218.5 °C; IR (neat) 3087, 1668, 1641, 1586, 1459 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 4.31 (dd, J = 14.6, 4.3 Hz, 1H), 4.51 (dd, J = 14.6, 9.9 Hz, 1H), 6.03 (dd, J = 9.8, 4.4 Hz, 1H), 7.04 (t, J

= 7.8 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.30 (m, 1H), 7.34–7.40 (complex, 8H), 7.74–7.76 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 47.1, 64.3, 109.3, 116.5, 121.1, 121.6, 124.3, 125.9, 127.0, 128.6, 129.0, 129.3, 129.4, 130.2, 136.8, 142.2, 148.2, 148.6, 161.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_5O$ $[M + H]^+$ 382.1668, found 382.1647.



6,11-Dihydro-5*H*-benzo[*d*]tetrazolo[1,5-*a*]azepine (13oa),[77d] 10,11-Dihydro-5*H*-benzo[*e*]tetrazolo[1,5-*a*]azepine (13ob),[77d] 1,3,4,5-Tetrahydro-2*H*-benzo[*d*]azepin-2-one (14oa),[139] 1,2,4,5-Tetrahydro-3*H*-benzo[*c*]azepin-3-one (14ob),[140] 4,5,10,11-Tetrahydrobenzo[*e*]tetrazolo[1,5-*a*][1,3]diazocine (15oa), and 4,5,6,11-Tetrahydrobenzo[*f*]-tetrazolo[1,5-*a*][1,3]diazocine (15ob; Scheme 22). Following the general procedure **D**, a solution of purified *β*-tetralone **12o** (58.5 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (10.6 μL, 0.120 mmol, 0.30 equiv). The reaction mixture was stirred at room temperature for 22 h. Purification with a 4 g normal phase silica flash column on a CombiFlash Rf system with a gradient elution from 0–35% EtOAc/hexanes over 60 min afforded tetrazole regioisomer **13oa** (eluted between 25–28% EtOAc/hexanes) as a pale creamish-orange solid, followed by a mixture of tetrazole regioisomers **13oa** and **13ob** (eluted between 28–30% EtOAc/hexanes)

as an off-white solid, and tetrazole regioisomer **13ob** (eluted between 30–32% EtOAc/hexanes) as a creamish solid (combined yield of **13oa** and **13ob**: 37.3 mg, 0.200 mmol, 50% yield; ratio of **13oa**:**13ob** = 58:42). Recrystallization of **13oa** from CH_2Cl_2–hexanes mixture afforded colorless square-shaped, plate-like crystals. Recrystallization of **13ob** from EtOAc afforded colorless plate-like crystals. Continuation with the chromatography by changing to a more polar solvent system (0–5% MeOH/CH_2Cl_2 over 30 min) afforded an impure mixture of lactams **14oa** and **14ob**, and aminotetrazoles **15oa** and **15ob** (eluted between 3.0–3.3% MeOH/CH_2Cl_2) as an orange semisolid. This mixture of four compounds was further purified by preparative TLC developing three times with 70% EtOAc/hexanes. Bands corresponding to aminotetrazoles (high R_f two overlapping bands) and lactams (low R_f two overlapping bands) were scraped from the plate and eluted separately with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration of elutions containing low R_f bands afforded lactam **14oa** as a colorless amorphous solid and a slightly impure mixture of lactams **14oa** and **14ob** as a colorless waxy solid (combined yield of **14oa** and **14ob**: 5.0 mg, 0.031 mmol, 8% yield; ratio of **14oa**:**14ob** = 69:31). Recrystallization of **14oa** from CH_2Cl_2 afforded colorless fine crystals. Concentration of elutions containing high R_f bands afforded a slightly impure aminotetrazole **15oa** as a colorless waxy solid and a mixture of aminotetrazoles **15oa** and **15ob** as a colorless solid (combined yield of **15oa** and **15ob**: 8.0 mg, 0.040 mmol, 10% yield; ratio of **15oa**:**15ob** = 60:40). Recrystallization of **15oa** from CH_2Cl_2–MeOH mixture afforded partial recrystallization into colorless, fine plate-like crystals and an off-white solid film. Tetrazole **13oa**: R_f = 0.42 (50% EtOAc/hexanes); mp 148–151 °C (lit.[77d] mp 156–157 °C); IR (neat) 1525, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.37 (m, 2H), 4.40 (s, 2H), 4.61 (m, 2H), 7.25–7.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 30.5, 49.3, 128.4, 128.9, 129.4,

129.5, 134.5, 137.0, 151.6; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_4$ $[M + H]^+$ 187.0984, found 187.0978.

Tetrazole **13ob**: R_f = 0.32 (50% EtOAc/hexanes); mp 135.5–137 °C (lit.[77d] mp 145–146 °C); IR (neat) 1524, 1417 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.22–3.25 (m, 2H), 3.35–3.38 (m, 2H), 5.63 (s, 2H), 7.27–7.31 (m, 1H), 7.34–7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 29.0, 51.5, 127.9, 129.3, 129.6, 130.3, 132.7, 139.9, 153.1; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_4$ $[M + H]^+$ 187.0984, found 187.0981.

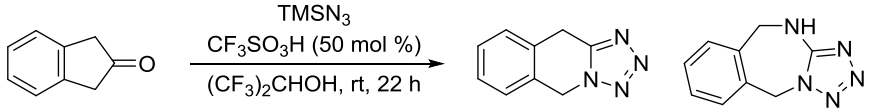
Lactam **14oa**: R_f = 0.39 (70% EtOAc/hexanes, run three times); mp 154–157 °C, melted slowly above 125 °C (lit.[139] mp 159–160 °C); IR (neat) 3176, 1660, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.13 (m, 2H), 3.58 (m, 2H), 3.85 (s, 2H), 6.05 (br s, 1H), 7.11–7.22 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.5, 41.7, 42.7, 127.1, 127.5, 130.0, 130.6, 132.0, 137.0, 173.7; HRMS (ESI) *m/z* calcd for $C_{10}H_{12}NO$ $[M + H]^+$ 162.0919, found 162.0920.

For lactam **14ob** in a mixture of **14oa** and **14ob** (ratio of **14oa**:**14ob** = ca. 14:86 by ^1H NMR): R_f = 0.34 (70% EtOAc/hexanes, run three times); IR (neat, for a mixture) 3247, 1661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, lactam **14ob**) δ 2.82 (m, 2H), 3.11 (m, 2H, partially obscured by peaks of **14oa**), 4.37 (d, J = 5.4 Hz, 2H), 6.38 (br s, 1H), 7.11–7.12 (m, 1H, partially obscured by peaks of **14oa**), 7.16–7.21 (m, 2H, partially obscured by peaks of **14oa**), 7.25–7.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, lactam **14ob**) δ 28.7, 34.6, 46.2, 126.7, 128.4, 128.5, 129.8, 136.1, 139.2, 175.4; HRMS (ESI) *m/z* calcd for $C_{10}H_{12}NO$ $[M + H]^+$ 162.0919, found 162.0929.

Aminotetrazole **15oa**: R_f = 0.67 (70% EtOAc/hexanes, run three times); mp 174–180 °C, melted slowly above 140 °C; IR (neat) 3231, 1585 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.52 (t, J = 6.6 Hz, 2H), 4.51 (s, 2H), 4.78 (t, J = 6.6 Hz, 2H), 5.91 (br s, 1H), 7.14–7.17

(m, 1H), 7.21–7.26 (complex, 3H; partially obscured by solvent peak); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.4, 46.4, 48.6, 128.4, 129.3, 131.0, 131.6, 135.3, 135.9 (peak for a quaternary carbon of tetrazole ring was not observed); HRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_5$ $[M + H]^+$ 202.1093, found 202.1096.

For aminotetrazole **15ob** in a mixture of **15oa** and **15ob** (ratio of **15oa**:**15ob** = ca. 37:63 by ^{1}H NMR): R_f = 0.62 (70% EtOAc/hexanes, run three times); IR (neat, for a mixture) 3246, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, aminotetrazole **15ob**) δ 3.26 (m, 2H), 3.51 (m, 2H, partially obscured by peaks of **15oa**), 5.44 (s, 2H), 5.59 (br s, 1H), 7.18–7.23 (m, 1H, partially obscured by peaks of **15oa**), 7.25–7.34 (m, 2H), 7.45 (dd, *J* = 7.3, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, aminotetrazole **15ob**) δ 36.8, 46.6, 50.1, 128.1, 130.1, 130.8, 131.4, 132.3, 139.7, 157.7 (crossover peaks for the quaternary carbon of the tetrazole ring for **15oa** and **15ob** were observed in HMBC); HRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_5$ $[M + H]^+$ 202.1093, found 202.1088.

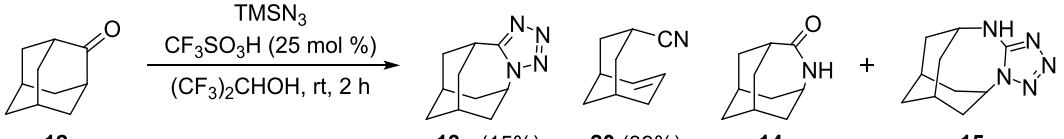


12p **13p** (12%) **15p** (9%)

5,10-Dihydrotetrazolo[1,5-*b*]isoquinoline (13p) and 5,10-Dihydro-4*H*-benzo[*e*]tetrazolo[1,5-*a*][1,3]diazepine (15p; Scheme 22). Following the general procedure **D**, a solution of 2-indanone **12p** (52.9 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (17.7 μL, 0.200 mmol, 0.50 equiv). The reaction mixture was stirred at room temperature for 22 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded impure tetrazole **13p** (eluted between 1.4–2.6% MeOH/CH_2Cl_2) and impure aminotetrazole **15p** (eluted between 3.2–3.5% MeOH/CH_2Cl_2). Subsequent

purification of impure tetrazole **13p** using a 4 g flash column on a CombiFlash Rf system (0–40% EtOAc/hexanes over 35 min) afforded **13p** (eluted between 30–36% EtOAc/hexanes) as a colorless solid (8.4 mg, 0.049 mmol, 12% yield). The impure aminotetrazole **15p** was further purified by preparative TLC developing two times with 2% MeOH/CH_2Cl_2 and one time with 60% EtOAc/hexanes. The band corresponding to **15p** was scraped from the plate and eluted with 2% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded **15p** as a colorless crystalline solid (6.7 mg, 0.036 mmol, 9% yield). Tetrazole **13p**: R_f = 0.43 (2% MeOH/CH_2Cl_2); mp 164–167 °C; IR (neat) 1544, 1500, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.41 (t, J = 2.6 Hz, 2H), 5.63 (t, J = 2.5 Hz, 2H), 7.35–7.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 48.0, 127.0, 127.6, 128.2, 128.6, 128.9, 129.5, 150.9; HRMS (ESI) *m/z* calcd for $C_9H_9N_4$ $[M + H]^+$ 173.0827, found 173.0857.

Aminotetrazole **15p**: R_f = 0.14 (2% MeOH/CH_2Cl_2); mp 177–180 °C; IR (neat) 3245, 1611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.55 (d, J = 4.7 Hz, 2H), 5.60 (s, 2H), 7.24 (m, 1H), 7.33–7.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.4, 50.2, 129.0, 129.2 (2C), 130.2, 133.0, 136.8, 155.7; HRMS (ESI) *m/z* calcd for $C_9H_{10}N_5$ $[M + H]^+$ 188.0936, found 188.0932.



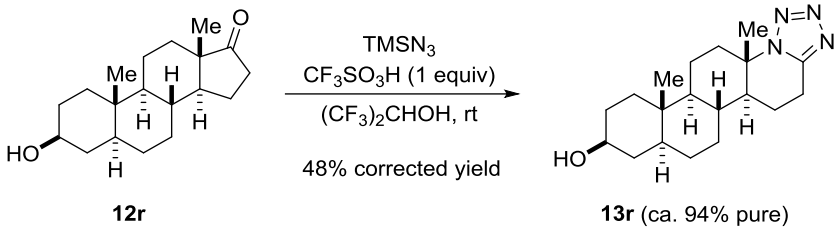
(5*r*,7*R*,9*S*,11*s*)-6,7,8,9,10,11-Hexahydro-5*H*-5,9:7,11-dimethanotetrazolo[1,5-*a*]-azonine (13q),[93] (1*R*,3*R*,5*S*)-*rel*-Bicyclo[3.3.1]non-6-ene-3-carbonitrile (20),[93] (1*R*,3*r*,6*s*,8*S*)-4-Azatricyclo[4.3.1.1^{3,8}]undecan-5-one (14q),[141] and (5*s*,7*R*,9*S*,11*r*)-4,5,6,

7,8,9,10,11-Octahydro-5,9:7,11-dimethanotetrazolo[1,5-*a*][1,3]diazecine (15q; Scheme 23). Following the general procedure **D**, a solution of 2-adamantanone **12q** (60.1 mg, 0.400 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.5 equiv) in HFIP (1.0 mL) was treated with TfOH (8.9 μL, 0.100 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded an impure carbonitrile **20** (eluted between 100% CH_2Cl_2), tetrazole **13q** containing grease (eluted between 1.0–2.4% MeOH/CH_2Cl_2), and a slightly impure mixture of lactam **14q** and aminotetrazole **15q** (eluted at 2.9–3.7% MeOH/CH_2Cl_2). The unreacted 2-adamantanone was not isolated during this purification. Further purification of carbonitrile **20** using a 4 g flash column on a CombiFlash Rf system (0–5% EtOAc/hexanes over 25 min) afforded **20** (eluted between 2.8–3.4% EtOAc/hexanes) as a colorless amorphous solid (23.0 mg, 0.156 mmol, 39% yield). Trituration of tetrazole **13q** with hexanes twice, pipetting out the hexanes layers, and drying the solid under vacuum afforded **13q** as a colorless crystalline solid (11.4 mg, 0.0599 mmol, 15% yield). Recrystallization of **13q** from EtOAc afforded colorless, plate-like crystals. The impure mixture of lactam **14q** and aminotetrazole **15q** was purified by preparative TLC developing two times with 3% MeOH/CH_2Cl_2. A single band corresponding to both **14q** and **15q** was scraped from the plate and eluted with 6% MeOH/CH_2Cl_2 through a phase separator tabless. Concentration afforded a very slightly impure mixture of **14q** and **15q** as a colorless solid (for **14q**: ca. 1.7 mg, 0.010 mmol, 2% corrected yield and for **15q**: ca. 7.0 mg, 0.034 mmol, 8% corrected yield; ratio of **14q**:**15q** = ca. 20:80 by ^{1}H NMR). Tetrazole **13q**: R_f = 0.35 (2% MeOH/CH_2Cl_2); mp 225–229 °C, melted slowly above 195 °C with decomposition (lit.[93] mp 253–255 °C); IR (neat) 2907, 1459 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79–1.83 (m, 2H), 1.87–1.93 (complex, 4H),

2.05–2.16 (complex, 4H), 2.26 (br s, 2H), 3.66 (t, J = 5.7 Hz, 1H), 5.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7 (2C), 27.1, 32.0 (2C), 33.8 (2C), 34.6, 53.0, 160.6; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}N_4$ $[M + H]^+$ 191.1297, found 191.1298.

Carbonitrile **20**: R_f = 0.39 (10% EtOAc/hexanes); mp 165–180 °C, melted slowly with decomposition (lit.[93] mp 160–165 °C and lit.[142] mp 176.5–181.5 °C); IR (neat) 3023, 2229, 1439 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (m, 1H), 1.71–1.80 (m, 2H), 1.88–1.95 (m, 2H), 2.02 (m, 1H), 2.17–2.26 (m, 2H), 2.39–2.49 (m, 2H), 2.95 (m, 1H), 5.83–5.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 25.7, 27.5, 30.4, 30.5, 31.9, 34.5, 124.3, 129.4, 131.8; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}N$ $[M + H]^+$ 148.1126, found 148.1134.

Mixture of lactam **14q** and aminotetrazole **15q** (ca. 20:80): R_f = 0.33 (3% MeOH/CH_2Cl_2); IR (neat) 3267, 3202, 3069, 1634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54–1.61 (m, 3H), 1.67–1.86 (complex, 10H), 1.89–1.98 (complex, 5H), 2.10 (m, 2H), 2.30 (m, 4H), 2.70 (m, 1H), 3.32 (m, 1H), 3.92 (q, J = 8.4 Hz, 1H), 5.31 (t, J = 8.0 Hz, 1H), 6.65 (br s, 1H), 7.44 (d, J = 7.4 Hz, 1H); ^{1}H NMR (**14q**, diagnostic peaks only) δ 2.10 (m, 2H), 2.70 (m, 1H), 3.32 (m, 1H), 6.65 (br s, 1H); ^{1}H NMR (**15q**, diagnostic peaks only) δ 3.92 (q, J = 8.4 Hz, 1H), 5.31 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, peaks of **14q** in a mixture) δ 27.2 (2C), 30.9 (2C), 34.9, 36.7 (2C), 41.7, 46.0, 182.5; ^{13}C NMR (125 MHz, $CDCl_3$, peaks of **15q** in a mixture) δ 22.6 (2C), 32.4, 35.8 (2C), 37.8 (2C), 43.6, 49.5, 153.1; HRMS (ESI) *m/z* calcd for **14q**, $C_{10}H_{16}NO$ $[M + H]^+$ 166.1232, found 166.1230; HRMS (ESI) *m/z* calcd for **15q**, $C_{10}H_{16}N_5$ $[M + H]^+$ 206.1406, found 206.1405.



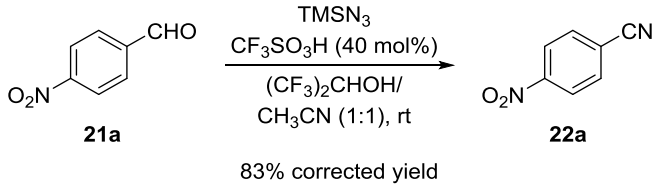
(5a*S*,5b*R*,7a*S*,9*S*,11a*S*,11b*S*,13a*S*)-11a,13a-Dimethyl-4,5,5a,5b,6,7,7a,8,9,10,11, 11a,11b,12,13,13a-hexadecahydronaphtho[2,1-*f*]tetrazolo[1,5-*a*]quinolin-9-ol (13r; Scheme 23). Following the general procedure **D**, a solution of *trans*-androsterone **12r** (58.1 mg, 0.200 mmol, 1.0 equiv) and $TMSN_3$ (57.6 mg, 0.500 mmol, 2.5 equiv) in HFIP (0.50 mL) was treated with TfOH (17.7 μL, 0.200 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 3 h. Concentration, followed by quenching with Et_3N (ca. 0.050 mL), and purification using a 4 g flash column on a CombiFlash Rf system (0–10% MeOH/CH_2Cl_2 over 60 min) afforded an impure tetrazole **13r** (eluted between 2.8–3.5% MeOH/CH_2Cl_2). Further purification of the impure tetrazole **13r** using a 12 g flash column on a CombiFlash Rf system (0–60% EtOAc/hexanes over 65 min) afforded a slightly impure **13r** (eluted between ca. 52–57% EtOAc/hexanes) as a colorless solid (32.0 mg, 0.0968 mmol, 48% corrected yield; ca. 94% pure by ^{1}H NMR). Tetrazole **13r**: R_f = 0.18 (60% EtOAc/hexanes, run twice); IR (neat) 3391, 1522, 1452, 1041 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 3H), 0.84–0.88 (m, 1H), 0.93–1.03 (m, 2H), 1.12 (tt, J = 12.5, 3.1 Hz, 1H), 1.25–1.34 (complex, 2H), 1.35 (s, 3H), 1.36–1.46 (complex, 3H), 1.48–1.53 (complex, 2H), 1.54–1.62 (m, 2H), 1.66–1.76 (m, 2H), 1.80–1.90 (complex, 3H), 1.95 (m 1H), 2.18 (apparent dd, J = 13.1, 7.7 Hz, 1H), 2.79 (dt, J = 12.8, 3.4 Hz, 1H), 2.87 (m, 1H), 3.21 (m, 1H), 3.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 18.4, 20.5, 21.2, 21.6, 28.4, 31.2, 31.4, 35.2, 35.8, 36.9, 37.1, 37.9, 44.3, 49.0, 53.4, 61.5, 71.0, 151.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{31}N_4O$ $[M + H]^+$ 331.2498, found 331.2484.

Experimental Procedures for Section 1.4

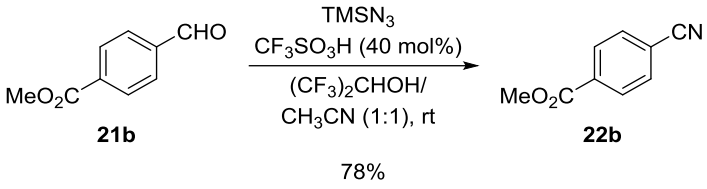
General Procedure for the Optimization of Reaction Conditions for the Synthesis of 4-Nitrobenzonitrile 22a (Table 11). To a solution of 4-nitrobenzaldehyde **21a** (0.25 or 0.50 mmol, 1.0 equiv) and NaN_3 or $TMSN_3$ (1.5–2.0 equiv) in HFIP or HFIP/ACN mixture (0.50, 1.0, or 2.0 mL) was added a catalyst (effervescence due to nitrogen gas evolution was immediately observed). The vial was capped and the reaction mixture was allowed to stir at rt (23 or 25 °C) for a specified period (45 min to 24 h). The reaction mixture was concentrated under nitrogen. The residue obtained was diluted with an appropriate solvent (CH_2Cl_2 or EtOAc) and was either filtered through a Pasteur pipette containing a cotton plug to get a crude ^1H NMR ratio (for entries 1 and 2) or purified using a 4 or 12 g flash column on a CombiFlash Rf system with a gradient elution of 0–10% EtOAc/hexanes (for entries 3–7). Concentration of the appropriate fractions afforded 4-nitrobenzonitrile **22a** containing a small amount (ca. 3–6%) of **21a** (except for entry 5, where **22a** was obtained pure).

General Procedure E for the Synthesis of Aromatic Nitriles (Table 12). To a solution of aromatic aldehyde (0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in a premixed HFIP/ACN mixture (2.0 mL, 1:1) in a nitrogen-flushed two dram vial was added TfOH (17.7 μL, 0.200 mmol, 0.40 equiv) (exotherm and brisk effervescence due to nitrogen gas evolution was immediately observed). The vial was capped and the reaction mixture was allowed to stir at rt for 20–45 min. The reaction mixture was concentrated under nitrogen. The residue obtained was suspended in CH_2Cl_2–hexanes mixture and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system with a gradient elution of either 0–10 or 0–30%

EtOAc/hexanes over 40 min afforded a corresponding aromatic nitrile upon concentration of appropriate fractions.

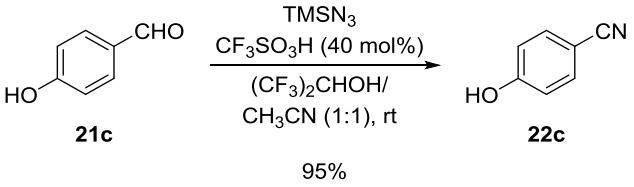


4-Nitrobenzonitrile (22a).[66j] Following the general procedure **E**, a solution of 4-nitrobenzaldehyde **21a** (75.6 mg, 0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in HFIP/ACN mixture (2.0 mL, 1:1) was treated with TfOH (17.7 μL, 0.200 mmol, 0.40 equiv). The reaction mixture was stirred at rt for 45 min. Purification using a 4 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 40 min) afforded 4-nitrobenzonitrile **22a** along with a small amount of unreacted **21a** (eluted between 2.3–4.0% EtOAc/hexanes) as a colorless crystalline solid (61.6 mg, 0.416 mmol, 83% corrected yield; contains ca. 4% of **21a** as determined by ^{1}H NMR).

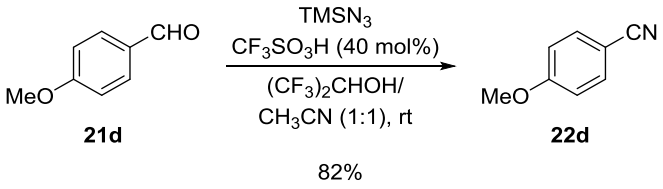


Methyl 4-cyanobenzoate (22b).[66j] Following the general procedure **E**, a solution of methyl 4-formylbenzoate **21b** (82.1 mg, 0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in HFIP/ACN mixture (2.0 mL, 1:1) was treated with TfOH (17.7 μL, 0.200 mmol, 0.40 equiv). The reaction mixture was stirred at rt for 30 min. Purification using a 4 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 40 min)

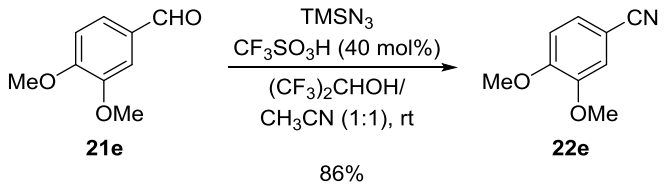
afforded methyl 4-cyanobenzoate **22b** (eluted between 2.5–4.2% EtOAc/hexanes) as a colorless crystalline solid (63.0 mg, 0.391 mmol, 78% yield).



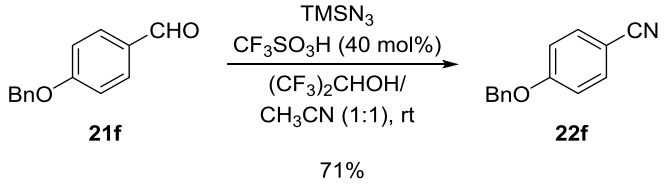
4-Hydroxybenzonitrile (22c).[66j] Following the general procedure **E**, a solution of 4-hydroxybenzaldehyde **21c** (61.1 mg, 0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in HFIP/ACN mixture (2.0 mL, 1:1) was treated with TfOH (17.7 μL, 0.200 mmol, 0.40 equiv). The reaction mixture was stirred at rt for 30 min. Purification using a 4 g flash column on a CombiFlash Rf system (0–30% EtOAc/hexanes over 40 min) afforded 4-hydroxybenzonitrile **22c** (eluted between 15–20% EtOAc/hexanes) as a colorless crystalline solid (56.5 mg, 0.474 mmol, 95% yield).



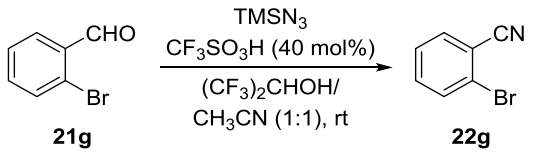
4-Methoxybenzonitrile (22d).[66j] Following the general procedure **E**, a solution of *p*-anisaldehyde **21d** (68.1 mg, 0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in HFIP/ACN mixture (2.0 mL, 1:1) was treated with TfOH (17.7 μL, 0.200 mmol, 0.40 equiv). The reaction mixture was stirred at rt for 30 min. Purification using a 4 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 40 min) afforded 4-methoxybenzonitrile **22d** (eluted between 2.3–3.2% EtOAc/hexanes) as a colorless crystalline solid (54.4 mg, 0.409 mmol, 82% yield).



3,4-Dimethoxybenzonitrile (22e).[66j] Following the general procedure **E**, a solution of 3,4-dimethoxybenzaldehyde **21e** (83.1 mg, 0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in HFIP/ACN mixture (2.0 mL, 1:1) was treated with TfOH (17.7 μL, 0.200 mmol, 0.40 equiv). The reaction mixture was stirred at rt for 20 min. Purification using a 4 g flash column on a CombiFlash Rf system (0–30% EtOAc/hexanes over 40 min) afforded 3,4-dimethoxybenzonitrile **22e** (eluted between 11–16% EtOAc/hexanes) as a colorless crystalline solid (70.0 mg, 0.429 mmol, 86% yield).



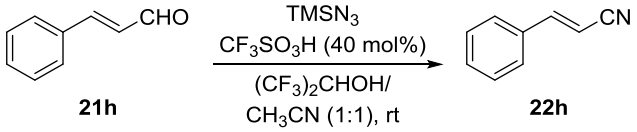
4-(Benzyloxy)benzonitrile (22f).[66j] Following the general procedure **E**, a solution of 4-(benzyloxy)benzaldehyde **21f** (106 mg, 0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in HFIP and ACN mixture (2.0 mL, 1:1) was treated with TfOH (17.7 μL, 0.200 mmol, 0.40 equiv). The reaction mixture was stirred at rt for 20 min. Purification using a 4 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 40 min) afforded 4-(benzyloxy)benzonitrile **22f** (eluted between 2.3–3.2% EtOAc/hexanes) as a colorless crystalline solid (74.1 mg, 0.354 mmol, 71% yield).



21g **22g**

68%

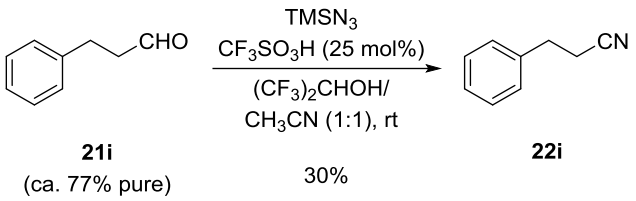
2-Bromobenzonitrile (22g).[66j] Following the general procedure **E**, a solution of 2-bromobenzaldehyde **21g** (92.5 mg, 0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in HFIP/ACN mixture (2.0 mL, 1:1) was treated with TfOH (17.7 μL, 0.200 mmol, 0.40 equiv). The reaction mixture was stirred at rt for 30 min. Purification using a 4 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 40 min) afforded 2-bromobenzonitrile **22g** (eluted between 2.0–2.5% EtOAc/hexanes) as a colorless crystalline solid (61.7 mg, 0.339 mmol, 68% yield).



21h **22h**

90%

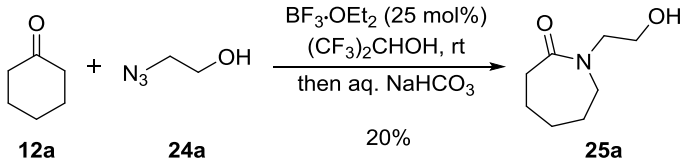
Cinnamonitrile (22h).[66j] Following the general procedure **E**, a solution of *trans*-cinnamaldehyde **21h** (66.1 mg, 0.500 mmol, 1.0 equiv) and $TMSN_3$ (115 mg, 1.00 mmol, 2.0 equiv) in HFIP/ACN mixture (2.0 mL, 1:1) was treated with TfOH (17.7 μL, 0.200 mmol, 0.40 equiv). The reaction mixture was stirred at rt for 45 min. Purification using a 4 g flash column on a CombiFlash Rf system (0–10% EtOAc/hexanes over 40 min) afforded cinnamonitrile **22h** (eluted between 2.3–2.8% EtOAc/hexanes) as a colorless oil (58.0 mg, 0.449 mmol, 90% yield).



3-Phenylpropionitrile (22i).[143] Following a slight modification of the general procedure **E**, a solution of hydrocinnamaldehyde **21i**, ca. 77% pure (26.8 mg, 0.200 mmol, 1.0 equiv) and $TMSN_3$ (69.1 mg, 0.600 mmol, 3.0 equiv) in HFIP/ACN mixture (1.0 mL, 1:1) was treated with TfOH (4.4 μL, 0.0500 mmol, 0.25 equiv). The reaction mixture was stirred at rt for 1 h. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% EtOAc/hexanes over 40 min) afforded 3-phenylpropionitrile **22i** (eluted between 2.8–3.4% EtOAc/hexanes) as a colorless oil (8.0 mg, 0.061 mmol, 30% yield).

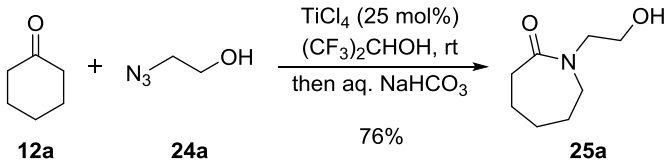
Experimental Procedures for Section 1.5

General Procedure F for the Preliminary Optimization of Reaction Conditions for the Synthesis of *N*-Hydroxyalkyl Lactams 25 (Table 13). To a solution of ketone **12** (0.400 or 1.00 mmol, 1.0 equiv) and 2-azidoethan-1-ol **24a** (0.520–1.50 mmol, 1.3–1.5 equiv) in HFIP (1.6 or 2.5 mL) in a nitrogen-flushed two or four dram vial was added a catalyst (0.0400–0.400 mmol, 0.10–1.0 equiv) (effervescence due to nitrogen gas evolution and/or slight exotherm was observed). The vial was capped and the reaction mixture was stirred at rt or 25 °C for 0.5–24 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was treated with a saturated aqueous $NaHCO_3$ solution (1.0–2.0 mL) at rt or 25 °C for 6–20 h. Purification using a 4 g flash column on a CombiFlash Rf system with a gradient elution of 0–5 or 0–10% MeOH/CH_2Cl_2 over 50 min afforded **25** after concentration of appropriate fractions.

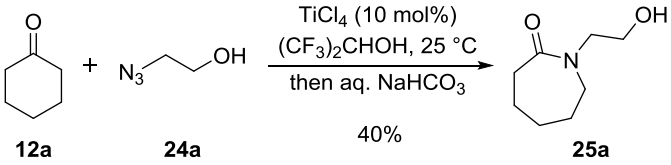


1-(2′-Hydroxyethyl)azepan-2-one (25a).[105a] Following the general procedure **F**, a solution of cyclohexanone **12a** (98.1 mg, 1.00 mmol, 1.0 equiv) and 2-azidoethanol **24a** (131 mg, 1.50 mmol, 1.5 equiv; a solution of **24a** in Et_2O was used) in HFIP (2.5 mL) was treated with BF_3·OEt_2 (30.9 μL, 0.250 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at rt for 0.5 h. The reaction mixture was concentrated under nitrogen gas. To the resulting residue was added a saturated aqueous $NaHCO_3$ solution (2.0 mL) and CH_2Cl_2 (1.0 mL), and the reaction mixture was stirred at rt for 12 h. The CH_2Cl_2 layer was removed and the aqueous layer was extracted with CH_2Cl_2 (1 × 2 mL) and the combined organic layers were loaded on a silica gel/Na_2SO_4 mixture in a sample cartridge.

Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded **25a** (eluted between 2.4–3.2% MeOH/CH_2Cl_2) as a pale yellow oil (32.0 mg, 0.204 mmol, 20%).

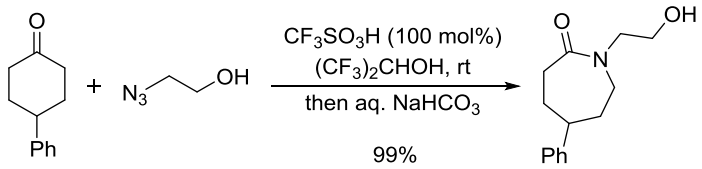


Following the general procedure **F**, a solution of cyclohexanone **12a** (98.1 mg, 1.00 mmol, 1.0 equiv) and 2-azidoethanol **24a** (131 mg, 1.50 mmol, 1.5 equiv; a solution of **24a** in Et_2O was used) in HFIP (2.5 mL) was treated with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.250 mL, 0.250 mmol, 0.25 equiv). The vial was capped and the reaction mixture was stirred at rt for 0.5 h. The reaction mixture was concentrated under nitrogen gas. To the resulting residue was added a saturated aqueous $NaHCO_3$ solution (2.0 mL) and CH_2Cl_2 (1.0 mL), and the reaction mixture was stirred at rt for 12 h. The CH_2Cl_2 layer was removed and the aqueous emulsion was extracted with CH_2Cl_2 (1 × 2 mL) and the combined organic layers were loaded on a silica gel/Na_2SO_4 mixture in a sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded **25a** (eluted between 1.9–3.4% MeOH/CH_2Cl_2) as a yellow oil (119 mg, 0.757 mmol, 76%).



Following the general procedure **F**, a solution of cyclohexanone **12a** (39.3 mg, 0.400 mmol, 1.0 equiv) and 2-azidoethanol **24a** (45.3 mg, 0.520 mmol, 1.3 equiv; a solution of

24a in Et_2O was used) in HFIP (1.6 mL) was treated with a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (40.0 μL, 0.0400 mmol, 0.10 equiv). The vial was capped and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under nitrogen gas and dried under vacuum. To a suspension of the resulting residue in CH_2Cl_2 (1.0 mL) was added a saturated aqueous $NaHCO_3$ solution (1.0 mL) and the reaction mixture was stirred at 25 °C for 20 h. The reaction mixture was again concentrated under nitrogen gas and the residue obtained was diluted with CH_2Cl_2 and dried over Na_2SO_4. The solution in CH_2Cl_2 was loaded on a silica gel in a sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded **25a** (eluted between 2.7–3.5% MeOH/CH_2Cl_2) as a pale yellow oil (25.0 mg, 0.159 mmol, 40%).



12b **24a** **25b**

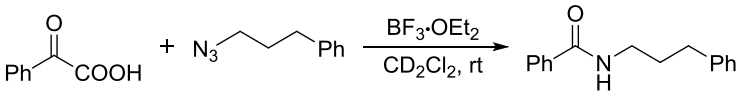
1-(2′-Hydroxyethyl)-5-phenylazepan-2-one (25b).[108] Following the general procedure **F**, a solution of 4-phenylcyclohexanone **12b** (69.7 mg, 0.400 mmol, 1.0 equiv) and 2-azidoethanol **24a** (52.3 mg, 0.600 mmol, 1.5 equiv; contains some unidentified impurities) in HFIP (1.6 mL) was treated with TfOH (35.4 μL, 0.400 mmol, 1.0 equiv). The vial was capped and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated under nitrogen gas and dried under vacuum. The colorless residue was treated with a saturated aqueous $NaHCO_3$ solution (1.0 mL) at rt for 6 h. The reaction mixture was again concentrated under nitrogen gas and the residue obtained was suspended in CH_2Cl_2/MeOH mixture and loaded on a silica gel in a sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–10% MeOH/CH_2Cl_2 over 50 min) afforded

25b (eluted between 6.4–7.2% MeOH/CH_2Cl_2) as an off-white oily solid (92.7 mg, 0.397 mmol, 99% corrected yield; contains a trace amount of the similar impurities present in **24a**).

General Experimental Procedure for the Initial Screening of Reaction Conditions for the Synthesis of Dihydrooxazines 26 (Table 14). To a solution of 4-nitrobenzaldehyde **21a** (30.2 mg, 0.200 mmol, 1.0 equiv) or benzaldehyde **21j** (21.2 mg, 0.200 mmol, 1.0 equiv) and 3-azidopropan-1-ol **24b** (30.3 mg, 0.300 mmol, 1.5 equiv; contains some unidentified impurities) in HFIP (0.5 mL) in a nitrogen-flushed vial was added a catalyst (0.0200 or 0.0500 mmol, 0.10 or 0.25 equiv). The vial was capped and the reaction mixture was stirred at rt for 6 or 24 h. The reaction mixture was concentrated under nitrogen gas and dried under vacuum. A solution of the resulting residue in CH_2Cl_2 was loaded on a silica gel in a sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system with a gradient elution of 0–5% MeOH/CH_2Cl_2 over 45 or 50 min afforded impure **26** after concentration of appropriate fractions (for entries 1, 3, and 4: slightly impure samples of **26** were obtained; for entry 2: the isolated sample of **26** contains ca. 50% of unidentified impurities, which was originally present in **24b**).

Experimental Procedures for Section 1.7

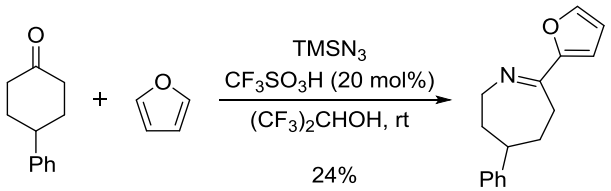
Experimental Procedure for the Synthesis of *N*-(3-Phenylpropyl)benzamide (30j)[144] via a Decarboxylative Amidation Reaction (Table 16, entry 1)



36 **29** 16% **30j**

To a solution of phenylglyoxylic acid **36** (50.0 mg, 0.333 mmol, 1.0 equiv) and (3-azidopropyl)benzene **29** (64.3 mg, 0.400 mmol, 1.2 equiv) in CD_2Cl_2 (1.0 mL) at rt under nitrogen atmosphere was added $BF_3{\cdot}OEt_2$ (0.144 mL, 1.17 mmol, 3.5 equiv) slowly over 2 min and the resulting yellow solution was stirred at rt for 52 h. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc twice. The combined organic layers were washed with brine once, dried over Na_2SO_4, and concentrated. A solution of the resulting residue in CH_2Cl_2 was loaded on a silica gel in a sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–25% EtOAc/hexanes) afforded **30j** (eluted out at 20% EtOAc/hexanes) as a pale yellow oil (13.0 mg, 0.0544 mmol, 16%).

Experimental Procedure for the Synthesis of 7-(Furan-2-yl)-4-phenyl-3,4,5,6-tetrahydro-2*H*-azepine (41)[145] via an Intercepted Schmidt Reaction with Furan (Scheme 35c)



12b furan **41**

To a solution of 4-phenylcyclohexanone **12b** (34.9 mg, 0.200 mmol, 1.0 equiv), $TMSN_3$ (24.2 mg, 0.210 mmol, 1.05 equiv), and furan (40.8 mg, 0.600 mmol, 3.0 equiv) in

HFIP (0.5 mL) at rt in a nitrogen-flushed one dram vial was added TfOH (3.6 μL, 0.0400 mmol, 0.20 equiv). The vial was capped and the reaction mixture was stirred at rt for 22 h. The reaction mixture was concentrated under nitrogen gas. The residue obtained was diluted with CH_2Cl_2 and loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–5% MeOH/CH_2Cl_2 over 50 min) afforded **41** (eluted between 4.0–4.8% MeOH/CH_2Cl_2) as a pale yellow oil in 24% yield (11.5 mg, 0.0481 mmol). R_f = 0.31 (5% MeOH/CH_2Cl_2); IR (neat) 1627, 1485 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.49 (apparent q, J = 12.8 Hz, 1H), 1.64 (m, 1H), 1.92–2.01 (m, 2H), 2.64 (m, 1H), 2.87 (tt, J = 12.2, 3.5 Hz, 1H), 3.01 (ddd, J = 14.4, 6.9, 1.0 Hz, 1H), 3.60 (t, J = 11.8 Hz, 1H), 4.23 (ddd, J = 12.6, 6.3, 1.2 Hz, 1H), 6.44 (dd, J = 3.4, 1.8 Hz, 1H), 6.79 (d, J = 3.3 Hz, 1H), 7.12–7.18 (m, 3H), 7.23–7.28 (m, 2H), 7.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3, 31.3, 33.9, 49.7, 51.5, 111.7, 112.0, 126.5, 126.9, 128.7, 144.9, 147.2, 153.6, 164.8; HRMS (ESI) *m/z* calcd for $C_{16}H_{18}NO$ $[M + H]^+$ 240.1388, found 240.1385.

Chapter 2

Copper-Catalyzed Oxaziridine-Mediated C–H Bond Oxidation

2.1 Introduction

Oxaziridine

Oxaziridines were first reported by Emmons[146] and by virtue of their inherently weak N–O bond in a strained three-membered heterocyclic ring, they possess unusually high reactivity.[147] These characteristics also impart low basicity to the oxaziridine nitrogen compared to amines. Due to ring strain and inductive effect of adjacent oxygen atom, nitrogen tends to be more pyramidal and has a high inversion barrier.[148] The configurational stability at the nitrogen atom can lead to chirality in oxaziridine, and may allow for the preferential formation of a single enantiomer or diastereomer depending on the *N*-substituent.[148-149] For *N*-alkyl oxaziridines, the energy barrier for nitrogen inversion was determined to be 25–32 kcal/mol. The inversion barrier was found to be smaller for *N*-substituents capable of π-conjugation or hyperconjugation.[148] Thermal isomerizations of oxaziridines have been shown to involve only nitrogen inversion mechanism without bond cleavage (Figure 17).[149c,150]

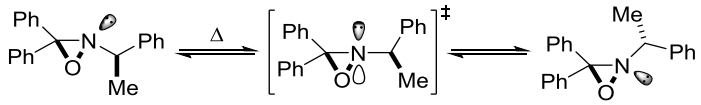


Figure 17. Thermal epimerization of an oxaziridine.

The oxygen and the nitrogen atom in the neutral oxaziridine behave as electrophiles and this unusual property has been exploited for a variety of heteroatom-transfer reactions and rearrangements[151] (Figure 18).[147b,c,152] Oxaziridines such as *N*-sulfonyloxaziridines

(Davis' oxaziridines)[153] have been widely utilized for oxidation reactions such as epoxidation of alkenes, oxidation of sulfides to sulfoxides, and α-hydroxylation of carbonyl compounds, in addition to various amination[152a,154] and cycloaddition[155] reactions.[147b,153] An asymmetric α-hydroxylation reaction[153,156] using a chiral (camphorsulfonyl)oxaziridine was one of the key step in the total synthesis of Taxol both by Holton[157] and Wender.[158]

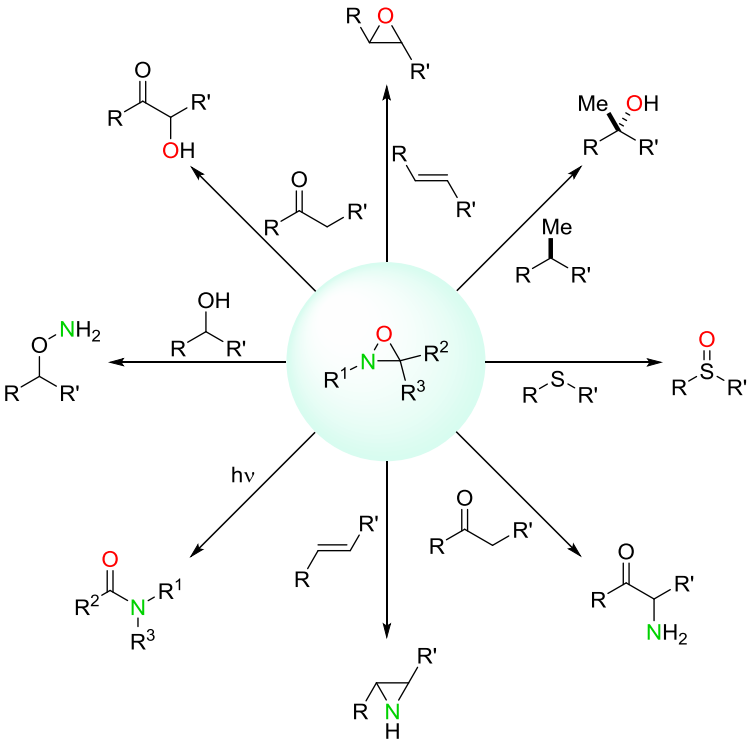
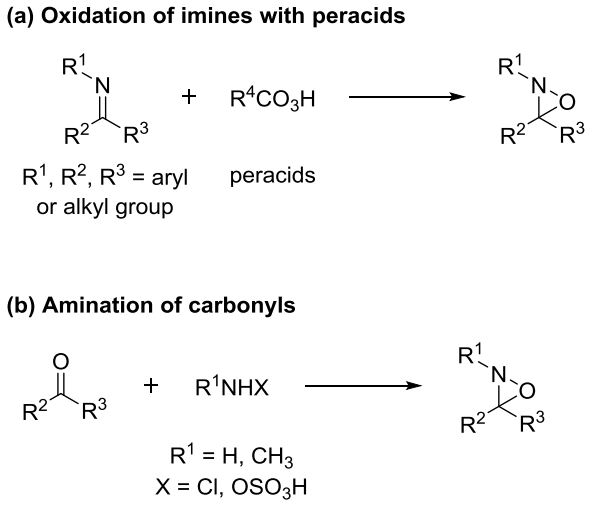


Figure 18. Reactions of oxaziridines.

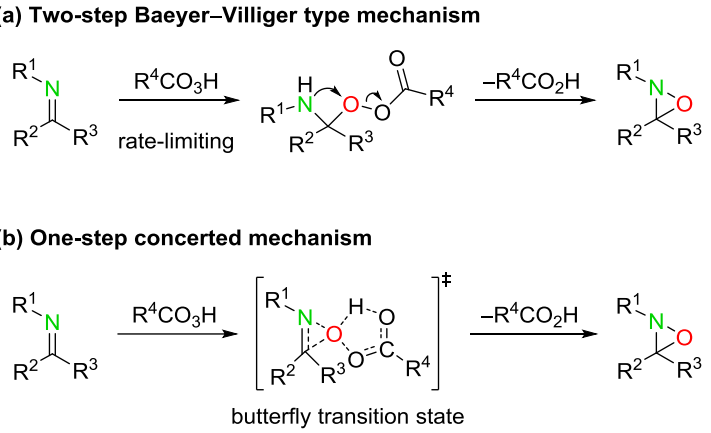
The most common approaches for oxaziridine synthesis are: (a) the oxidation of imines with peracids such as *m*-CPBA or Oxone, and (b) the electrophilic amination of carbonyl compounds with *N*-chloroalkylamines or *N*-alkylhydroxylamine-*O*-sulfonic acids (Scheme 36).[147a,b,152a] Enantiopure oxaziridines could be prepared via either the oxidation of chiral imines or oxidation of imines with chiral peracids. Other less common methods for the synthesis of oxaziridines involve photoisomerization of nitrones[159] and conjugate addition of hydroxamic acids to methyl propiolate.[160]

Scheme 36. Main Synthetic Routes to Oxaziridines



The mechanism for the formation of oxaziridine through imine oxidation by peracids has been well-studied.[151b,161] The two-step nucleophilic, Baeyer–Villiger type mechanism is generally accepted for the oxidation of imines rather than the concerted "butterfly mechanism"[162] commonly believed for the epoxidation of alkenes (Scheme 37). In the Baeyer–Villiger type process, the peracid first adds to the imine to form a tetrahedral intermediate, which is followed by the nucleophilic attack of the nitrogen onto the electron-deficient oxygen atom to afford the oxaziridine. The oxidation of imines is stereoselective but lacks stereospecificity as the initial imine geometry is not reflected in the oxaziridine products. The electron-poor imines can also be preferentially oxidized at much lower temperatures in the presence of alkenes suggesting the electrophilic attack of the imines. Such circumstantial evidence in addition to computational study[161e] and detailed kinetic study of the oxidation reaction[161a,b] have supported the two-step Baeyer–Villiger mechanism and the initial addition of peracids to the imine was found to be rate-determining under most conditions.

Scheme 37. Plausible Mechanisms for the Oxidation of Imines by Peracids

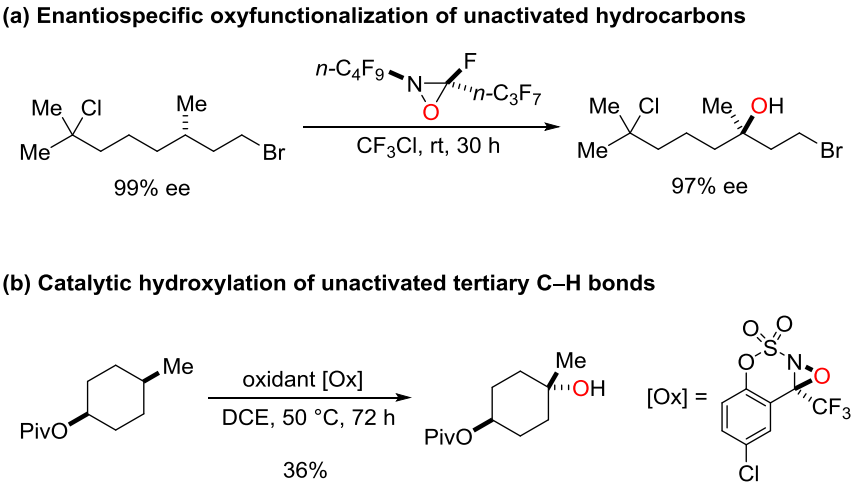


2.2 Copper-Catalyzed Oxaziridine-Mediated Intramolecular C–H Bond Oxidation

The past decade has seen numerous advances in the development of new and versatile reagents and catalysts to mimic nature's ability to selectively oxidize C–H bonds, which has long intrigued synthetic chemists.[163,164] C–H oxidation reactions, in particular allylic C–H oxidations, have received substantial attention due to their considerable potential for synthetic applications.[165] The copper-catalyzed allylic oxidation using organic peroxide is well-known and often referred to as the Kharasch–Sosnovsky reaction.[166]

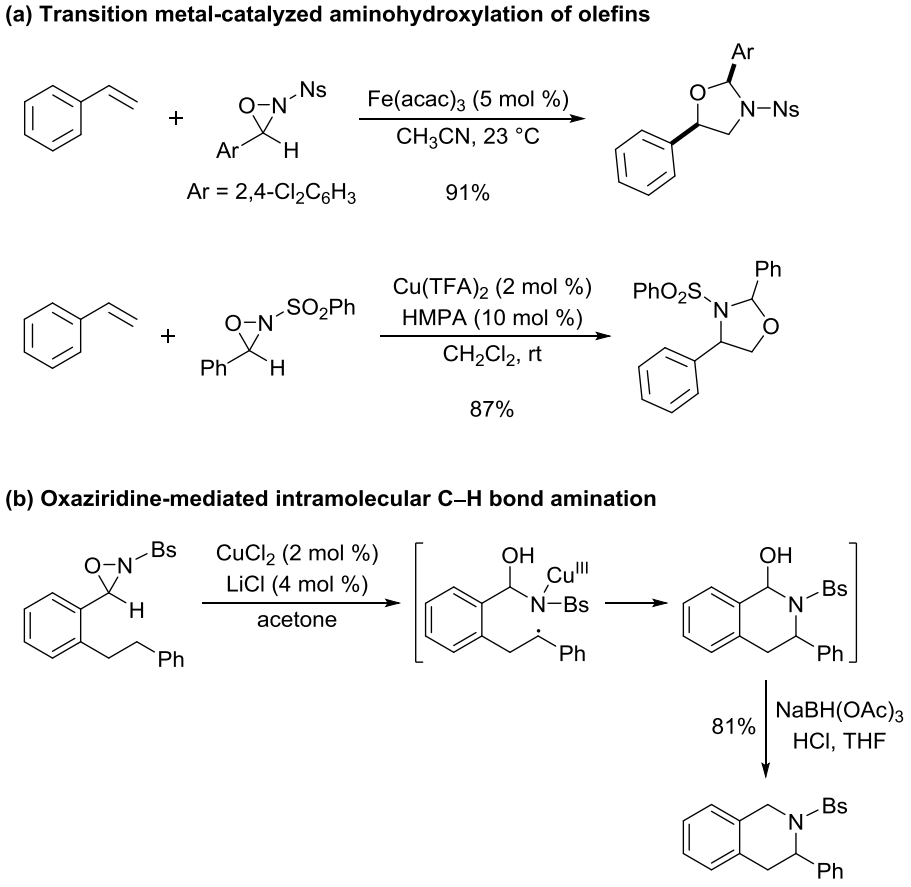
The oxidizing ability of oxaziridines resulting from the presence of strong electron-withdrawing substituents such as perfluoroalkyl groups have been utilized for the oxygenation of unactivated tertiary C–H bonds (Scheme 38).[152b,167] The use of perfluorinated oxaziridines has been limited as the syntheses of such compounds are often difficult and expensive.[152b,167b] Moreover, the oxidized products are often obtained in modest yields and the reactions have limited substrate scope especially insofar as the presence of alkene always leads to epoxide formation rather than C–H oxidation.[167a,b]

Scheme 38. Oxaziridine-Mediated Oxidation of Unactivated C–H Bonds

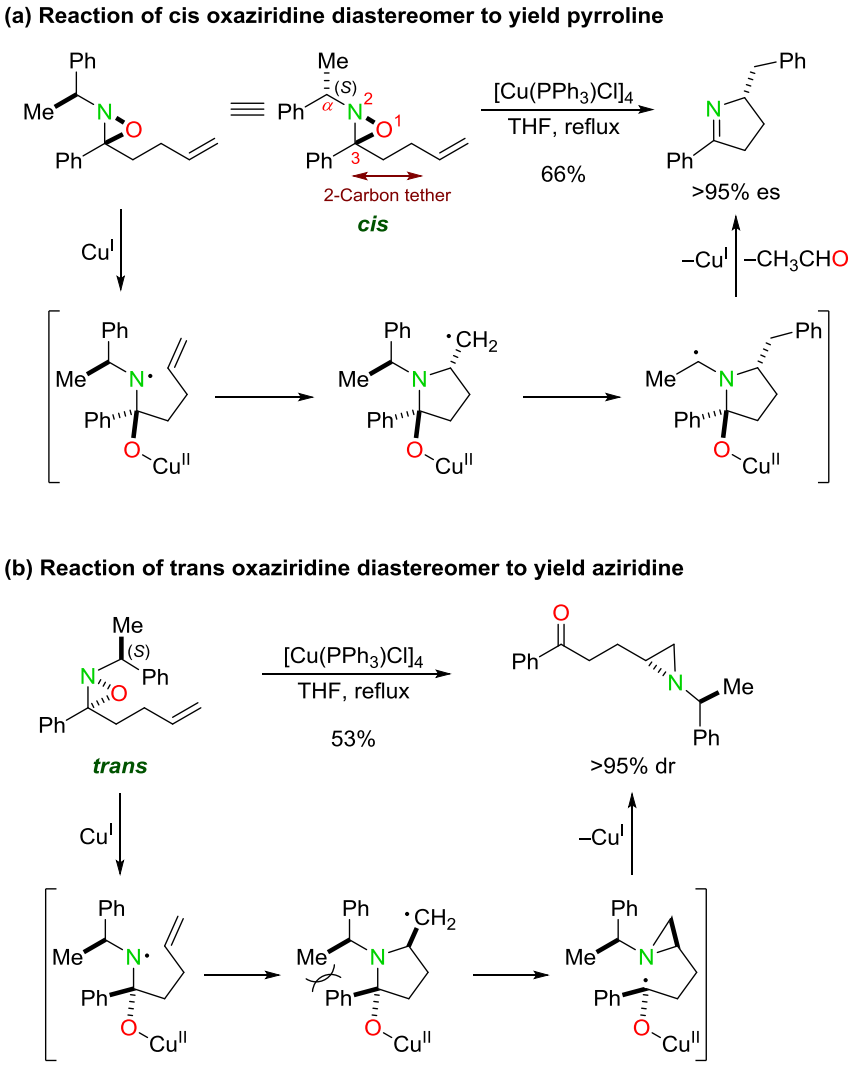


Recently, copper and other transition metal-catalyzed aminohydroxylation reactions of olefins using *N*-sulfonyloxaziridines have been developed by Yoon and co-workers (Scheme 39a).[168] They also reported the copper-catalyzed oxaziridine-mediated regioselective intramolecular C–H bond amination reaction (Scheme 39b).[169] This first reported example of formal nitrogen insertion from *N*-sulfonyl oxaziridines constitutes a radical-mediated reaction of oxaziridines, in which a benzylic C–H hydrogen atom was ultimately transferred to a Cu(II)-coordinated oxaziridine.

Scheme 39. Oxaziridine-Mediated Aminohydroxylation and C–H Bond Amination Reactions



Scheme 40. Copper(I)-Catalyzed Reaction of Oxaziridines

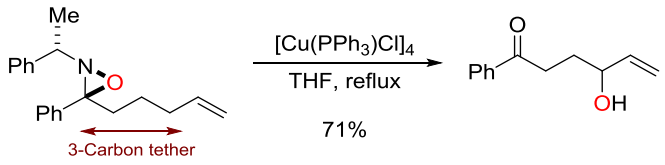


In 1992, Aubé and co-workers reported the copper-catalyzed reactions of chiral 3-aryl oxaziridines to afford enantiomerically-pure pyrrolines and aziridines (Scheme 40).[170] The stereochemistry of the starting oxaziridines was found to have a remarkable influence on the course of the reaction. Thus, either pyrrolines or aziridines were obtained through two different highly selective reaction pathways. In each case, the oxaziridine ring-opening occurred via single-electron transfer (SET) to afford a nitrogen-center radical/oxygen anion pair. This mode of reaction was related to that previously proposed by Emmons, Minisci, Black, and other pioneers of oxaziridine chemistry for reactions promoted by low-valent

metals like Fe(II) or Cu(I).[146,171] This reactive intermediate then underwent addition to the attached olefin; the product observed depended on the relative stereochemistry between the α center of the *N*-phenylethyl group and the oxaziridine C-3 atom.

While exploring the scope of the reactions shown in Scheme 40, Belgin Gülgeze extended the linker between the oxaziridine and alkene from two to three carbons (cf. Schemes 40 and 41).[172] Under identical conditions as before, she found that the reaction of oxaziridine with a three carbon linker **42aa** afforded an allylic alcohol **43a** in 71% yield (Scheme 41)[172] instead of a tetrahydropyridine or aziridine, either of which might have been expected in analogy with Scheme 40. These results were interesting, in part because they represented the chemoselective oxidation of an sp^3 C–H bond, but also because they diverged from previously reported oxaziridine reactivity. For example, C–H oxidation by oxaziridines typically requires strong electron-withdrawing substituents.[152b,167] Moreover, alkene epoxidation has been observed with oxaziridines[152b,167b,171e,173] but no epoxide was formed in these reactions.

Scheme 41. Copper(I)-Catalyzed Oxaziridine-Mediated Intramolecular C–H Bond Oxidation



42aa (±)-**43a**

For the reasons mentioned above and because of general contemporary interest in mild means of carrying out C–H oxidation chemistry, we chose to further investigate this reaction through a collection of studies of catalyst optimization, substrate scope, and preliminary mechanistic studies.[174]

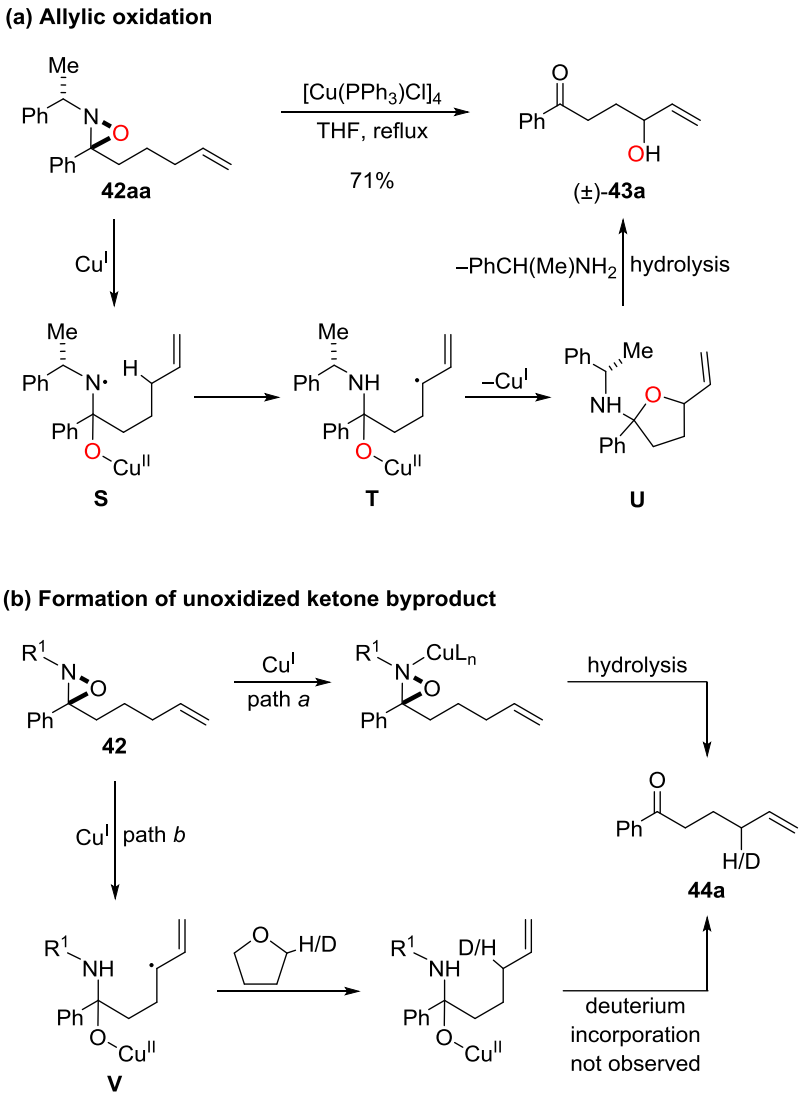
Results and Discussions

Initial Observations and Mechanistic Framework. We believe that the reaction of oxaziridine **42aa** proceeds through a radical mechanism as outlined in Scheme 42a. In the first step, SET from the metal catalyst to the oxaziridine gives a radical/anion pair **S** as previously proposed.[170a,171e,175] 1,5-Hydrogen atom transfer to the nitrogen-centered radical via abstraction from the allylic C–H bond[164j,176] then generates the carbon-centered allylic radical **T**. Presumably, the longer tether length, which permits a six-membered transition structure culminating in an allylic hydrogen atom makes this hydrogen transfer step more facile compared to addition to the olefin as observed previously.[170a] Conversion of **T** to intermediate **U** can be viewed in several ways. First, an oxygen-centered radical would be generated via homolysis, coupled with regeneration of the Cu(I) catalyst; the 2-aminotetrahydrofuran intermediate **U** might then form by radical recombination. Alternatively, the radical species might attack the bound copper atom to afford an allyl Cu(III) oxide, which would undergo reductive elimination (related Cu(III) species have been proposed in ring-opening reactions of diaziridinones[177]). Finally, SET between the allylic radical and the oxygen radical could afford an allylic cation/oxygen-centered anion pair that would suffer cyclization to afford the hemiaminal **U**. In any case, hydrolysis of **U** then leads to the observed allylic alcohol product **43a**.

The major side product of the reaction is unoxidized ketone **44a** from which the oxaziridine was initially derived (Scheme 42b). This could in principle arise from Lewis acid-catalyzed hydrolysis of the oxaziridine (path *a*)[146,178] or by a mechanism involving the intermolecular quenching of the allylic radical **V** or the primary intermediate similar to **S** by solvent (path *b*).[171a,179] We note that ketones and other byproducts have also been observed in other SET reactions of oxaziridines with ferrous ions.[146,171a] When one example of an oxaziridine **42ab** (for structure, see Table 17, entry 2) was subjected to the above

conditions in THF-d_8, no incorporation of deuterium was observed in the ketone isolated from that experiment, which is consistent with path *a* being operative for this side reaction.

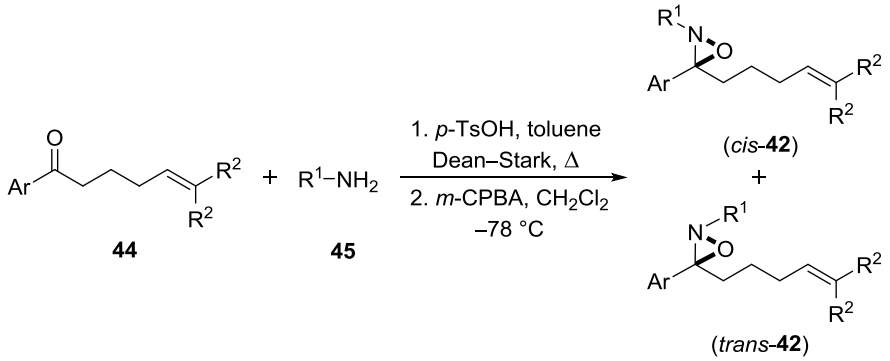
Scheme 42. Proposed Mechanism



Exploration of Reaction Conditions. To examine this oxaziridine-mediated intramolecular C–H bond oxidation, we began with the screening of nitrogen substituents on the oxaziridine and optimization of the reaction conditions. To do so, oxaziridines were prepared as described in previous reports.[151c,161f,170a,c] In general, imines were formed by

combining ketone **44** and the respective amine **45** in refluxing toluene using a Dean–Stark apparatus. The imine solution was then cooled to –78 °C and treated with purified *m*-CPBA (olefin epoxidation is known not to compete with oxaziridination under these circumstances[161f,170a,180] and that was the case here as well; Scheme 43). The oxidation of a mixture (*E* and *Z* isomers) of chiral, enantiomerically pure imines by peracid can give rise to four non-racemic oxaziridine diastereomers (see isomers **I**–**IV** in Figure 19).[149b,c,181] Where possible, a pure oxaziridine isomer was isolated from the stereoisomeric mixture of oxaziridines. The stereochemical assignments for oxaziridine diastereomers were made based on established spectroscopic trends (see Table S26 in the Experimental Section).[151b,161f,170a,181-182]

Scheme 43. General Preparation of Oxaziridines



Although there is no particular nomenclature for assigning oxaziridine stereoisomers, we and others have used cis or syn versus trans or anti to describe the relationship between the nitrogen substituent and the highest priority substituent at C-3 of the oxaziridine ring (Figure 19).[151c,161c,181,183] For example, in **I** and **II**, the nitrogen substituent (α-methylbenzyl group) and aryl group (Ar) are on the same side with respect to the oxaziridine ring and thus are designated as cis isomers. On the other hand, for **III** and **IV**, those two substituents are on opposite side of the oxaziridine ring and are therefore classified as trans isomers.

Additionally, in cases where the nitrogen atom bears a chiral substituent, the use of like and unlike may be used to describe the relative stereochemical relationships between the chiral substituent on the nitrogen atom and the stereogenic nitrogen center of the oxaziridine ring.[181,184] Hence, in the case of **I** and **IV**, where the nitrogen center has an *R* configuration and its substituent (α-methylbenzyl group) has an *S* configuration, they are assigned as unlike, whereas in the case of **II** and **III**, where the nitrogen center has an *S* configuration, they are assigned as like.[181] Previous work has shown that the ratio of oxaziridine diastereomers are obtained in a following order (**I** > **IV** > **II** > **III**) when synthesized through the peracid oxidation of imine.[172,181] Also, *E*- and *Z*-nomenclature have been commonly used for assigning the stereochemistry of oxaziridines.[149b,185] In this context, we prefer using cis and trans notation for assigning oxaziridine diastereomers bearing an achiral nitrogen substituent as shown for **V** (Figure 19).

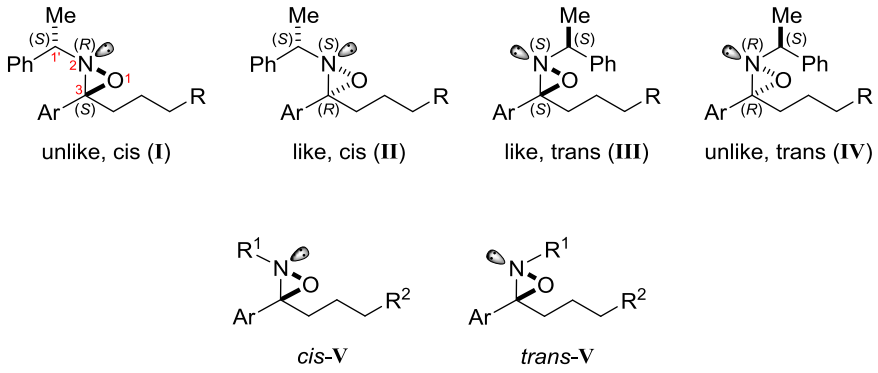
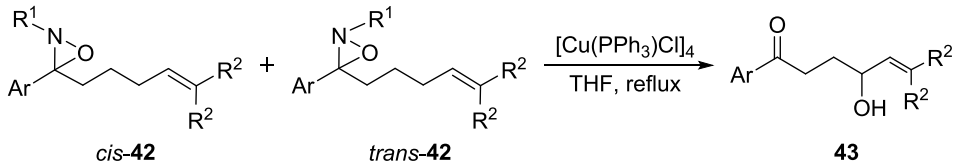


Figure 19. Stereochemical nomenclature for oxaziridine stereoisomers.

Experiments using the single diastereomer of oxaziridine **42aa** with $[Cu(PPh_3)Cl]_4$ (shown in Schemes 41 and 42a) gave racemic allylic alcohol **43a** in 71% yield (enantiomeric composition of **43a** was determined by Mosher ester analysis).[172] The same reaction of oxaziridine **42aa** with $[Cu(PPh_3)Cl]_4$ was repeated to afford **43a** in 69% yield (ca. 5% ee by chiral GC analysis) demonstrating good reproducibility of the transformation

(Table 17, entry 1). Consequently, we focused our initial efforts on exploring the racemic reaction of oxaziridines derived from simple primary amines and aryl-4-alkenyl ketones (Table 17). Although a variety of oxaziridines derived from branched amines were effective in executing the transformation to allylic alcohols, no such product was obtained from an oxaziridine bearing an *N*-benzyl group (Table 17, entry 4). It is possible that the relatively more accessible nitrogen atom in this system is better able to directly coordinate with the copper catalyst, resulting in hydrolysis being more competitive with SET, but the reasons for the failure of this substrate to undergo the catalytic process of interest were not further explored. Among the various nitrogen substituents tried, oxaziridines derived from cyclohexylamine **45b** gave the best results and were chosen for the optimization of reaction conditions and exploration of substrate scope. Such oxaziridines gave results comparable to those from α-methylbenzylamine (cf. entries 1 and 2, 5 and 6, and 7 and 8). Moreover, cyclohexylamine is inexpensive, achiral (thus lowering the number of oxaziridine stereoisomers), and conveniently has a relatively high boiling point compared to other simple aliphatic amines.

Table 17. Screening of Amine Substituent[a]



cis-**42** *trans*-**42** **43**

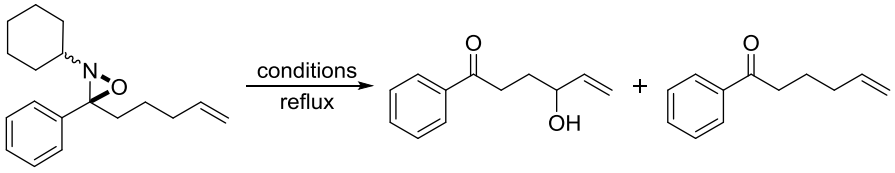
entry	oxaziridine **42**	Ar	R^1	R^2	oxaziridine (cis:trans ratio)	product **43**	yield (%)[b,c]
1	**42aa**	Ph	(*S*)-PhCH(Me)	H	ca. 92:8[d]	**43a**	69
2	**42ab**	Ph	*c*-C_6H_{11}	H	>98:2[e]	**43a**	74
3	**42ac**	Ph	Ph_2CH	H	77:23[f]	**43a**	22 (26)[g,h,i]
4	**42ad**	Ph	$PhCH_2$	H	>95:5	**43a**	0[j]
5	**42ba**	3,4-di-OMePh	(*S*)-PhCH(Me)	H	>98:2[e]	**43b**	48
6	**42bb**	3,4-di-OMePh	*c*-C_6H_{11}	H	>98:2[e]	**43b**	37[k]
7	**42ca**	Ph	(*S*)-PhCH(Me)	Me	90:10	**43c**	74[i]
8	**42cb**	Ph	*c*-C_6H_{11}	Me	63:37	**43c**	64[k]
9	**42cc**	Ph	Ph_2CH	Me	70:30	**43c**	65[l,m]

[a]Reaction was performed using 1 equiv of oxaziridine and 5 mol % $[Cu(PPh_3)Cl]_4$ in THF (10–20 mL) under refluxing conditions for 3 h under an argon atmosphere, unless otherwise noted. [b]Isolated yields. [c]In all cases, unoxidized ketones **44** were also obtained (see the Experimental Section for details). [d]Oxaziridine diastereomers were contaminated with ca. 12% of **44a**. [e]Only single diastereomer was observed by ^1H and ^{13}C NMR. [f]Oxaziridine diastereomers were contaminated with ca. 12% of dibenzhydrylamine impurity. [g]Yield in parentheses is based on the recovery of the oxaziridine substrate. [h]The reaction mixture was refluxed for 1.5 h. [i]4.5 mol % $[Cu(PPh_3)Cl]_4$ was used. [j]Unoxidized ketone **44a** was the only observed product (recovered in 96% yield). [k]The reaction mixture was refluxed for 1 h. [l]3.7 mol % $[Cu(PPh_3)Cl]_4$ was used. [m]The reaction mixture was refluxed for 8 h. *c*-C_6H_{11} = Cyclohexyl.

The initial results for the transformation of the oxaziridines to allylic alcohols with $[Cu(PPh_3)Cl]_4$ (Scheme 41) were encouraging, so we examined the reactions of an equal mixture of *cis*- and *trans*-oxaziridine diastereomers of **42ab** with other copper and iron salts, known to promote SET reactions (Table 18).[146,170a,c,171a,179a] In general, all of the reactions examined afforded varying quantities of oxidized product **43a** with unoxidized

ketone **44a** except for the control reaction (entry 1), in which no product was observed in the absence of copper source. In some cases, minor side products were also observed but not characterized.[170c,171a] A range of results were obtained when we examined the effects of solvent and different copper salts (entries 2–15). Use of either Cu(II) (entry 13) or Cu(I) (entry 14) sources resulted in similar yield for the reaction. In contrast, iron salts were wholly ineffective (entries 10–12).

Table 18. Optimization of Reaction Conditions for the Transformation of Oxaziridines to Allylic Alcohols[a]



42ab (cis:trans = 1:1) (±)-**43a** **44a**

entry	catalyst (5 mol %)	ligand (5 mol %)	solvent	yield (%)[b]	
				43a	**44a**
1	none	–	THF	–	trace[c]
2	$[Cu(PPh_3)Cl]_4$	–	THF	46	23
3	$[Cu(PPh_3)Cl]_4$	–	Toluene	14	47
4	$[Cu(PPh_3)Cl]_4$	–	*i*-PrOH	30	25
5	$[Cu(PPh_3)Cl]_4$	–	Benzene	6	72
6	$[Cu(PPh_3)Cl]_4$	–	CH_2Cl_2	41	36
7	$Cu(OTf)_2$	–	THF	53	26
8	$Cu(acac)_2$[d]	–	THF	16	9
9	$CuBr{\cdot}SMe_2$	–	THF	16	67
10	$Fe(acac)_2$[c,e]	–	THF	–	–
11	$Fe(acac)_3$[c]	–	THF	–	–
12	$FeBr_2$[c,f]	–	THF	4	14
13	$CuCl_2$	–	THF	50	22
14	CuCl	–	THF	50	17
15	CuCl and LiCl	–	THF	31	31
16	CuCl	2,2′-Bipyridyl	THF	51	14

17	CuCl	(*S*)-BINAP	THF	61[g]	9
18	**CuCl**	***rac*-BINAP**	**THF**	**63**	**9**
19	CuCl	*rac*-BINAP	CH_3CN	63	8
20	CuCl[h]	*rac*-BINAP[h]	THF	58	8
21	CuCl[i]	*rac*-BINAP[i]	THF	54	3
22	CuCl	*rac*-BINAP	MeOH	–[j]	76
23	CuCl	dppp[k]	THF	43	9
24	CuCl[c]	Xantphos	THF	–	11
25	CuCl	dcppe[l]	THF	53	6
26	CuCl	(*S*)-Xylyl-P-Phos	THF	50	5
27	CuCl	bdppmb[m]	THF	56	17

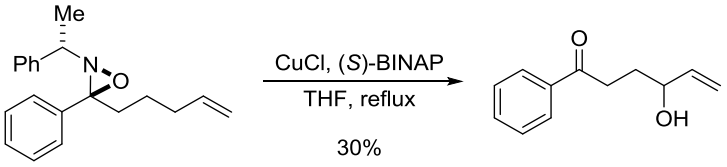
[a]Reaction was performed using 1 equiv of oxaziridine, 5 mol % catalyst, and 5 mol % ligand in solvent under refluxing conditions for 1 h under an argon atmosphere, unless otherwise noted. [b]Isolated yields. [c]Oxaziridine was completely recovered except for entries 12 and 24. [d]The reaction mixture was refluxed for 1.5 h. [e]The reaction mixture was refluxed for 4 h. [f]The reaction mixture was refluxed for 2.5 h. [g]Allylic alcohol **43a** was obtained in ca. 5% ee by chiral GC analysis. [h]10 mol % of CuCl and *rac*-BINAP were used. [i]1 mol % of CuCl and *rac*-BINAP were used. [j]No product was observed in this case. [k]dppp = 1,3-Bis(diphenylphosphino)propane. [l]dcppe = Bis(dicyclohexylphosphinophenyl)ether. [m]bdppmb = 1,2-Bis(diphenylphosphinomethyl)benzene.

We also investigated various additives in attempts to improve the conversion to desired product (Table 18, entries 16–27). Interestingly, allylic alcohol **43a** was obtained in significantly higher yield when the reaction was catalyzed by a CuCl/BINAP complex (entries 17–19). Moreover, the ratio of **43a** to **44a** was considerably increased using these conditions (cf. entry 2 with entry 18). No improvement in yield was observed with other phosphine ligands (entries 23–27). No enantioselectivity was observed with (*S*)-BINAP (entry 17) and the yield obtained was comparable to that obtained using *rac*-BINAP. On the basis of these results, we chose to adopt CuCl and *rac*-BINAP as our standard reaction conditions, along with the originally identified $[Cu(PPh_3)Cl]_4$, both in 5 mol % (note that for the tetrameric $[Cu(PPh_3)Cl]_4$, this corresponds to 20 mol % of Cu(I)). Reaction yields

were only slightly affected when the reaction was carried out with 10 vs 1 mol % of CuCl/*rac*-BINAP (cf. entries 20 and 21). Solvent had a substantial effect on reaction yields, either with or without additives, with THF and ACN being best among those examined (entries 18 and 19). In contrast, nonpolar hydrophobic solvents were essentially useless in this context (entries 3 and 5).

We observed initially that the reaction of non-racemic **42aa** with achiral $[Cu(PPh_3)Cl]_4$ gave racemic allylic alcohol **43a** (see Schemes 41 and 42a and Table 17, entry 1). Similarly, the reaction of racemic mixture of diastereomers **42ab** (cis:trans = 1:1) with chiral CuCl/(*S*)-BINAP complex did not afford any enantioselectivity (see Table 18, entry 17). Finally, the combination of chiral substrate **42aa** and chiral CuCl/(*S*)-BINAP complex to bring about the asymmetric transformation was attempted. Unfortunately, again allylic alcohol **43a** was obtained as a racemic mixture (ca. 5% ee by chiral GC analysis) and with a significantly lower yield of 30% (Scheme 44).

Scheme 44. Reaction of Non-Racemic Oxaziridine Diastereomer with Chiral Catalyst/Ligand Complex



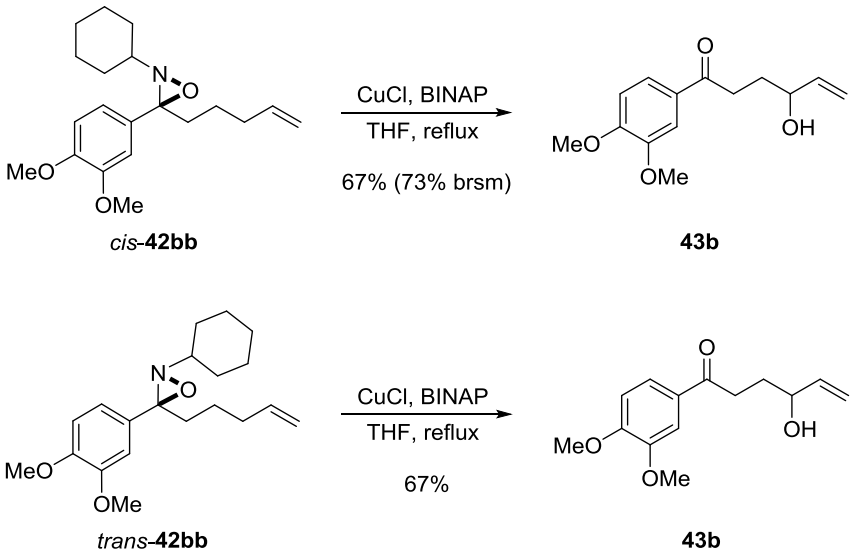
42aa (±)-**43a** (ca. 5% ee)

The absence of enantioselectivity of the reaction may be explained in the context of the proposed mechanism (Scheme 42a). Even if the hydrogen abstraction step were stereoselective, the conformational flexibility of the allylic side chain could combine with a lack of facial selectivity in the ensuing radical- or SET-mediated recombination step. The failure of a chiral additive to overcome these obstacles could be due to (1) too much

distance between the ligand and the forming C–O bond, (2) the complete disassociation of the ligand prior to this stage of the reaction, or (3) simply not enough chiral differentiation afforded by the ligands tried.

We were able to separate the two oxaziridine diastereomers of the 3,4-dimethoxyphenyl substrate **42bb**. Subjecting each separately to identical reaction conditions afforded **43b** in comparable yields (Scheme 45). Pragmatically, this means that one need not worry about obtaining diastereomerically pure samples for carrying out the oxidation process (in stark contrast to the chemistry shown in Scheme 40). It is also consistent with a mechanism in which N–O bond cleavage is the first step (affording, here, enantiomeric intermediates; also see Scheme 42a).

Scheme 45. Examination of Oxaziridine Diastereomers



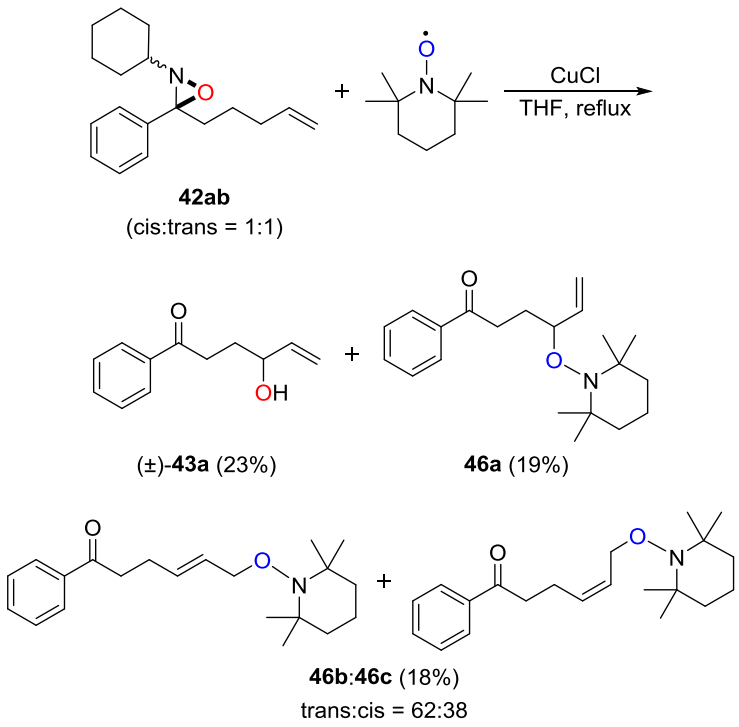
cis-**42bb** **43b**

trans-**42bb** **43b**

The involvement of radicals in the copper-catalyzed allylic oxidations by peroxy esters, also accounting for the regeneration of the active copper(I) species, has been supported by kinetic and electron spin resonance (ESR) studies.[166b,186] Recently, Yoon and co-workers have proposed and provided good evidence for a radical mechanism for the

oxaziridine-mediated oxyamination reaction and oxidative functionalization of alkenes with Davis-type oxaziridines.[168c,e] Although strong evidence for the generation of the radical species was obtained, they were unable to trap the radical intermediate leading to the aminohydroxylation product using standard trapping reagents such as TEMPO.[168c] In order to support the mechanistic hypothesis proposed for the present C–H oxidation, we too decided to attempt a radical-trapping experiment with TEMPO.[171b,187]

Scheme 46. Radical-Trapping Experiment with TEMPO

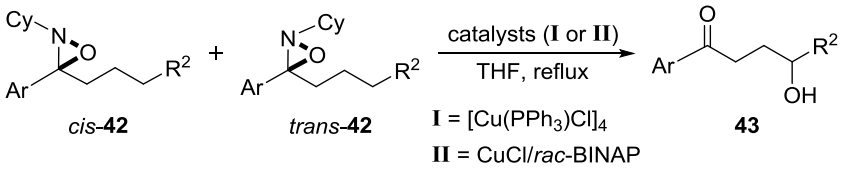


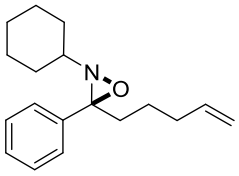
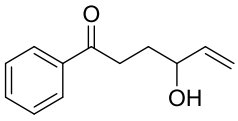
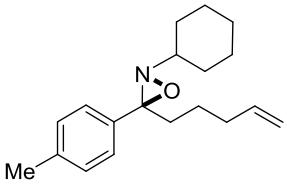
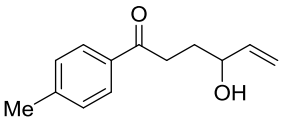
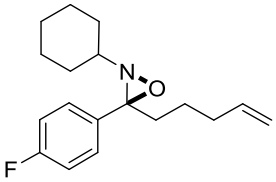
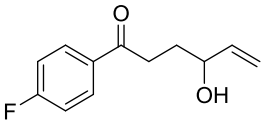
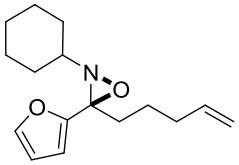
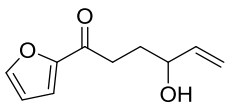
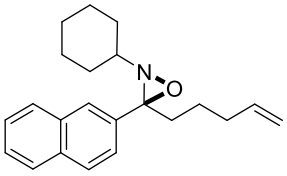
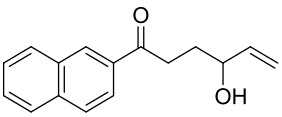
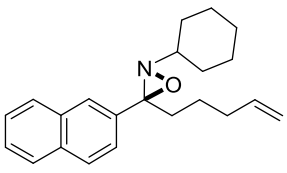
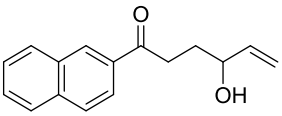
To this end, the reaction was carried out under the standard conditions with a stoichiometric amount of TEMPO added (Scheme 46). The product profile of this experiment included three products that incorporated TEMPO in addition to allylic alcohol **43a**, which was obtained in 23% yield. Thus, the internally substituted product **46a** was obtained in 19% yield and terminal radical-trapped products were obtained as a mixture of trans and cis isomers (**46b**:**46c** = 62:38) in a combined 18% yield. The formation of these

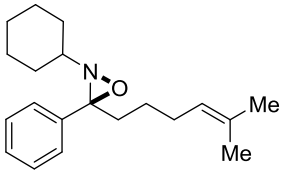
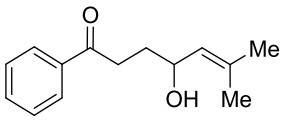
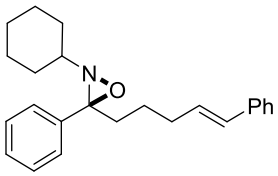
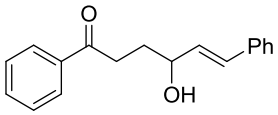
TEMPO adducts provides strong evidence for the intermediacy of the allylic radical en route to the allylic alcohol.

Reaction Scope and Limitations. The scope of this transformation was then investigated (Table 19). Oxaziridine substrates were tested with two catalyst systems, $[Cu(PPh_3)Cl]_4$ and a mixture of CuCl and *rac*-BINAP. For the simple phenyl-substituted compound, both catalysts gave similar yields (entry 1). Substrates containing electron-rich (Table 19, entry 2 and Scheme 45) and electron-poor (entry 3) aromatic ring, as well as a furanyl group at C-3 (entry 4), all led to oxidation product. As observed for *cis*- and *trans* - **42bb** (Scheme 45), oxaziridine diastereomers **42gb** containing a naphthyl substituent also afforded the product **43g** in comparable yield (entries 5 and 6). The reaction proceeded in good yields with substituted alkenes as well (entries 7 and 8). Consistent with the proposed mechanism (see Scheme 42a), oxidation of the methylene group closest to the oxaziridine was exclusively observed. The use of CuCl/BINAP complex resulted in better yields in most but not all cases (e.g., the sterically demanding case in entries 5 and 6). Oxaziridines bearing ortho substitution on the C-3 phenyl group or with substitution alpha to the oxaziridine ring could not be synthesized using our standard protocol, presumably because of an increase in the steric environment around the carbonyl group (Figure 20). Replacement of phenyl with cyclohexene group also did not lead to the oxaziridine formation. The synthesis of *N*-sulfonyloxaziridine with tethered alkene at C-3 was unsuccessful as the formation of imine with benzenesulfonamide could not be achieved under various conditions (Figure 20).

Table 19. Substrate Scope for Intramolecular C–H Oxidation[a]



entry	oxaziridine	cis:trans ratio	product	catalyst: yield (%)[b,c]
1		>98:2[d] >98:2[d]		**I**[e]: 74 **II**: 74
	42ab		**43a**	
2		– 48:52		**I**: ND **II**: 57
	42db		**43d**	
3		88:12 58:42		**I**: 50 **II**: 66
	42eb		**43e**	
4		>95:5 –		**I**: 51 **II**: ND
	42fb		**43f**	
5		90:10 90:10		**I**[e]: 57[f] **II**: 46 (57)[g]
	cis-**42gb**		**43g**	
6		16:84 16:84		**I**[e]: 41[h] **II**: 53 (73)[g]
	trans-**42gb**		**43g**	

entry	oxaziridine	cis:trans ratio	product	catalyst: yield (%)[b,c]
7	 **42cb**	63:37 >95:5	 **43c**	**I**: 64 **II**: 75
8	 **42hb**	60:40 60:40	 **43h**	**I**: 72 **II**: 69

[a]Reaction was performed using 1 equiv of oxaziridine, 5 mol % catalyst, and 5 mol % ligand in THF under refluxing conditions for 1 h under an argon atmosphere, unless otherwise noted. [b]Isolated yields. [c]In all cases, unoxidized ketones **44** were obtained as a side product. [d]Only single diastereomer was observed by ^{1}H and ^{13}C NMR. [e]The reaction mixture was refluxed for 3 h. [f]4.5 mol % $[Cu(PPh_3)Cl]_4$ was used. [g]Yield in parentheses represents the yield based on the recovery of the starting oxaziridine. [h]4.2 mol % $[Cu(PPh_3)Cl]_4$ was used. ND = Not determined.

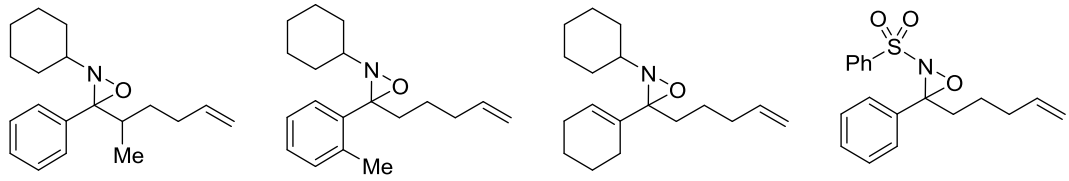
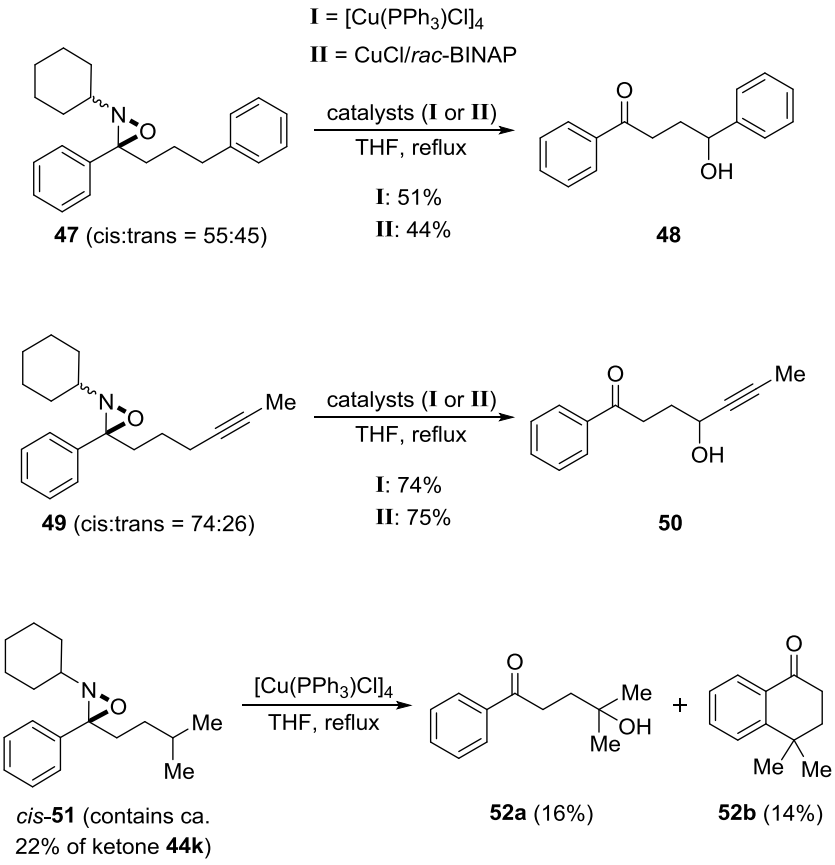


Figure 20. Unsuccessfully targeted oxaziridines.

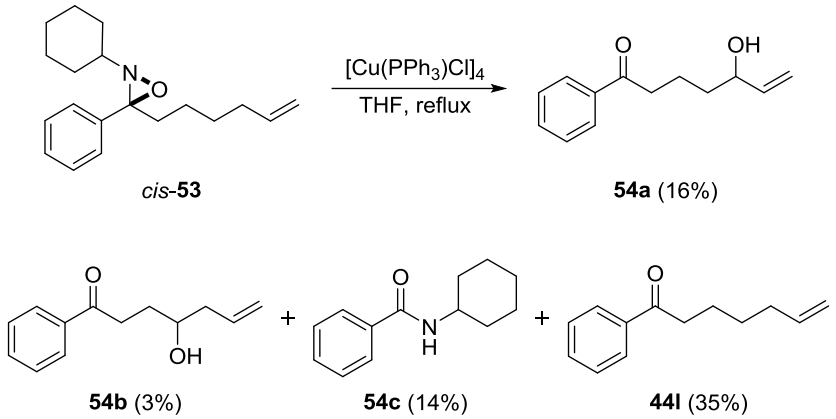
In addition to the olefin-containing substrates, it proved possible to oxidize benzylic and propargylic C–H bonds in modest to good yields (Scheme 47). The potential versatility of this transformation was further shown through the oxidation of the unactivated tertiary C–H bond to afford the tertiary alcohol **52a**, albeit in low yield (Scheme 47). In this case, a cyclized product **52b** was also obtained, which could result from radical cyclization between the tertiary radical and the phenyl group[170b,c] or from electrophilic aromatic substitution with a tertiary carbocation formed from the ionization of tertiary alcohol.[188]

Scheme 47. Survey of Non-Alkenyl Oxaziridines



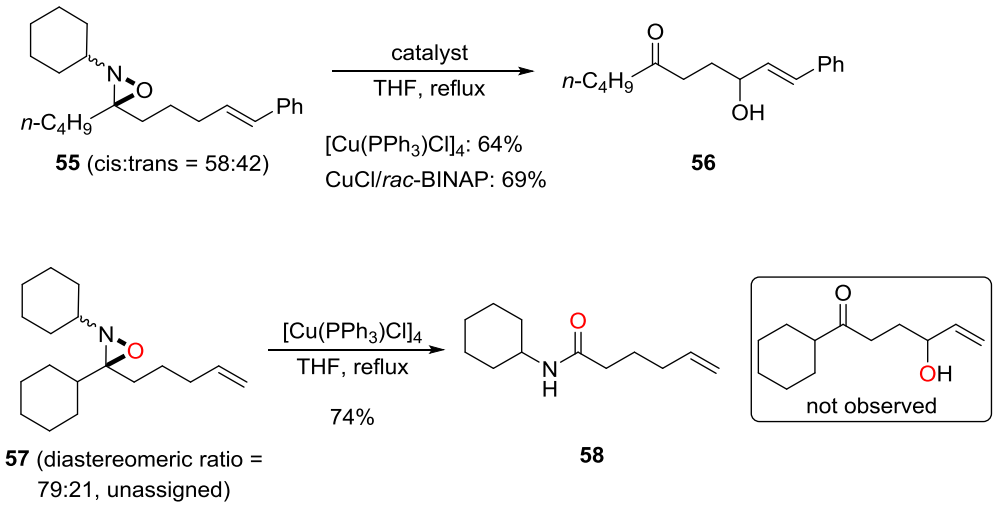
Two additional cases help delineate the limits of this oxidation reaction. When we examined the behavior of a single diastereomer *cis*-**53** of the oxaziridine substrate bearing a four-carbon tether in the presence of $[Cu(PPh_3)Cl]_4$ (Scheme 48), we observed three different products in low yields in addition to the usual reversion to ketone. Allylic alcohol **54a** arising from 1,6-hydrogen transfer was obtained in very low yield, whereas homoallylic alcohol **54b** from 1,5-hydrogen transfer was formed in trace amount. Amide **54c** was also obtained in low yield resulting from β-scission.[146,170c] These results are consistent with the need for both a stable radical intermediate for oxidation as well as a favorable geometry for hydrogen atom abstraction. Similar transformation of the mixture of oxaziridine diastereomers (*cis*- and *trans*-**53**) with CuCl/BINAP complex was less effective than the $[Cu(PPh_3)Cl]_4$ (see the Experimental Section for details).

Scheme 48. Reaction of Oxaziridine with a Four-Carbon Tether



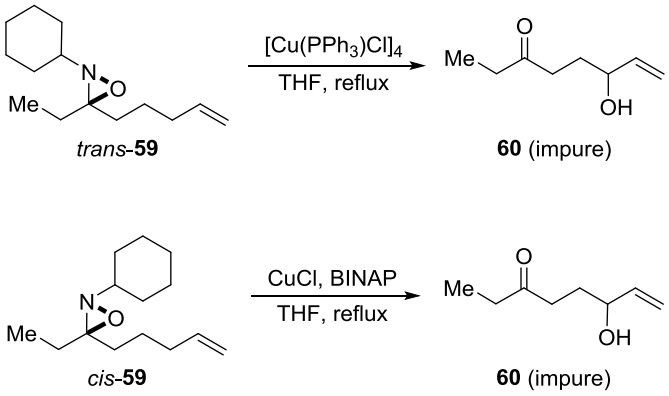
In our previous work, we found that the cyclization reactions shown in Scheme 40 were derailed when the oxaziridine′s C-3 aryl group was replaced with an alkyl substituent capable of forming a stable carbon-centered radical. In those instances, the main reaction pathway was *β*-scission of the C–C bond adjacent to the proposed *N*-centered radical.[170b,c] In the present case, we found divergent behavior for primary vs secondary alkyl groups at the analogous position. Accordingly, the substrate bearing an *n*-butyl subsituent at C-3 afforded the allylic alcohol **56** in good yield but the cleaved amide product **58** was observed upon reaction of the oxaziridine with a cyclohexyl substituent (Scheme 49).

Scheme 49. Dependence of Product on 3-Alkyl Substituent



Another oxaziridine substrate with an ethyl subsituent at C-3 was also examined. Thus, reactions of *trans*- and *cis*-diastereomers of oxaziridine **59** were performed separately with $[Cu(PPh_3)Cl]_4$ and CuCl/*rac*-BINAP, respectively (Scheme 50). In both cases, allylic alcohol **60** obtained was contaminated with unidentified byproducts and impurities. Although various purification attempts were unsuccessful, ^{1}H NMR spectra for the impure sample of **60** in both cases showed characteristic peaks of allylic alcohol. However, the product was volatile and obtained in a small amount rendering its further purification unfeasible.

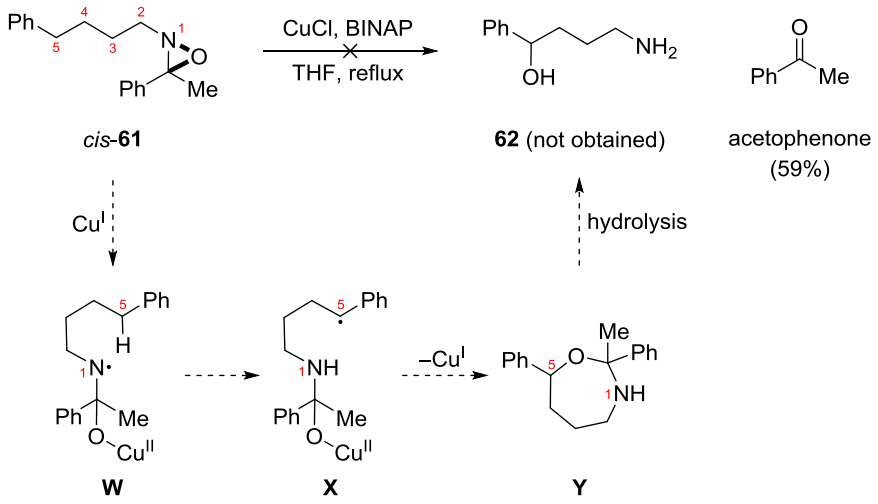
Scheme 50. Evaluation of Oxaziridine Substrate with 3-Ethyl Substituent



Given the success with the transformation of oxaziridines to allylic alcohols, we considered the formation of amino alcohol from an analogous transformation by changing the position of the reactive site on the oxaziridine substrate. During this attempt, we synthesized oxaziridine diastereomers **61**, which incorporated a potentially labile C–H bond as a part of the amine substituent rather than the oxaziridine C-3 alkyl side chain. The formation of **62** was expected based on the mechanism shown in Scheme 51, where initial 1,5-hydrogen atom transfer to a nitrogen-centered radical **W** could in principle lead to a carbon-centered benzylic radical **X**. The radical recombination of an ensuing oxygen-

centered radical and the benzylic radical would then form the heminaminal intermediate **Y**, which upon hydrolysis would yield the desired product **62** and acetophenone (PhCOMe). Unfortunately, the reaction of oxaziridine diastereomer *cis*-**61** with CuCl/*rac*-BINAP under analogous reaction conditions did not lead to amino alcohol **62** (Scheme 51). Instead, a complex mixture was observed from which acetophenone was recovered in ca. 59% yield. The slower ring-closure kinetic rate for the formation of seven-membered cyclic heminaminal **Y** compared to the faster Lewis acid-catalyzed hydrolysis of oxaziridine **61** to acetophenone could be one potential reason for the failure of this reaction.

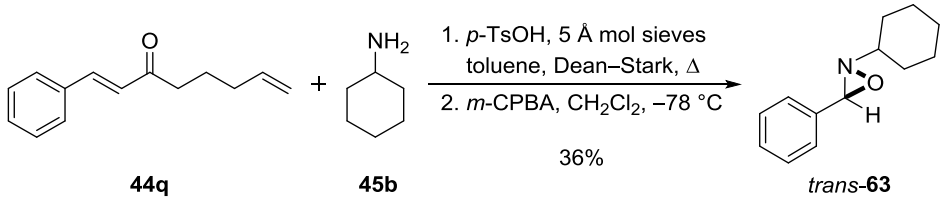
Scheme 51. Failed Attempt towards the Synthesis of Amino Alcohol 62

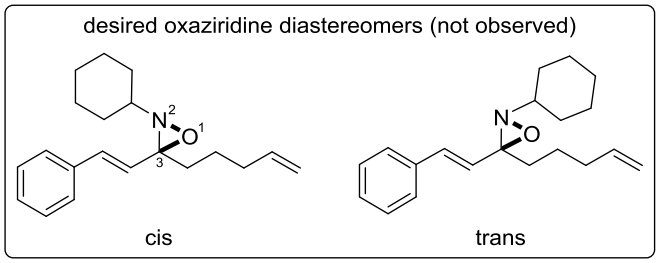


When α,β-unsaturated ketone **44q** was subjected to oxaziridination conditions, an unexpected product *trans*-**63** was obtained instead of the desired *cis*- and *trans*-oxazirdine diastereomers containing the cinnamyl group at C-3 position (shown in the box; Scheme 52). The formation of *trans*-**63** could be explained through the mechanism shown in Scheme 53. Instead of a desired 1,2-addition to provide imine, a conjugate addition (1,4-addition) of cyclohexylamine **45b** to enone **44q** could form an aminoenol intermediate **AA**, which can tautomerize to an aminoketone **AB**. Under thermal conditions in the presence of

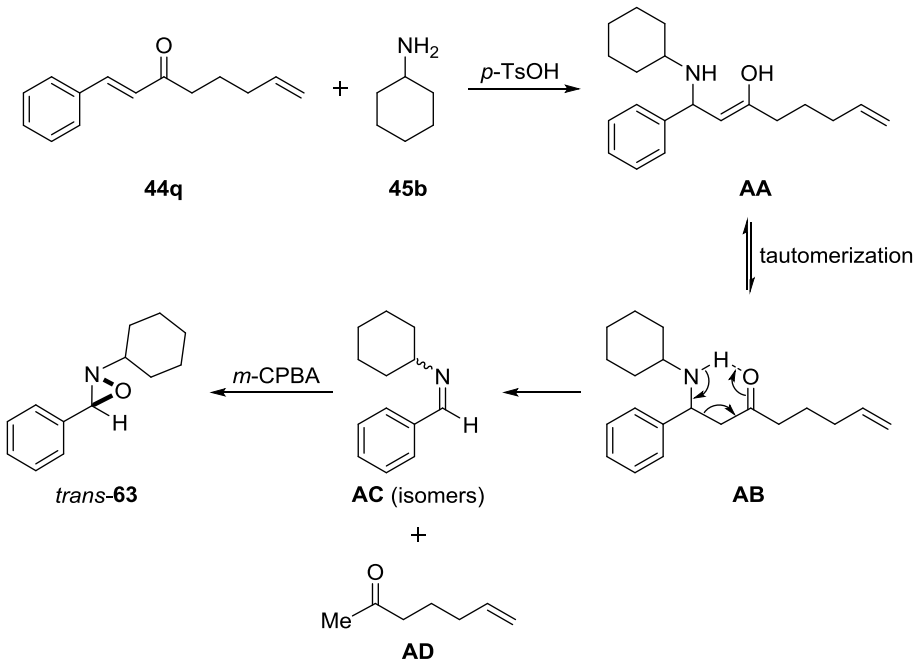
the acid catalyst, the aminoketone **AB** could undergo retro-Mannich reaction[189] to give aldimine isomers **AC** and heptenone **AD**. Presumably, the *E*- and *Z*-isomerization of **AC** could result in a thermodynamically more stable anti isomer (*E*)-**AC** at lower temperature,[190] which upon oxidation with *m*-CPBA would yield oxaziridine *trans*-**63**. The structure of *trans*-**63** was determined by NMR and HRMS and was further confirmed by comparing the chemical shifts of its characteristic peaks in ^{1}H and ^{13}C NMR with the reported values.[185,191]

Scheme 52. Unexpected Formation of Oxaziridine *trans*-63



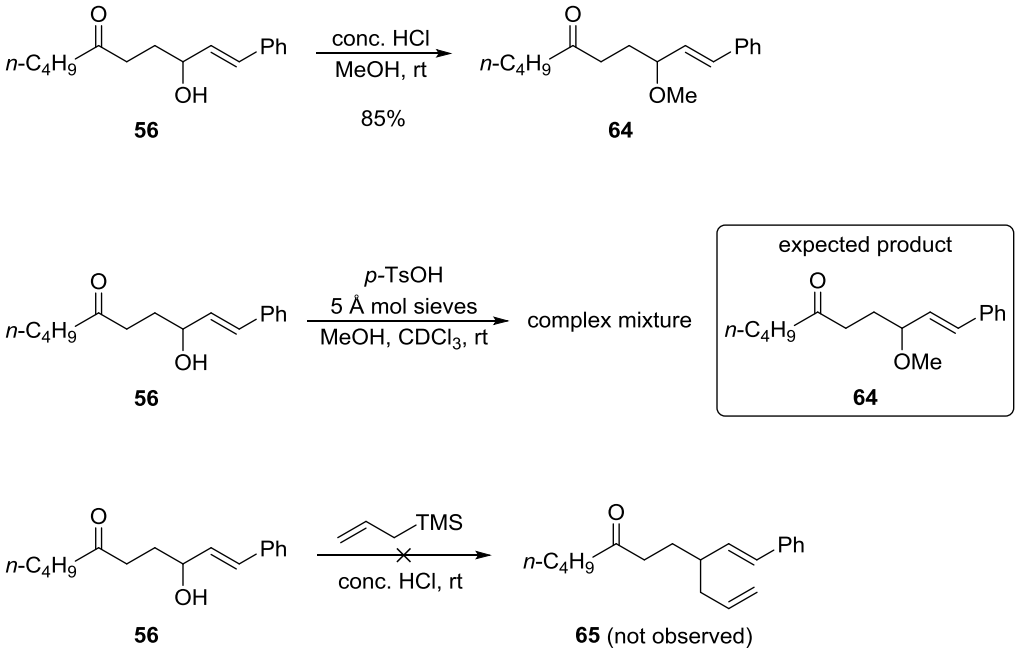


Scheme 53. Plausible Mechanism for the Formation of *trans*-63



The transformation of allylic and benzylic alcohols to their corresponding ether derivatives through solvolytic etherification is known.[192] When allylic alcohol **56** was treated with methanol (MeOH, CH_3OH) in the presence of HCl, allylic ether **64** was obtained in good yield (Scheme 54). The reaction proceeds via the formation of a stabilized carbonium intermediate. Although allylic transposition is possible, however, given the stability of highly conjugated allylic carbocation, only a direct substitution of the acid-activated alcohol by MeOH takes place giving rise to the more stable product.[193] Reaction with *p*-TsOH using superstoichiometric amount of MeOH (ca. 20 equiv) in $CDCl_3$ gave a complex mixture (Scheme 54). For the HCl-catalyzed reaction of **56**, changing the nucleophile from alcohol to allyl silane did not lead to the desired allyl-substituted product **65**.

Scheme 54. Conversion of Allylic Alcohol to Allylic Ether



Conclusions

In summary, we have developed an efficient regio- and chemoselective copper-catalyzed transformation of oxaziridines to allylic alcohols via an intramolecular C–H bond oxidation. The reaction works well with a variety of substrates, but activated C–H bonds are preferred. Support for a radical mechanism has been demonstrated through radical-trapping experiment with TEMPO. Future work will focus on further development of the scope of this oxidation reaction, including additional substrate types (hopefully to include intermolecular variations) and the exploration of asymmetric transformations.

2.3 Experimental Section

General Information. All reactions were performed under an inert atmosphere (argon or nitrogen) in flame-dried glassware. The stainless steel needles used for handling anhydrous solvents and reagents were oven dried and flushed with dry argon prior to use. Plastic syringes were flushed with dry argon before use. All chemicals were used as received from commercial source without further purification. Methylene chloride and THF were dried by passage through neutral alumina columns using a commercial solvent purification system prior to use. TLC was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Preparative TLC was carried out using silica gel GF TLC plates (UV 254 nm, 1000 microns). Visualization was accomplished with UV light and Seebach's stain or aqueous $KMnO_4$ by heating. Flash chromatography was carried out using standard grade silica gel (40–63 μm particle size, 230 × 400 mesh) with compressed nitrogen as a source of positive pressure. Preparative reverse-phase HPLC purification was performed using UV detection (photodiode array detector). The method utilized a Prep C18 OBD column (30 × 150 mm, 5 μm) and gradient system eluting from 70:30 (**B**:**A**) to 99:1 (**B**:**A**) (solvent system **A**: water:ACN (99:1) containing 0.10% TFA and solvent system **B**: ACN:water (99:1) containing 0.1% TFA) at a constant flow rate of 50 mL/min and a run time of 13 min. The fractions were collected using an automated fraction collector. IR spectra were acquired as thin films or solids. All NMR samples were recorded in $CDCl_3$. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent (δ 7.26 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR). Coupling constants are given in Hertz (Hz). HRMS data were taken using a time of flight (TOF) mass analyzer and an electrospray ion source. Melting points were determined in open capillary tubes using a capillary melting point apparatus and are

uncorrected. Chiral gas chromatography was carried out on a GC System with triple-axis HED-EM detector (5975C VL MSD) and helium as the carrier gas; a B-DM chiral capillary column (30.0 m × 250 μm × 0.12 μm nominal) was employed. The temperature was programmed from 45 °C to 190 °C with a run time of 24.50 min.

Experimental Procedures

General Procedure G for the Synthesis of Oxaziridine Substrates. To a solution of starting ketone **44** (1.0 equiv) in toluene was added amine **45** (1.5 equiv), PTSA (0.050 equiv), and activated 4 or 5 Å molecular sieves and the reaction mixture was allowed to reflux using a Dean–Stark apparatus for 60 h (24 h for compound **42aa**, **42aa′**, and **42aa″** and 72 h for compound **42ba** and **42ba′**) under nitrogen atmosphere (most of the toluene was distilled off into Dean–Stark trap before cooling). The crude solution of imine was then cooled to –78 °C, diluted with CH_2Cl_2, and treated slowly with a solution of purified *m*-CPBA[194] (>95%, 1.2 equiv) in CH_2Cl_2 under nitrogen atmosphere. The reaction was stirred for 30 min at –78 °C, quenched with saturated aqueous solution of sodium thiosulfate ($Na_2S_2O_3$), and allowed to warm to rt. The resulting mixture was filtered under suction and washed with CH_2Cl_2. The filtrate was diluted with water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 once, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ twice and brine once, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on a silica gel or preparative TLC afforded the product. The assignment of oxaziridine diastereomers with their structures is given at the end of the Experimental Section (see Table S26).

General Procedure H for Grignard Reaction Followed by PCC Oxidation. ***Grignard reaction.*** A flame-dried two-necked round bottom flask equipped with a dropping funnel was charged with magnesium turnings (1.2 equiv) and 1–2 small crystals of iodine in THF under an argon atmosphere. A solution of 5-bromo-1-pentene (1.2 equiv) in THF was added drop wise to the stirring suspension of magnesium to maintain a gentle refluxing of THF (I_2 color disappears). After the addition, the reaction mixture was gently refluxed for 1 h, after which it was cooled to 0 °C. A solution of aldehyde (1.0 equiv) in THF was added slowly to the cooled suspension at 0 °C over 10 min. The reaction mixture was then stirred at rt for 1–2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with ether twice. The combined organic extracts were washed with water and brine once, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude alcohol, which was used for the next oxidation step without purification.

PCC Oxidation. To a stirring solution of a crude alcohol in CH_2Cl_2 was added pyridinium chlorochromate (PCC) (1.5–2.0 equiv) and the reaction mixture was stirred at rt under nitrogen atmosphere for 1.5–2 h (12 h for compound **44f**). The reaction mixture was filtered through Celite, rinsing with several portions of CH_2Cl_2 or ether, and the filtrate was concentrated under reduced pressure. Purification by chromatography on a silica gel afforded the ketone product.

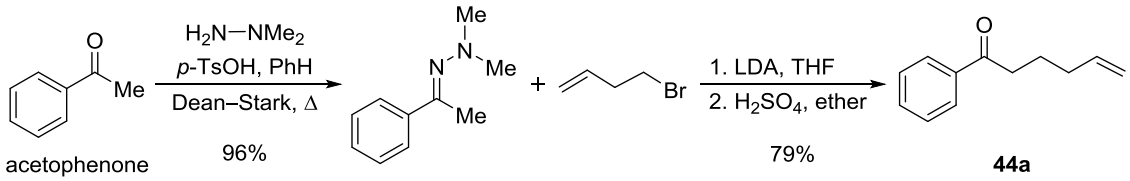
General Procedure I for Intramolecular C–H Oxidation Using $[Cu(PPh_3)Cl]_4$.[195] A flame-dried two-necked round bottom flask equipped with a reflux condenser was charged with $[Cu(PPh_3)Cl]_4$ and THF under an argon atmosphere. The solution was degassed with argon at rt for ca. 5 min and was then allowed to reflux for 30 min. A

solution of oxaziridine in THF was added slowly by a syringe to the refluxing solution of the catalyst, and refluxing was continued for an additional 1–3 h. The solvent was removed under reduced pressure, and the crude mixture was purified by chromatography on a silica gel to afford the product. All successful oxidation products were accompanied by unoxidized ketones **44** (eluted out at 100% CH_2Cl_2 during chromatographic purification), from which oxaziridine was initially derived.

General Procedure J for Intramolecular C–H Oxidation Using CuCl and *rac*-BINAP. A flame-dried two-necked round bottom flask equipped with a reflux condenser was charged with CuCl, *rac*-BINAP, and THF under an argon atmosphere. The solution was degassed with argon at rt for ca. 5 min and was then allowed to reflux for 30 min. A solution of oxaziridine in THF was added slowly by a syringe to the refluxing solution of the catalyst, and refluxing was continued for an additional 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified by chromatography on a silica gel to afford the product. All successful oxidation products were accompanied by unoxidized ketones **44** (eluted out at 100% CH_2Cl_2 during chromatographic purification), from which oxaziridine was initially derived.

General Procedure for the Screening of Amine Substituent Using $[Cu(PPh_3)Cl]_4$ (Table 17). A flame-dried two-necked round bottom flask equipped with a reflux condenser was charged with $[Cu(PPh_3)Cl]_4$ (3.7–5.0 mol %) and THF (7–13 mL) under an argon atmosphere. The solution was degassed with argon at rt for ca. 5 min and was then allowed to reflux for 30 min. A solution of oxaziridine (1.0 equiv) in THF (3–8 mL) was added slowly by a syringe to the refluxing solution of the catalyst, and refluxing was continued for an additional 1–8 h. The solvent was removed under reduced pressure, and

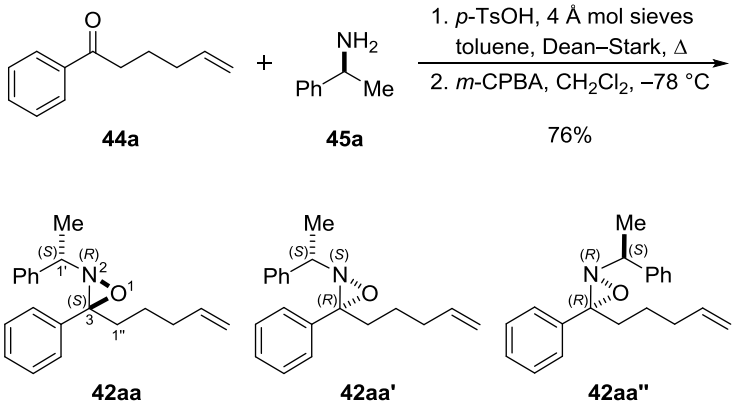
the crude mixture was purified by chromatography on a silica gel to afford the product. All successful oxidation products were accompanied by unoxidized ketones **44** (eluted out at 100% CH_2Cl_2 during chromatographic purification), from which oxaziridine was initially derived.



1-Phenylhex-5-en-1-one (44a).[196] A solution of acetophenone (20.0 g, 166 mmol, 1.0 equiv), *N,N*-dimethylhydrazine (25.0 g, 416 mmol, 2.5 equiv), and PTSA (1.58 g, 8.32 mmol, 0.050 equiv) in benzene (110 mL) was refluxed for 23 h under nitrogen atmosphere with removal of water by a Dean–Stark apparatus. The reaction mixture was concentrated and the residue was purified by vacuum distillation to afford the corresponding hydrazone as a yellow oil in 96% yield (26.0 g, 160 mmol).

To a cooled 1.0 M LDA solution (47.5 mL, 47.5 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added the solution of hydrazone (7.00 g, 43.2 mmol, 1.0 equiv) in THF (30 mL) slowly over 15 min and the reaction mixture was allowed to stir at 0 °C for 5 h. The reaction mixture was then cooled to –78 °C and a solution of 4-bromo-1-butene (7.00 g, 51.8 mmol, 1.2 equiv) in THF (15 mL) was added slowly over 10 min. The reaction was warmed to rt and stirred for 16 h. The reaction mixture was concentrated and the residue was diluted with ether (30 mL) and then treated with an ice-cold solution of dilute H_2SO_4 (30 mL) for 30 min to hydrolyze the hydrazone. The resulting solution was diluted with water and extracted with ether (2 × 35 mL) and the combined organic extracts were washed with water (2 × 25 mL) and brine (20 mL), dried over Na_2SO_4, and

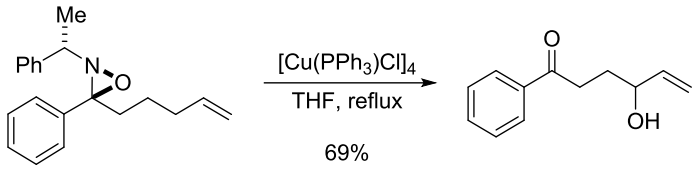
concentrated. Purification by chromatography on a silica gel (1% ether/hexanes) afforded the ketone **44a** as a colorless oil in 79% yield (6.00 g, 34.5 mmol).



(2*R*,3*S*,1′*S*)-3-(Pent-4′′-en-1′′-yl)-3-phenyl-2-(1′-phenylethyl)-1,2-oxaziridine (unlike, *cis*-42aa), (2*S*,3*R*,1′*S*)-3-(Pent-4′′-en-1′′-yl)-3-phenyl-2-(1′-phenylethyl)-1,2-oxaziridine (like, *cis*-42aa′), and (2*R*,3*R*,1′*S*)-3-(Pent-4′′-en-1′′-yl)-3-phenyl-2-(1′-phenylethyl)-1,2-oxaziridine (unlike, *trans*-42aa′′). Following the general procedure **G**, starting ketone **44a** (1.00 g, 5.74 mmol, 1.0 equiv), (*S*)-α-methylbenzylamine **45a** (0.950 mL, 7.46 mmol, 1.3 equiv), PTSA (54.4 mg, 0.287 mmol, 0.050 equiv), and activated 4 Å molecular sieves (10.0 g) in toluene (50 mL) was refluxed for 24 h. The crude solution of imine was cooled to rt, diluted with CH_2Cl_2 (25 mL), and was transferred to a flask containing a suspension of purified *m*-CPBA (1.18 g, 6.88 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL) at –78 °C under nitrogen atmosphere. The reaction was stirred for 30 min at –78 °C, quenched with saturated $Na_2S_2O_3$, and allowed to warm to rt. The resulting mixture was filtered and washed with CH_2Cl_2. The filtrate was diluted with water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (15 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated. Purification by chromatography on a silica gel

(0.5% ether/hexanes) afforded a mixture of three oxaziridine diastereomers (**42aa**, **42aa′**, and **42aa″**) and starting ketone **44a** as a colorless oil (1.28 g, 4.36 mmol, 76% corrected yield; **42aa**:**42aa′**:**42aa″** = ca. 91:5:4 by ^{1}H NMR). Subsequent purification by chromatography on a silica gel (0.5% EtOAc/hexanes) again afforded a mixture of oxaziridine diastereomers and starting ketone **44a** (**42aa**:**42aa′**+**42aa″**:**44a** = ca. 74:14:12 by ^{1}H NMR), followed by another mixture of oxaziridine diastereomers and **44a** (**42aa**:**42aa′**:**42aa″**:**44a** = ca. 71:9:6:14 by ^{1}H NMR). A pure sample of **42aa** for characterization was obtained from a fraction collected during this purification. First diastereomer **42aa** (major): R_f = 0.72 (5% EtOAc/hexanes, run twice); IR (neat) 2976, 2928, 1640, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19–1.31 (m, 2H), 1.40–1.51 (m, 1H), 1.48 (d, J = 6.4 Hz, 3H), 1.74 (m, 1H), 1.91–2.05 (m, 2H), 2.21 (m, 1H), 2.99 (q, J = 6.4 Hz, 1H), 4.86–4.94 (m, 2H), 5.68 (m, 1H), 6.86–6.91 (m, 2H), 7.12 (br s, 2H), 7.19–7.23 (m, 3H), 7.26–7.30 (m, 2H), 7.33–7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 23.2, 33.7, 37.9, 62.8, 88.4, 115.0, 127.6, 127.6, 127.9, 128.2, 128.4, 128.8, 135.0, 138.4, 140.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}NO$ $[M + H]^+$ 294.1858, found 294.1840.

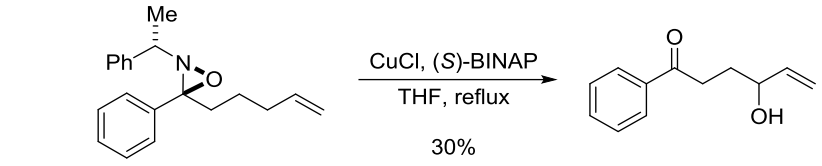
From a mixture of **42aa**, **42aa′**, and **42aa″** containing **44a**: Second diastereomer **42aa′**: R_f = 0.60 (5% EtOAc/hexanes, run twice); ^{1}H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 1.14 (d, J = 6.6 Hz, 3H). Third diastereomer **42aa″**: R_f = 0.60 (5% EtOAc/hexanes, run twice); ^{1}H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 1.62 (d, J = 6.3 Hz, 3H).



42aa (major diastereomer)
42aa+**42aa′**:**42aa′′** (cis:trans) = ca. 92:8;
contains ca. 12% of **44a**

43a (ca. 5% ee)

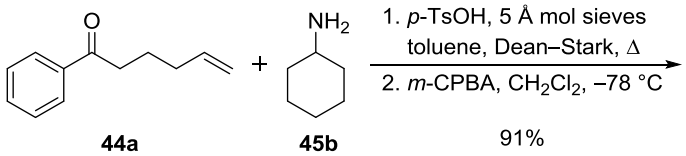
4-Hydroxy-1-phenylhex-5-en-1-one (43a; Table 17, entry 1). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (49.1 mg, 0.0341 mmol, 0.050 equiv) in THF (13 mL) was reacted with a solution of the mixture of oxaziridine diastereomers **42aa**, **42aa′**, and **42aa′′** (ca. 200 mg, 0.682 mmol, 1.0 equiv; **42aa**+**42aa′**:**42aa′′** (cis:trans) = ca. 92:8, contains ca. 12% of starting ketone **44a**) in THF (2 mL). The reaction mixture was refluxed for 3 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to 0.5% MeOH/CH_2Cl_2) afforded 90.0 mg (0.473 mmol, 69% yield; ca. 5% ee by chiral GC, retention times for the two enantiomers were 13.88 and 13.99 min, respectively) of the allylic alcohol **43a** as a yellow oil. Allylic alcohol **43a**: R_f = 0.32 (25% EtOAc/hexanes); IR (neat) 3420, 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90–1.98 (m, 1H), 2.01–2.09 (m, 1H), 2.12 (d, J = 3.4 Hz, 1H), 3.13 (t, J = 7.0 Hz, 2H), 4.24 (br s, 1H), 5.13 (dt, J = 10.4, 1.3 Hz, 1H), 5.27 (dt, J = 17.2, 1.4 Hz, 1H), 5.86–5.94 (m, 1H), 7.43–7.47 (m, 2H), 7.53–7.57 (m, 1H), 7.96–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 34.5, 72.4, 115.1, 128.2, 128.7, 133.3, 137.0, 140.8, 200.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}O_2$ $[M + H]^+$ 191.1072, found 191.1091. Ketone **44a** was not recovered.



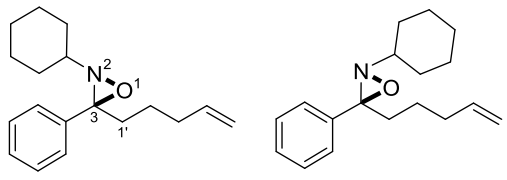
42aa (major diastereomer)
42aa+**42aa′**:**42aa′′** (cis:trans) = ca. 92:8;
contains ca. 12% of **44a**

43a (ca. 5% ee)

Conversion of 42aa into 43a (Scheme 44). Following the general procedure **J**, CuCl (1.69 mg, 0.0170 mmol, 0.049 equiv) and (*S*)-BINAP (10.6 mg, 0.0170 mmol, 0.049 equiv) in THF (9 mL) was reacted with a solution of the mixture of oxaziridine diastereomers **42aa**, **42aa′**, and **42aa′′** (ca. 102 mg, 0.348 mmol, 1.0 equiv; **42aa**+**42aa′**:**42aa′′** (cis:trans) = ca. 92:8, contains ca. 12% of starting ketone **44a**) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 20.0 mg (0.105 mmol, 30% yield; ca. 5% ee by chiral GC) of **43a** as a pale yellow oil and 39.0 mg of the mixture of oxaziridine diastereomers **42aa**, **42aa′**, and **42aa′′** and ketone **44a** (**42aa**+**42aa′**+**42aa′′**:**44a** = ca. 70:30).



44a **45b**



cis-**42ab** *trans*-**42ab**

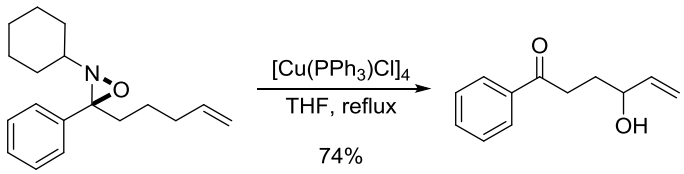
(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(pent-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*cis*-42ab) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-(pent-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*trans*-42ab). Following the general procedure **G**, ketone **44a** (5.50 g, 31.6 mmol, 1.0 equiv), cyclohexylamine **45b** (5.42 mL, 47.4 mmol, 1.5 equiv), PTSA (300 mg, 1.58 mmol, 0.050 equiv), and activated 5 Å molecular sieves (35.0 g) in toluene (150 mL) was refluxed for 60

h, followed by oxidation with *m*-CPBA (6.54 g, 37.9 mmol, 1.2 equiv) in CH_2Cl_2 (150 mL). Purification by chromatography on a silica gel (0.5–1.0% EtOAc/hexanes) afforded the mixture of major diastereomer *cis*-**42ab** and **44a**, followed by the mixture of major and minor *trans*-**42ab** diastereomers as colorless oils (7.80 g, 28.7 mmol, 91% yield; *cis*-**42ab**:*trans*-**42ab** = ca. 59:41 by ^{1}H NMR). Subsequent purification of the mixture of *cis*-**42ab** and **44a** by chromatography on a silica gel (0.5% EtOAc/hexanes) afforded *cis*-**42ab**.

A pure sample of major diastereomer *cis*-**42ab** and minor diastereomer *trans*-**42ab** for characterization was obtained from another experiment, where ketone **44a** (1.00 g, 5.75 mmol, 1.0 equiv), cyclohexylamine **45b** (0.986 mL, 8.62 mmol, 1.5 equiv), PTSA (54.6 mg, 0.287 mmol, 0.050 equiv), and activated 5 Å molecular sieves (7.00 g) in toluene (35 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (1.19 g, 6.90 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL). Purification by chromatography on a silica gel (0.5–1.0% EtOAc/hexanes) afforded major diastereomer *cis*-**42ab**, minor diastereomer *trans*-**42ab**, and their mixture as colorless oils (1.12 g, 4.13 mmol, 72% yield; *cis*-**42ab**:*trans*-**42ab** = ca. 55:45 by ^{1}H NMR). Major diastereomer *cis*-**42ab**: R_f = 0.62 (5% EtOAc/hexanes, run twice); IR (neat) 2931, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72–0.83 (m, 1H), 0.97–1.18 (m, 2H), 1.19–1.35 (m, 3H), 1.40–1.51 (m, 3H), 1.52–1.60 (m, 1H), 1.67–1.76 (m, 3H), 1.83–1.88 (m, 1H), 1.93–2.07 (m, 2H), 2.36 (m, 1H), 4.87–4.96 (m, 2H), 5.70 (m, 1H), 7.35–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.1, 24.2, 25.8, 28.6, 31.8, 33.7, 38.1, 61.0, 87.7, 115.0, 127.8, 128.2, 128.7, 135.3, 138.5; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}NO$ $[M + H]^+$ 272.2014, found 272.1992.

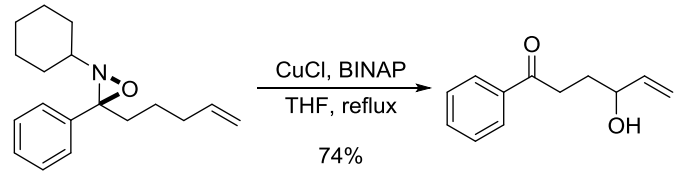
Minor diastereomer *trans*-**42ab**: R_f = 0.52 (5% EtOAc/hexanes, run twice); IR (neat) 2932, 1449cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17–1.38 (m, 3H), 1.40–1.59 (m, 4H), 1.65–1.73 (m, 2H), 1.81–1.84 (m, 2H), 1.97–2.14 (m, 4H), 2.29 (m, 1H), 2.58 (m, 1H),

4.93–5.01 (m, 2H), 5.72 (m, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.6, 24.7, 25.9, 29.1, 29.3, 32.1, 33.8, 61.3, 85.8, 115.4, 126.1, 128.2, 128.3, 128.5, 138.0, 139.9; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}NO$ $[M + H]^+$ 272.2014, found 272.1988.



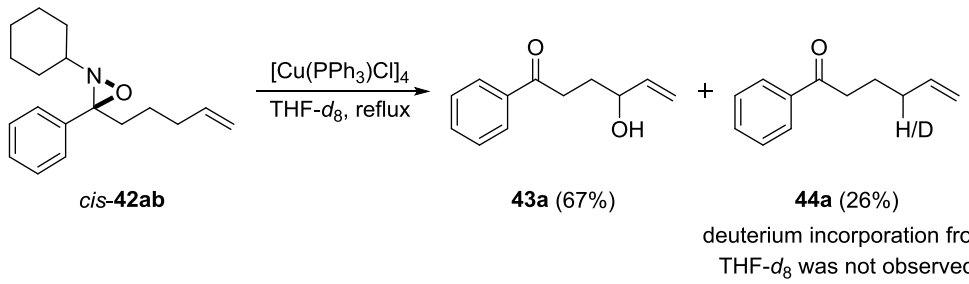
cis-**42ab** **43a**

Conversion of *cis*-42ab into 43a (Table 17, entry 2 and Table 19, entry 1). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (40.0 mg, 0.0276 mmol, 0.050 equiv) in THF (10 mL) was reacted with a solution of oxaziridine *cis*-**42ab** (150 mg, 0.553 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was refluxed for 3 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 99.2:0.5:0.3) afforded 78.0 mg (0.410 mmol, 74% yield) of the allylic alcohol **43a** as a yellow oil and 18.0 mg (0.103 mmol, 19% yield) of **44a**.



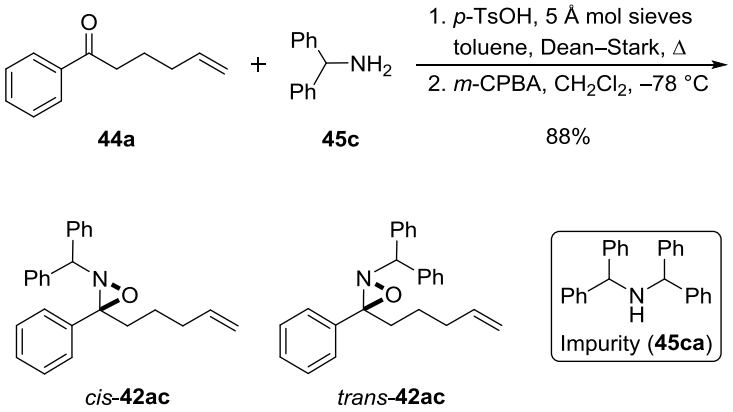
cis-**42ab** **43a**

Following the general procedure **J**, CuCl (2.73 mg, 0.0276 mmol, 0.050 equiv) and *rac*-BINAP (17.1 mg, 0.0276 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine *cis*-**42ab** (150 mg, 0.553 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 78.0 mg (0.410 mmol, 74% yield) of **43a** as a yellow oil and 6.00 mg (0.0344mmol, 6% yield) of **44a**.



cis-**42ab** **43a** (67%) **44a** (26%)
deuterium incorporation from THF-d_8 was not observed

Conversion of *cis*-42ab into 43a in THF-d_8 (Scheme 42b). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (40.0 mg, 0.0276 mmol, 0.050 equiv) in THF-d_8 (10 mL) was reacted with a solution of oxaziridine *cis*-**42ab** (150 mg, 0.553 mmol, 1.0 equiv) in THF-d_8 (5 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 99.2:0.5:0.3) afforded 70.0 mg (0.368 mmol, 67% yield) of the allylic alcohol **43a** as a yellow oil and 25.0 mg (0.143 mmol, 26% yield) of **44a**. No deuterium incorporation was observed in **44a** by ^{1}H NMR and HRMS.



44a **45c** 88%

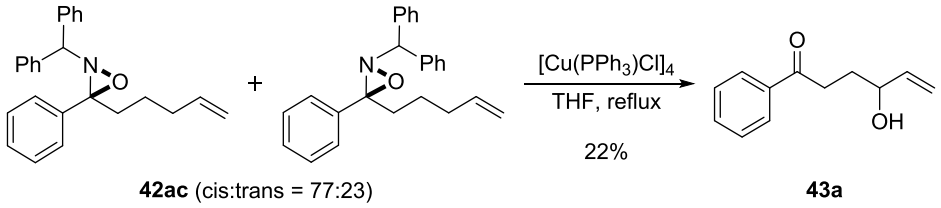
cis-**42ac** *trans*-**42ac**

(2*R*,3*S*)-*rel*-2-Benzhydryl-3-(pent-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*cis*-42ac) and (2*S*,3*S*)-*rel*-2-Benzhydryl-3-(pent-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*trans*-42ac). Following the general procedure **G**, ketone **44a** (0.500 g, 2.87 mmol, 1.0 equiv), benzhydrylamine **45c** (0.743 mL, 4.31 mmol, 1.5 equiv), PTSA (27.3 mg, 0.143 mmol, 0.050 equiv), and 5 Å molecular sieves (3.50 g) in toluene (35 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.594 g, 3.44 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.5% EtOAc/hexanes) afforded a partial

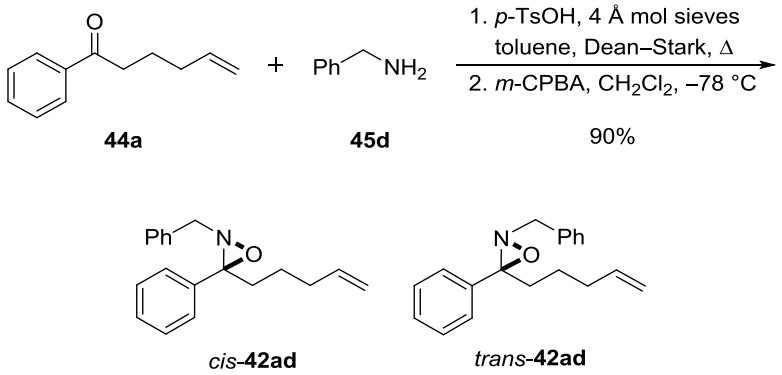
separation of impure *cis*-**42ac** and the mixture of major *cis*-**42ac** and minor *trans*-**42ac** diastereomers contaminated with dibenzhydrylamine impurity **45ca**[197] as a pale yellow oil (ca. 0.898 g, 2.53 mmol, 88% corrected yield; *cis*-**42ac**:*trans*-**42ac** = ca. 76:24 by ^{1}H NMR). Subsequent purification of small amounts of impure *cis*-**42ac** and impure mixture of *cis*- and *trans*-**42ac** separately by preparative TLC on a silica gel (2% EtOAc/hexanes, multiple runs) gave bands corresponding to *cis*-**42ac** and *trans*-**42ac**, which were scraped from the plate and eluted with 100% CH_2Cl_2 through a short bed of silica gel. Evaporation of solvents afforded analytical samples of *cis*-**42ac** and *trans*-**42ac** as colorless oils for characterization. Major diastereomer *cis*-**42ac**: R_f = 0.67 (5% EtOAc/hexanes, run twice); IR (neat) 2926, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.36 (m, 1H), 1.46–1.57 (m, 1H), 1.88 (m, 1H), 1.94–2.09 (m, 2H), 2.32 (m, 1H), 4.06 (s, 1H), 4.88–4.96 (m, 2H), 5.70 (m, 1H), 6.94–6.97 (m, 2H), 7.18–7.23 (m, 5H), 7.27–7.31 (m, 4H), 7.36–7.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 33.7, 37.7, 70.5, 88.6, 115.0, 127.3, 127.6, 127.9, 128.1, 128.3, 128.4, 128.5, 129.0, 134.7, 138.5, 139.5, 142.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{26}NO$ $[M + H]^+$ 356.2014, found 356.2044.

Minor diastereomer *trans*-**42ac**: R_f = 0.50 (5% EtOAc/hexanes, run twice); IR (neat) 2930, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.24 (m, 1H), 1.32–1.43 (m, 1H), 1.95–2.07 (m, 2H), 2.09–2.25 (m, 2H), 4.91–4.97 (m, 3H), 5.66 (m, 1H), 7.21–7.26 (m, 1H), 7.28–7.34 (m, 8H), 7.35–7.39 (m, 2H), 7.43–7.45 (m, 2H), 7.48–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 29.7, 33.7, 70.7, 86.7, 115.4, 126.3, 127.5, 127.82, 127.88, 128.0, 128.4, 128.6, 129.0, 138.0, 139.4, 140.1, 142.1; HRMS (ESI) *m/z* calcd for $C_{25}H_{26}NO$ $[M + H]^+$ 356.2014, found 356.2014.

Dibenzhydrylamine **45ca**: ^{1}H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$; diagnostic peaks only) δ 63.7.



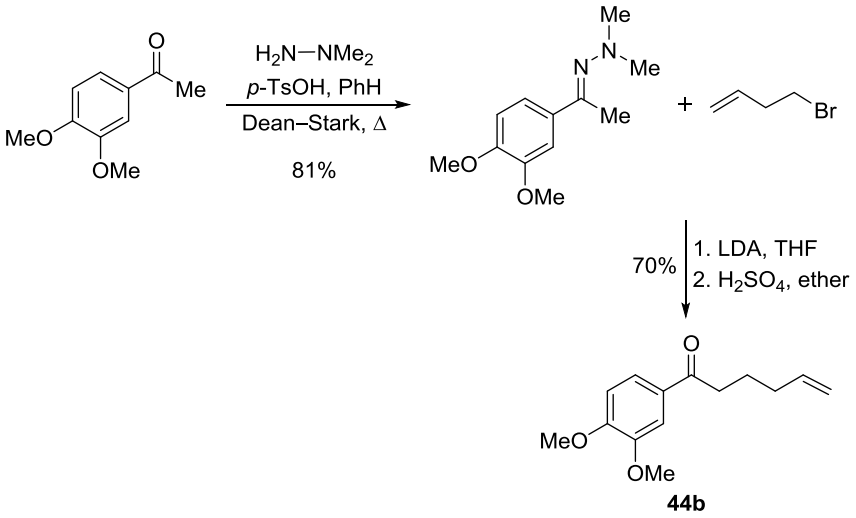
Conversion of 42ac into 43a (Table 17, entry 3). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (30.4 mg, 0.0211 mmol, 0.045 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomers **42ac** (165 mg, 0.464 mmol, 1.0 equiv; cis:trans = ca. 77:23, contaminated with 12% of dibenzhydrylamine) in THF (3 mL). The reaction mixture was refluxed for 1.5 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded the mixture of product and impurities which was further purified by chromatography on a silica gel (100% CH_2Cl_2 to 2.5% acetone/CH_2Cl_2) to afford 19.0 mg (0.10 mmol, 22% yield; 26% brsm) of **43a** as a yellow oil. Ketone **44a** was also obtained in 48% yield (39.0 mg, 0.224 mmol; 57% brsm) during the initial purification.



(2*R*,3*S*)-*rel*-2-Benzyl-3-(pent-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*cis*-42ad) and (2*S*,3*S*)-*rel*-2-Benzyl-3-(pent-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*trans*-42ad). Following the general procedure **G**, ketone **44a** (0.600 g, 3.44 mmol, 1.0 equiv), benzylamine **45d** (0.564 mL, 5.17 mmol, 1.5 equiv), PTSA (32.8 mg, 0.172 mmol, 0.050 equiv), and activated 4 Å molecular sieves (5.0 g) in toluene (40 mL) was refluxed for 60 h,

followed by oxidation with *m*-CPBA (0.713 g, 4.13 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.5–0.7% EtOAc/hexanes) afforded the mixture of major diastereomer *cis*-**42ad** and **44a**, followed by the mixture of major and minor *trans*-**42ad** diastereomers as a colorless oil (ca. 0.866 g, 3.10 mmol, 90% corrected yield; *cis*-**42ad**:*trans*-**42ad** = ca. 87:13 by ^{1}H NMR). Subsequent purification of the mixture of *cis*-**42ad** and *trans*-**42ad** by chromatography on a silica gel (0.6% EtOAc/hexanes) afforded a partial separation of pure *cis*-**42ad** and a small quantity of *trans*-**42ad** containing ca. 15% of *cis*-**42ad**. Major diastereomer *cis*-**42ad**: R_f = 0.55 (5% EtOAc/hexanes, run twice); IR (neat) 2927, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.38 (m, 1H), 1.46–1.57 (m, 1H), 1.82 (m, 1H), 1.95–2.09 (m, 2H), 2.36 (m, 1H), 3.43 (1/2 AB, J = 14.1 Hz, 1H), 3.52 (1/2 AB, J = 14.1 Hz, 1H), 4.89–4.97 (m, 2H), 5.71 (m, 1H), 7.20–7.22 (m, 2H), 7.25–7.28 (m, 2H), 7.29–7.32 (m, 1H), 7.42 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 33.7, 37.7, 59.3, 87.9, 115.0, 127.6, 127.8, 128.4, 128.5, 128.8, 129.0, 135.2, 136.7, 138.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NO$ $[M + H]^+$ 280.1701, found 280.1739.

Minor diastereomer *trans*-**42ad**: R_f = 0.45 (5% EtOAc/hexanes, run twice); IR (neat) 2926, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43–1.58 (m, 2H), 2.06–2.16 (m, 2H), 2.19–2.36 (m, 2H), 4.16 (s, 2H), 4.96–5.03 (m, 2H), 5.74 (m, 1H), 7.27–7.34 (m, 4H), 7.35–7.39 (m, 3H), 7.40–7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 29.2, 33.8, 58.2, 85.6, 115.6, 126.5, 127.8, 128.5, 128.6, 128.7, 128.8, 136.6, 137.9, 139.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NO$ $[M + H]^+$ 280.1701, found 280.1722.

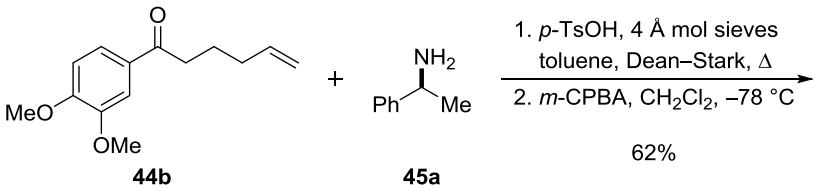


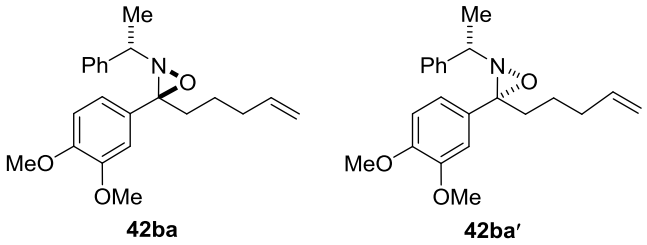
44b

1-(3,4-Dimethoxyphenyl)hex-5-en-1-one (44b). A solution of 3,4-dimethoxyacetophenone (15.0 g, 83.2 mmol, 1.0 equiv), *N*,*N*-dimethylhydrazine (15.0 g, 249 mmol, 3.0 equiv) and PTSA (0.791 g, 4.16 mmol, 0.050 equiv) in benzene (80 mL) was refluxed for 23 h under nitrogen atmosphere with removal of water by a Dean–Stark apparatus. The reaction mixture was concentrated under reduced pressure and the residue was purified by vacuum distillation to afford the corresponding hydrazone as a pale yellow solid in 81% yield (15.0 g, 67.5 mmol).

To a cooled 1.0 M LDA solution (9.90 mL, 9.90 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added the solution of hydrazone (2.00 g, 9.00 mmol, 1.0 equiv) in THF (15 mL) slowly over 15 min and was allowed to stir at 0 °C for 5 h. The reaction mixture was then cooled to –78 °C and a solution of 4-bromo-1-butene (1.45 g, 10.8 mmol, 1.2 equiv) in THF (5 mL) was added slowly over 10 min. The reaction was warmed to rt and stirred for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ether (15 mL) and then treated with an ice-cold solution of dilute H_2SO_4 (15 mL) for 30 min to hydrolyze the hydrazone. The resulting solution was diluted with water and extracted with ether (2 × 15 mL) and the combined organic extracts were washed with water (2 × 15 mL) and brine (15 mL), dried over

Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on a silica gel (10% EtOAc/hexanes) afforded the ketone **44b** as a white solid in 71% yield (1.50 g, 6.41 mmol). Ketone **44b**: R_f = 0.41 (15% EtOAc/hexanes, run twice); mp 52–54 °C; IR (neat) 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (m, 2H), 2.11–2.16 (m, 2H), 2.92 (t, J = 7.3 Hz, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 4.96–5.06 (m, 2H), 5.81 (m, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.3, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 33.4, 37.4, 56.1, 56.2, 110.1, 110.3, 115.4, 122.8, 130.4, 138.2, 149.1, 153.3, 199.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_3$ $[M]^+$ 234.1256, found 234.1236.

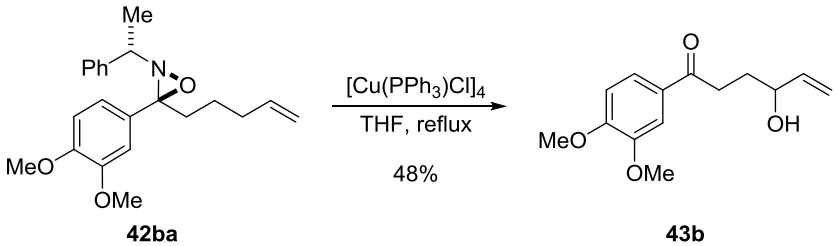




(2*R*,3*S*,1′*S*)-*rel*-3-(3,4-Dimethoxyphenyl)-3-(pent-4′′-en-1′′-yl)-2-(1′-phenylethyl)-1,2-oxaziridine (unlike, *cis*-42ba), (2*S*,3*R*,1′*S*)-*rel*-3-(3,4-Dimethoxyphenyl)-3-(pent-4′′-en-1′′-yl)-2-(1′-phenylethyl)-1,2-oxaziridine (like, *cis*-42ba′). Following the general procedure **G**, ketone **44b** (1.00 g, 4.27 mmol, 1.0 equiv), (*S*)-*α*-methylbenzylamine **45a** (0.815 mL, 6.41 mmol, 1.5 equiv), PTSA (40.6 mg, 0.213 mmol, 0.050 equiv), and activated 4 Å molecular sieves (7.0 g) in toluene (50 mL) was refluxed for 72 h, followed by oxidation with *m*-CPBA (0.883 g, 5.12 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL). Purification by chromatography on a silica gel (4–6% EtOAc/hexanes) afforded the major

42ba and the minor **42ba′** diastereomers as a colorless oil (0.940 g, 2.66 mmol, 62% yield; **42ba**:**42ba′** = ca. 83:17). A pure sample of **42ba′** for characterization was obtained during this purification. Major diastereomer **42ba**: R_f = 0.50 (10% EtOAc/hexanes, run twice); IR (neat) 1605, 1452, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19–1.31 (m, 1H), 1.40–1.51 (m, 1H), 1.47 (d, J = 6.5 Hz, 3H), 1.70 (m, 1H), 1.90–2.05 (m, 2H), 2.17 (m, 1H), 3.01 (q, J = 6.4 Hz, 1H), 3.62 (br s, 3H), 3.88 (s, 3H), 4.85–4.93(m, 2H), 5.68 (m, 1H), 6.39 (br s, 1H), 6.78 (d, J = 6.5 Hz, 2H), 6.92–6.96 (m, 2H), 7.18–7.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 23.2, 33.6, 37.9, 55.7, 56.0, 62.7, 88.2, 110.2, 110.8, 114.9, 120.6, 127.4, 127.51, 127.56, 128.3, 138.4, 141.2, 148.1, 149.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO_3$ $[M + H]^+$ 354.2069, found 354.2074.

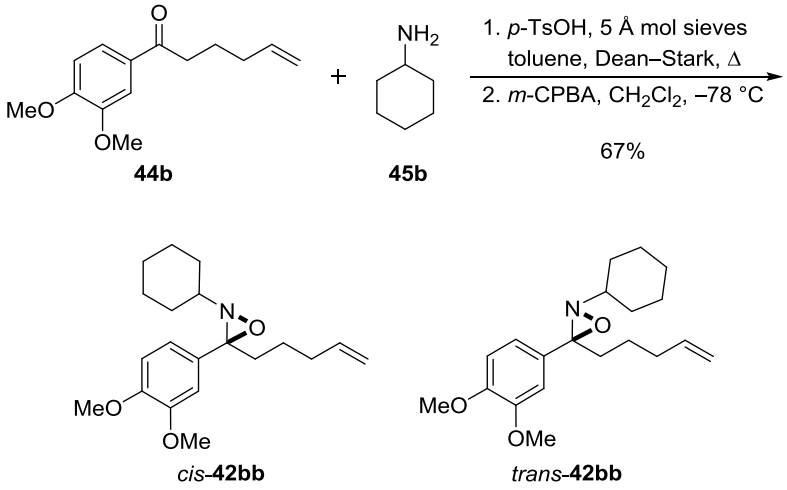
Minor diastereomer **42ba′**: R_f = 0.41 (10% EtOAc/hexanes, run twice); IR (neat) 1604, 1453, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6.6 Hz, 3H), 1.24–1.35 (m, 1H), 1.43–1.54 (m, 1H), 1.81 (m, 1H), 1.95–2.09 (m, 2H), 2.44 (m, 1H), 3.09 (q, J = 6.6 Hz, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 4.89–4.97(m, 2H), 5.71 (m, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 1.9 Hz, 1H), 7.07 (dd, J = 8.2, 2.0 Hz, 1H), 7.22–7.27 (m, 1H), 7.30–7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.3, 33.7, 37.8, 56.1, 56.3, 61.4, 88.5, 110.9, 111.2, 115.0, 120.6, 127.1, 127.2, 127.4, 128.6, 138.5, 143.2, 148.7, 149.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO_3$ $[M + H]^+$ 354.2069, found 354.2076.



42ba **43b**

1-(3,4-Dimethoxyphenyl)-4-hydroxyhex-5-en-1-one (43b; Table 17, entry 5). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (51.1 mg, 0.0354 mmol, 0.050 equiv) in

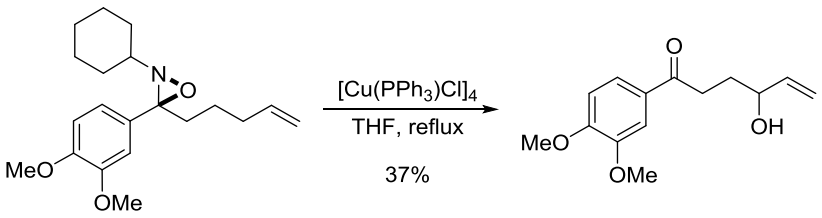
THF (12 mL) was reacted with a solution of oxaziridine **42ba** (250 mg, 0.708 mmol, 1.0 equiv) in THF (8 mL). The reaction mixture was refluxed for 3 h. Purification by chromatography on a silica gel (0–3% acetone/CH_2Cl_2) afforded 85.0 mg (0.340 mmol, 48% yield) of the allylic alcohol **43b** as a pink oil. Allylic alcohol **43b**: R_f = 0.23 (3% acetone/CH_2Cl_2); IR (neat) 3435, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.87–1.96 (m, 1H), 1.99–2.07 (m, 1H), 2.23 (d, J = 4.3 Hz, 1H), 3.08 (t, J = 7.0 Hz, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 4.23 (m, 1H), 5.12 (dt, J = 10.4, 1.4 Hz, 1H), 5.26 (dt, J = 17.2, 1.4 Hz, 1H), 5.89 (m, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 34.0, 56.1, 56.2, 72.4, 110.1, 110.3, 115.0, 123.0, 130.2, 140.9, 149.1, 153.4, 199.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}O_4$ $[M + H]^+$ 251.1283, found 251.1286. Ketone **44b** was also obtained in 27% yield (45.0 mg, 0.192 mmol).



(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(3,4-dimethoxyphenyl)-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*cis*-42bb) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-(3,4-dimethoxyphenyl)-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*trans*-42bb). Following the general procedure **G**, ketone **44b** (0.900 g, 3.84 mmol, 1.0 equiv), cyclohexylamine **45b** (0.659 mL, 5.76 mmol, 1.5 equiv), PTSA (36.5 mg, 0.192 mmol, 0.050 equiv), and activated 5 Å molecular sieves (6.50 g) in

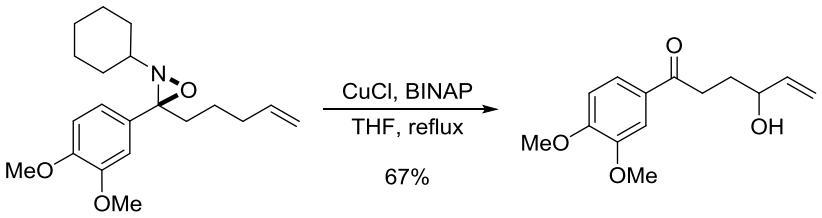
toluene (40 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.796 g, 4.61 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL). Purification by chromatography on a silica gel (4–6% EtOAc/hexanes) afforded the major diastereomer *cis*-**42bb** (0.610 g, 1.84 mmol, 48% yield) as a colorless oil, followed by the mixture of **44b** and minor diastereomer *trans*-**42bb** (0.246 g, 0.743 mmol, 19% corrected yield; *cis*-**42bb**:*trans*-**42bb** = ca. 71:29 by ^{1}H NMR). Subsequent purification of the mixture of **44b** and *trans*-**42bb** by chromatography on a silica gel (14% EtOAc/hexanes) afforded a partial separation of *trans*-**42bb** as a colorless oil. Major diastereomer *cis*-**42bb**: R_f = 0.33 (10% EtOAc/hexanes, run twice); IR (neat) 2930, 1450, 1257 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75–0.86 (m, 1H), 0.95–1.15 (m, 2H), 1.16–1.32 (m, 3H), 1.39–1.48 (m, 3H), 1.52–1.56 (m, 1H), 1.63–1.70 (m, 2H), 1.72–1.79 (m, 1H), 1.81–1.84 (m, 1H), 1.90–2.04 (m, 2H), 2.31 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.85–4.93 (m, 2H), 5.67 (m, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 1.9 Hz, 1H), 6.93 (dd, J = 8.2, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.11, 24.15, 25.8, 28.7, 31.7, 33.7, 38.1, 55.9, 56.1, 60.7, 87.5, 110.7, 110.9, 114.9, 120.3, 127.6, 138.4, 148.5, 149.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NO_3$ $[M + H]^+$ 332.2226, found 332.2223.

Minor diastereomer *trans*-**42bb**: R_f = 0.13 (10% EtOAc/hexanes, run twice); IR (neat) 2932, 1452, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16–1.36 (m, 3H), 1.41–1.55 (m, 4H), 1.65–1.70 (m, 2H), 1.80–1.84 (m, 2H), 1.95–2.02 (m, 2H), 2.04–2.16 (m, 2H), 2.28 (m, 1H), 2.56 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 4.94–5.01 (m, 2H), 5.73 (m, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 1.9 Hz, 1H), 6.93 (dd, J = 8.2, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.6, 24.8, 25.8, 28.9, 29.2, 32.1, 33.8, 56.0, 56.1, 61.4, 85.4, 109.3, 111.1, 115.4, 118.7, 132.5, 138.0, 149.13, 149.15; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NO_3$ $[M + H]^+$ 332.2226, found 332.2224.



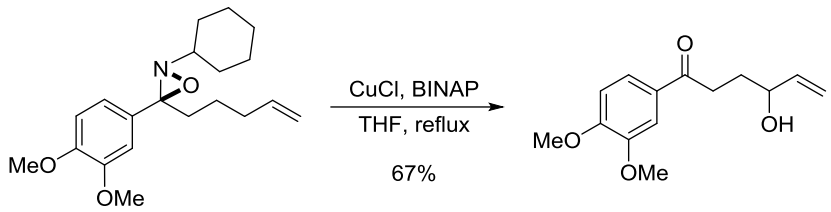
cis-**42bb** **43b**

Conversion of *cis*-42bb into 43b (Table 17, entry 6). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (21.8 mg, 0.0151 mmol, 0.050 equiv) in THF (7 mL) was reacted with a solution of oxaziridine *cis*-**42bb** (100 mg, 0.302 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.6:1.0:0.4) afforded 28.0 mg (0.112 mmol, 37% yield) of the allylic alcohol **43b** as a pink oil. R_f = 0.12 (35% EtOAc/hexanes). Ketone **44b** was also obtained in 57% yield (40.0 mg, 0.171 mmol).



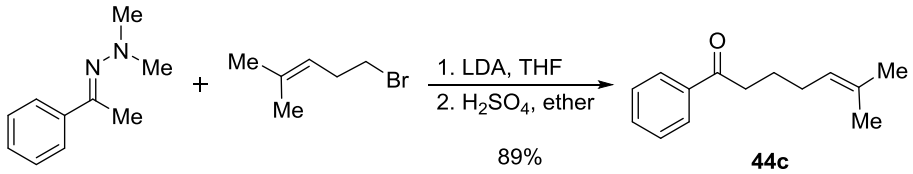
cis-**42bb** **43b**

Conversion of *cis*-42bb into 43b (Scheme 45). Following the general procedure **J**, CuCl (2.24 mg, 0.0226 mmol, 0.050 equiv) and *rac*-BINAP (14.0 mg, 0.0226 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine *cis*-**42bb** (150 mg, 0.453 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.6:1.0:0.4) afforded 76.0 mg (0.304 mmol, 67% yield; 73% brsm) of **43b** as a yellow oil and ca. 18.0 mg (0.0769 mmol, 17% corrected yield) of **44b**.



trans-**42bb** **43b**

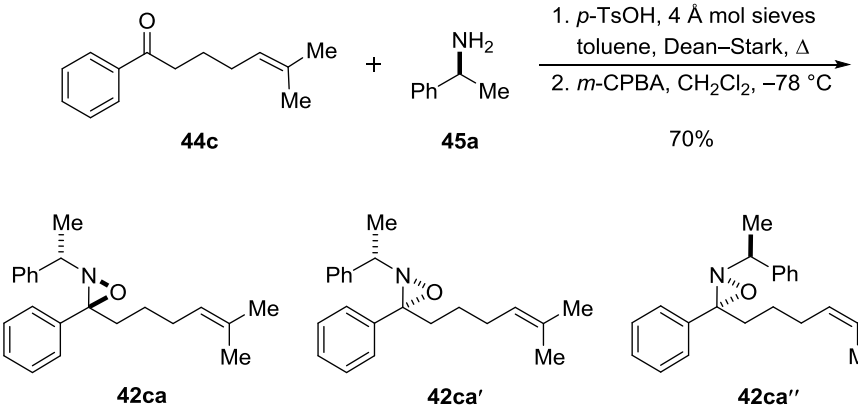
Conversion of *trans*-42bb into 43b (Scheme 45). Following the general procedure **J**, CuCl (1.72 mg, 0.0173 mmol, 0.050 equiv) and *rac*-BINAP (10.8 mg, 0.0173 mmol, 0.050 equiv) in THF (9 mL) was reacted with a solution of oxaziridine *trans*-**42bb** (115 mg, 0.347 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.6:1.0:0.4) afforded 58.0 mg (0.232 mmol, 67% yield) of **43b** as a yellow oil and 12.0 mg (0.0512 mmol, 15% yield) of **44b**.



44c

6-Methyl-1-phenylhept-5-en-1-one (44c). To a cooled 1.0 M LDA solution (10.1 mL, 10.1 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added the solution of hydrazone (1.50 g, 9.25 mmol, 1.0 equiv) in THF (15 mL) slowly over 15 min and was allowed to stir at 0 °C for 5 h. The reaction mixture was then cooled to –78 °C and a solution of 5-bromo-2-methyl-2-pentene (1.47 mL, 11.1 mmol, 1.2 equiv) in THF (5 mL) was added slowly over 10 min. The reaction was warmed to rt and stirred for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ether (15 mL) and then treated with an ice-cold solution of dilute H_2SO_4 (15 mL) for 30 min to hydrolyze the hydrazone. The resulting solution was diluted with water and extracted with ether (2 × 15 mL) and the combined organic extracts were washed with

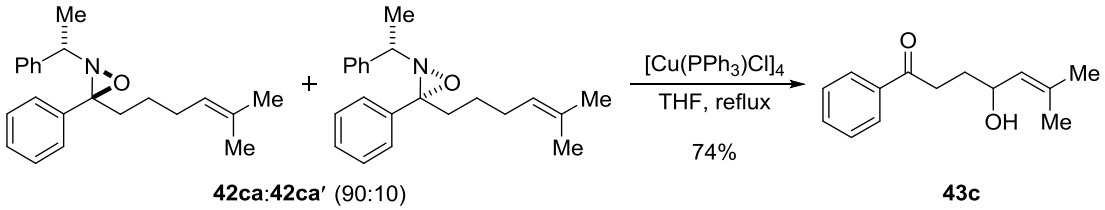
water (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on a silica gel (0.2–0.5% EtOAc/hexanes) afforded the ketone **44c** as a colorless oil in 89% yield (1.66 g, 8.24 mmol). Ketone **44c**: R_f = 0.43 (5% EtOAc/hexanes, run twice); IR (neat) 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.69 (d, J = 1.0 Hz, 3H), 1.78 (m, 2H), 2.08 (q, J = 7.2 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 5.13 (m, 1H), 7.43–7.47 (m, 2H), 7.52–7.56 (m, 1H), 7.93–7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 24.6, 25.9, 27.6, 38.1, 124.0, 128.2, 128.7, 132.6, 133.0, 137.3, 200.7; HRMS (EI) *m/z* calcd for $C_{14}H_{18}O$ $[M]^+$ 202.1358, found 202.1344.



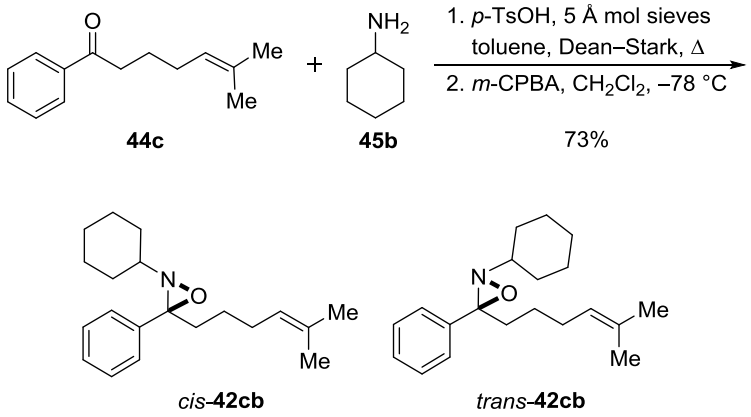
(2*R*,3*S*,1′*S*)-3-(5-Methylhex-4″-en-1″-yl)-3-phenyl-2-(1′-phenylethyl)-1,2-oxaziridine (unlike, *cis*-42ca), (2*S*,3*R*,1′*S*)-3-(5-Methylhex-4″-en-1″-yl)-3-phenyl-2-(1′-phenylethyl)-1,2-oxaziridine (like, *cis*-42ca′), and (2*R*,3*R*,1′*S*)-3-(5-Methylhex-4″-en-1″-yl)-3-phenyl-2-(1′-phenylethyl)-1,2-oxaziridine (unlike, *trans*-42ca″). Following the general procedure **G**, 6-methyl-1-phenylhept-5-en-1-one **44c** (1.00 g, 4.95 mmol, 1.0 equiv), (*S*)-α-methylbenzylamine **45a** (0.945 mL, 7.42 mmol, 1.5 equiv), PTSA (47.0 mg, 0.247 mmol, 0.050 equiv), and activated 4 Å molecular sieves (7.0 g) in toluene (50 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (1.02 g, 5.94 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL). Purification by chromatography on a silica gel (0.5–1%

EtOAc/hexanes) afforded the mixture of oxaziridine diastereomers (**42ca**, **42ca′**, and **42ca″**) and starting ketone **44c** as a colorless oil. Subsequent purification by chromatography on a silica gel (0.2% EtOAc/hexanes) afforded a partial separation of the mixture of the two diastereomers (**42ca** and **42ca′**), followed by the mixture of three diastereomers (**42ca**, **42ca′**, and **42ca″**) containing a trace amount of **44c** (1.11 g, 70% corrected yield; **42ca**:**42ca′**:**42ca″** = ca. 50:14:36 by ^{1}H NMR). A pure sample of the major diastereomer **42ca** for characterization was obtained during this purification. Major diastereomer **42ca**: R_f = 0.71 (5% EtOAc/hexanes, run twice); IR (neat) 1448, 764, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.23 (m, 1H), 1.33–1.44 (m, 1H), 1.48 (d, J = 6.4 Hz, 3H), 1.51 (s, 3H), 1.62 (d, J = 0.9 Hz, 3H), 1.72 (m, 1H), 1.83–1.98 (m, 2H), 2.21 (m, 1H), 2.99 (q, J = 6.4 Hz, 1H), 4.97–5.01(m, 1H), 6.87–6.91 (m, 2H), 7.12–7.23 (m, 5H), 7.26–7.30 (m, 2H), 7.32–7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 23.1, 24.1, 25.8, 28.0, 38.1, 62.8, 88.6, 124.2, 127.6, 127.8, 128.2, 128.3, 128.8, 131.9, 135.0, 140.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO$ $[M + H]^+$ 322.2171, found 322.2126.

From a mixture of **42ca**, **42ca′**, and **42ca″** containing **44c**: Second diastereomer **42ca′**: R_f = 0.60 (5% EtOAc/hexanes, run twice); ^{1}H NMR (400 MHz, C_6D_6; diagnostic peaks only) δ 3.19 (q, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6; diagnostic peaks only) δ 61.7, 87.8. Third diastereomer **42ca″**: R_f = 0.55 (5% EtOAc/hexanes, run twice); ^{1}H NMR (400 MHz, C_6D_6; diagnostic peaks only) δ 3.82 (q, J = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6; diagnostic peaks only) δ 62.9, 85.8.

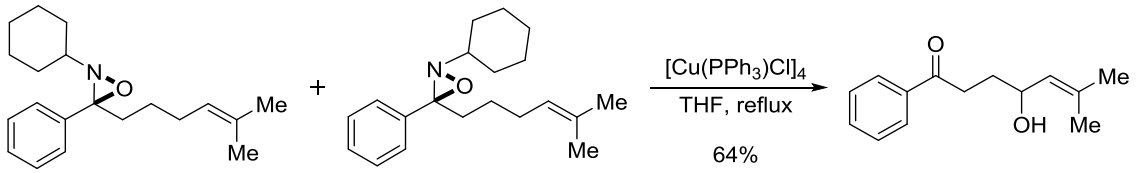


4-Hydroxy-6-methyl-1-phenylhept-5-en-1-one (43c; Table 17, entry 7). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (44.5 mg, 0.0342 mmol, 0.044 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomers **42ca** and **42ca′** (220 mg, 0.685 mmol, 1.0 equiv; **42ca**:**42ca′** = 90:10) in THF (8 mL). The reaction mixture was refluxed for 3 h. Purification by chromatography on a silica gel (1.5–2% acetone/CH_2Cl_2) afforded 110 mg (0.504 mmol, 74% yield) of the allylic alcohol **43c** as a yellow oil. Allylic alcohol **43c**: R_f = 0.26 (20% EtOAc/hexanes); IR (neat) 3410, 1679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (d, J = 0.8 Hz, 3H), 1.71 (d, J = 0.6 Hz, 3H), 1.74–1.76 (m, 1H), 1.87–2.01 (m, 2H), 3.08 (t, J = 7.3 Hz, 2H), 4.45 (m, 1H), 5.21 (m, 1H), 7.43–7.46 (m, 2H), 7.53–7.56 (m, 1H), 7.95–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 25.9, 32.0, 34.8, 68.2, 127.9, 128.2, 128.7, 133.1, 135.7, 137.2, 200.6; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_2Na$ $[M + Na]^+$ 241.1204, found 241.1189. Ketone **44c** was also obtained in 7% yield (10.0 mg, 0.0495 mmol).



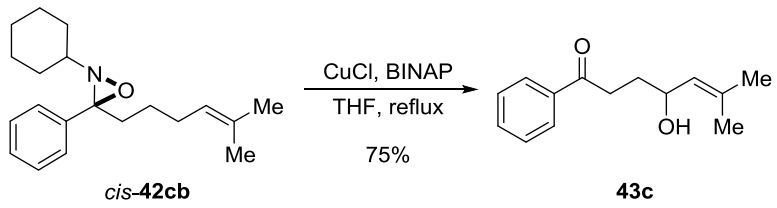
(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(5-methylhex-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*cis*-42cb) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-(5-methylhex-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*trans*-42cb). Following the general procedure **G**, 6-methyl-1-phenylhept-5-en-1-one **44c** (0.700 g, 3.46 mmol, 1.0 equiv), cyclohexylamine **45b** (0.594 mL, 5.19 mmol, 1.5 equiv), PTSA (32.9 mg, 0.173 mmol, 0.050 equiv), and activated 5 Å molecular sieves (5.0 g) in toluene (35 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.717 g, 4.15 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL). Purification by chromatography on a silica gel (0.5–0.6% EtOAc/hexanes) afforded a partial separation of the major diastereomer *cis*-**42cb** as a colorless oil, followed by the mixture of major and minor *trans*-**42cb** diastereomers (0.760 g, 2.54 mmol, 73% yield; *cis*-**42cb**:*trans*-**42cb** = ca. 56:44). Major diastereomer *cis*-**42cb**: R_f = 0.58 (5% EtOAc/hexanes, run twice); IR (neat) 2929, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72–0.83 (m, 1H), 0.97–1.16 (m, 2H), 1.17–1.28 (m, 2H), 1.31–1.42 (m, 2H), 1.43–1.49 (m, 2H), 1.52 (s, 3H), 1.52–1.58 (m, 1H), 1.62 (d, J = 0.8 Hz, 3H), 1.66–1.76 (m, 3H), 1.84–1.95 (m, 3H), 2.35 (m, 1H), 5.00 (m, 1H), 7.34–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 24.1, 24.1, 24.2, 25.8, 28.0, 28.6, 31.8, 38.3, 60.9, 87.8, 124.3, 127.8, 128.1, 128.7, 131.9, 135.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NO$ $[M + H]^+$ 300.2327, found 300.2318.

An analytical sample of the minor diastereomer *trans*-**42cb** containing ca. 12% of *cis*-**42cb** was obtained for characterization during the purification. Minor diastereomer *trans*-**42cb**: R_f = 0.51 (5% EtOAc/hexanes, run twice); IR (neat) 2930, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.35 (m, 3H), 1.36–1.49 (m, 3H), 1.52–1.59 (m, 1H), 1.56 (s, 3H), 1.66 (d, J = 0.8 Hz, 3H), 1.70–1.74 (m, 2H), 1.82–1.85 (m, 2H), 1.94–2.05 (m, 4H), 2.26 (m, 1H), 2.59 (m, 1H), 5.03 (m, 1H), 7.28–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 24.4, 24.7, 25.7, 25.9, 25.9, 28.2, 29.3, 29.4, 32.1, 61.2, 85.9, 123.9, 126.2, 128.2, 128.4, 132.4, 140.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NO$ $[M + H]^+$ 300.2327, found 300.2296.

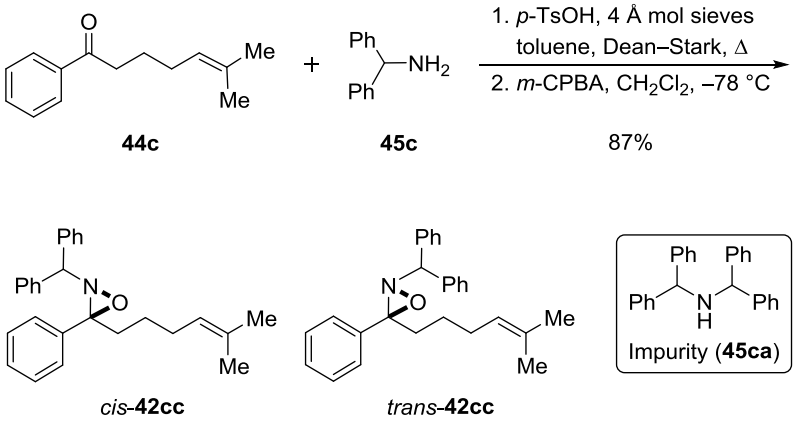


42cb (cis:trans = 63:37) **43c**

Conversion of 42cb into 43c (Table 17, entry 8 and Table 19, entry 7). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (36.2 mg, 0.0250 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomers **42cb** (150 mg, 0.501 mmol, 1.0 equiv; cis:trans = ca. 63:37) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded ca. 70.0 mg (0.321 mmol, 64% corrected yield by ^1H NMR; contaminated with ca. 10% of unidentified impurities) of the allylic alcohol **43c** as a pink oil and 19.0 mg (0.0940 mmol, 19% yield) of **44c**.



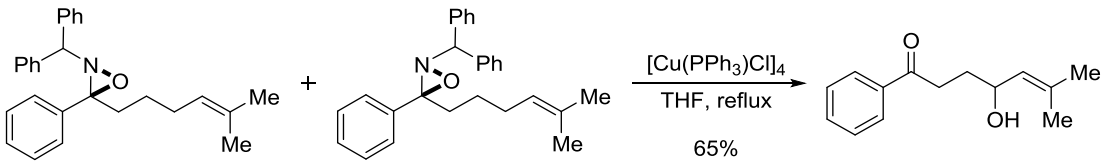
Conversion of 42cb into 43c (Table 19, entry 7). Following the general procedure **J**, CuCl (2.48 mg, 0.0250 mmol, 0.050 equiv) and *rac*-BINAP (15.6 mg, 0.0250 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine *cis*-**42cb** (150 mg, 0.501 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 82.0 mg (0.376 mmol, 75% yield) of **43c** as a yellow oil and 6.00 mg (0.0297 mmol, 6% yield) of **44c**.



(2*R*,3*S*)-*rel*-2-Benzhydryl-3-(5-methylhex-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*cis*-42cc) and (2*S*,3*S*)-*rel*-2-Benzhydryl-3-(5-methylhex-4′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*trans*-42cc). Following the general procedure **G**, 6-methyl-1-phenylhept-5-en-1-one **44c** (0.500 g, 2.47 mmol, 1.0 equiv), benzhydrylamine **45c** (0.639 mL, 3.71 mmol, 1.5 equiv), PTSA (23.5 mg, 0.123 mmol, 0.050 equiv), and activated 4 Å molecular sieves (3.0 g) in toluene (25 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.510 g, 2.96 mmol, 1.2 equiv) in CH_2Cl_2 (12 mL). Purification by chromatography on a

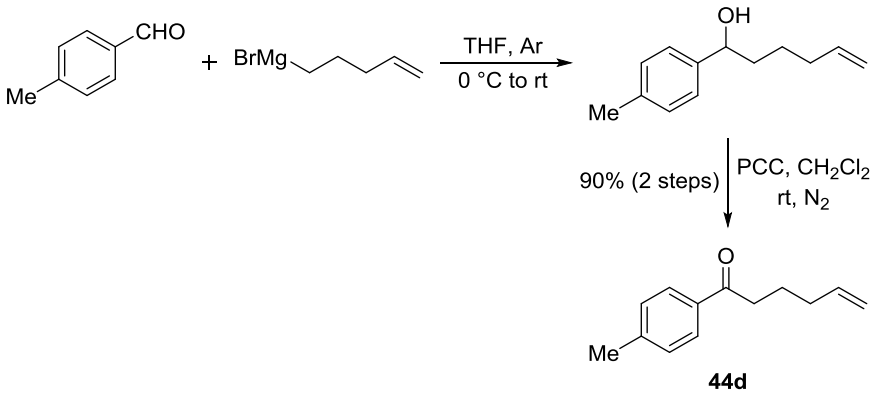
silica gel (0.5–0.7% EtOAc/hexanes) afforded a mixture of major *cis*-**42cc** and minor *trans*-**42cc** diastereomers containing ca. 6.5% of dibenzhydrylamine impurity and 4% of starting ketone **44c** as a colorless oil (ca. 0.826 g, 2.16 mmol, 87% corrected yield; *cis*-**42cc**:*trans*-**42cc** = ca. 72:28 by ^{1}H NMR). An analytical sample of the major diastereomer *cis*-**42cc** accompanied with 9% of dibenzhydrylamine was obtained for characterization during this purification. Major diastereomer *cis*-**42cc**: R_f = 0.60 (5% EtOAc/hexanes, run twice); IR (neat) 1448, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.31 (m, 1H), 1.41–1.52 (m, 1H), 1.55 (s, 3H), 1.66 (s, 3H), 1.86–2.02 (m, 3H), 2.35 (m, 1H), 4.09 (s, 1H), 5.04 (t, J = 6.9 Hz, 1H), 6.98–7.00 (m, 2H), 7.22–7.26 (m, 4H), 7.29–7.35 (m, 5H), 7.38 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 24.1, 25.8, 28.1, 37.9, 70.5, 88.7, 124.3, 127.3, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 128.9, 131.9, 134.8, 139.6, 142.4; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}NO$ $[M + H]^+$ 384.2327, found 384.2337.

From a mixture of *cis*-**42cc** and *trans*-**42cc** containing **44c** and dibenzhydrylamine impurity: Minor diastereomer *trans*-**42cc**: R_f = 0.45 (5% EtOAc/hexanes, run twice); ^{1}H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 4.91 (s, 1H).



Conversion of 42cc into 43c (Table 17, entry 9). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (37.7 mg, 0.0260 mmol, 0.037 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomers **42cc** (269 mg, 0.702 mmol, 1.0 equiv; cis:trans = ca. 70:30, containing ca. 6.4% of dibenzhydrylamine and 4% of **44c**) in THF (8 mL). The reaction mixture was refluxed for 3 h. Purification by chromatography on a silica gel (0–

1.5% acetone/CH_2Cl_2) afforded 100 mg (0.458 mmol, 65% yield) of the allylic alcohol **43c** as a brown oil and 18.0 mg (0.0891 mmol, 13% yield) of **44c**.

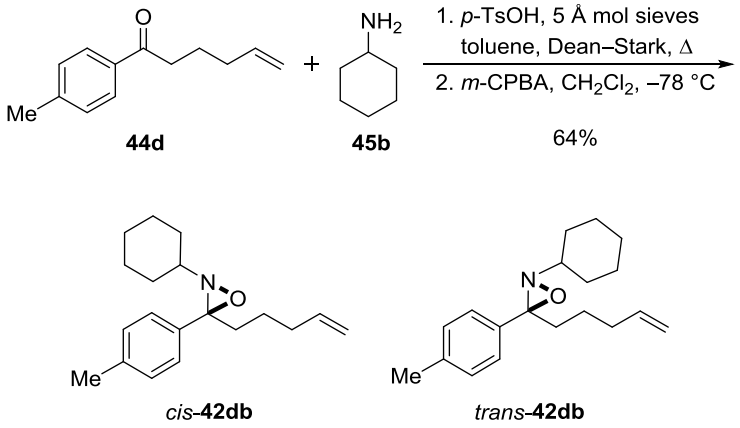


44d

1-(*p*-Tolyl)hex-5-en-1-one (44d). Following the general procedure **H**, a solution of 5-bromo-1-pentene (1.77 mL, 14.9 mmol, 1.2 equiv) in THF (10 mL) was added drop wise to a stirring suspension of magnesium turnings (0.364 g, 14.9 mmol, 1.2 equiv) and one small crystal of iodine in THF (10 mL). After refluxing gently for 20 min, the reaction mixture was cooled to 0 °C and treated with a solution of *p*-tolualdehyde (1.50 g, 12.4 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was then stirred at rt for 1 h. The aqueous work-up afforded the crude alcohol (2.50 g) as a colorless oil, which was used for the next oxidation step without further purification.

To a stirring solution of crude alcohol (2.47 g) in CH_2Cl_2 (50 mL) was added Celite (5.0 g) followed by PCC (5.38 g, 24.9 mmol, 2 equiv), and the reaction mixture was stirred at rt for 1.5 h. The reaction mixture was filtered through Celite, rinsing with several portions of CH_2Cl_2, and the filtrate was concentrated under reduced pressure. Purification by chromatography on a silica gel (0.8% EtOAc/hexanes) afforded 2.12 g (11.2 mmol, 90% yield over 2 steps) of the corresponding ketone **44d** as a colorless oil. Ketone **44d**: R_f = 0.52 (10% EtOAc/hexanes); IR (neat) 1681, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78–1.85 (m, 2H), 2.13 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 2.91 (t, J = 7.3 Hz, 2H), 4.95–

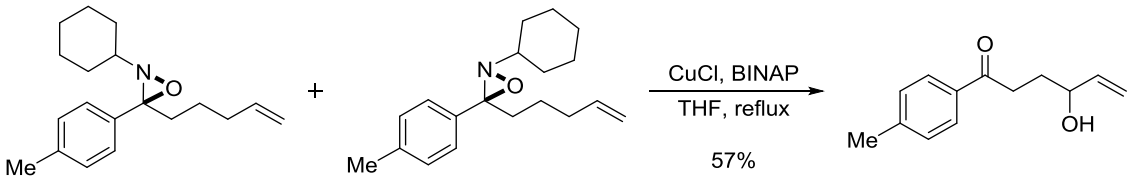
5.05 (m, 2H), 5.80 (m, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 23.4, 33.2, 37.6, 115.2, 128.1, 129.2, 134.6, 138.1, 143.6, 199.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O$ $[M + H]^+$ 189.1279, found 189.1284.



(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(pent-4′-en-1′-yl)-3-(*p*-tolyl)-1,2-oxaziridine (*cis*-42db) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-(Pent-4′-en-1′-yl)-3-(*p*-tolyl)-1,2-oxaziridine (*trans*-42db). Following the general procedure **G**, 1-(*p*-tolyl)hex-5-en-1-one **44d** (0.500 g, 2.65 mmol, 1.0 equiv), cyclohexylamine **45b** (0.456 mL, 3.98 mmol, 1.5 equiv), PTSA (25.2 mg, 0.132 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (35 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.550 g, 3.19 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.5% EtOAc/hexanes) afforded a mixture of oxaziridine diastereomers *cis*-**42db** and *trans*-**42db** and starting ketone **44d** as a colorless oil (0.480 g, 1.70 mmol, 64% corrected yield; *cis*-**42db**:*trans*-**42db** = ca. 55:45 by ^{1}H NMR). Subsequent purification of the mixture of *cis*-**42db**, *trans*-**42db**, and **44d** by chromatography on a silica gel (0.2% EtOAc/hexanes) afforded a partial separation of the mixture of *cis*-**42db** and *trans*-**42db** as a colorless oil. A small amount of the mixture of *cis*-**42db**, *trans*-**42db**, and **44d** was further purified by preparative TLC developing seven times with 2% EtOAc/hexanes. Bands corresponding to pure products were scraped from the plate and eluted with 100% CH_2Cl_2 through a short

bed of silica gel. Evaporation of solvents afforded analytical samples of the major *cis*-**42db** and the minor *trans*-**42db** diastereomers as colorless oils for characterization. Major diastereomer *cis*-**42db**: R_f = 0.65 (5% EtOAc/hexanes, run thrice); IR (neat) 2930, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74–0.86 (m, 1H), 0.97–1.18 (m, 2H), 1.19–1.34 (m, 3H), 1.39–1.58 (m, 4H), 1.66–1.78 (m, 3H), 1.83–1.87 (m, 1H), 1.92–2.06 (m, 2H), 2.30–2.39 (m, 4H), 4.86–4.94 (m, 2H), 5.69 (m, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 23.3, 24.0, 24.1, 25.8, 28.5, 31.7, 33.7, 38.1, 60.7, 87.6, 114.8, 127.7, 128.8, 132.1, 138.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}NO$ $[M + H]^+$ 286.2171, found 286.2137.

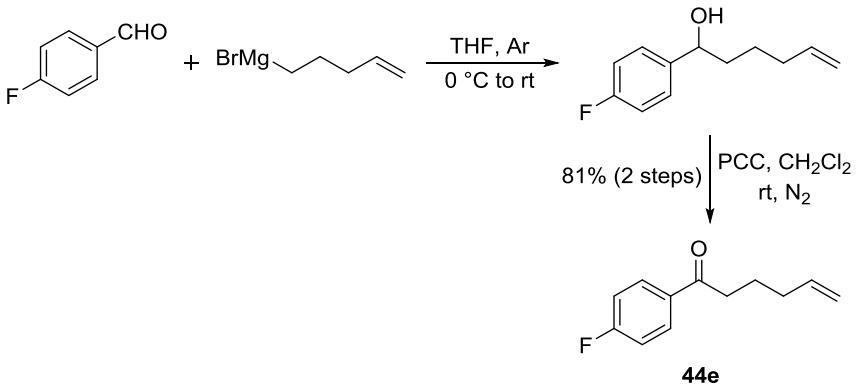
Minor diastereomer *trans*-**42db**: R_f = 0.51 (5% EtOAc/hexanes, run thrice); IR (neat) 2930, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.38 (m, 3H), 1.42–1.60 (m, 4H), 1.64–1.73 (m, 2H), 1.81–1.85 (m, 2H), 1.96–2.13 (m, 4H), 2.25–2.33 (m, 4H), 2.58 (m, 1H), 4.94–5.02 (m, 2H), 5.74 (m, 1H), 7.15 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 24.3, 24.6, 24.7, 25.8, 29.0, 29.2, 32.1, 33.8, 61.2, 85.6, 115.3, 126.0, 129.1, 136.9, 138.03, 138.07; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}NO$ $[M + H]^+$ 286.2171, found 286.2162.



42db (cis:trans = 48:52) **43d**

4-Hydroxy-1-(*p*-tolyl)hex-5-en-1-one (43d; Table 19, entry 2). Following the general procedure **J**, CuCl (2.60 mg, 0.0263 mmol, 0.050 equiv) and *rac*-BINAP (16.3 mg, 0.0263 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomers **42db** (150 mg, 0.526 mmol, 1.0 equiv; cis:trans = ca. 48:52) in THF (3 mL).

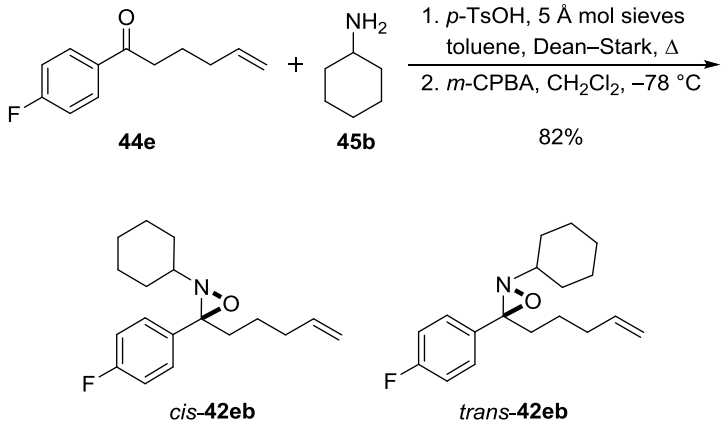
The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.8:1.0:0.2) afforded 61.0 mg (0.299 mmol, 57% yield) of the allylic alcohol **43d** as a yellow oil. Allylic alcohol **43d**: R_f = 0.32 (25% EtOAc/hexanes); IR (neat) 3411, 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88–1.97 (m, 1H), 1.99–2.07 (m, 1H), 2.23 (br s, 1H), 2.39 (s, 3H), 3.09 (t, J = 7.0 Hz, 2H), 4.22–4.24 (m, 1H), 5.12 (dt, J = 10.4, 1.3 Hz, 1H), 5.26 (dt, J = 17.2, 1.4 Hz, 1H), 5.89 (m, 1H), 7.24 (d, J = 7.9 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 31.1, 34.4, 72.4, 115.0, 128.4, 129.4, 134.5, 140.9, 144.0, 200.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2$ $[M + H]^+$ 205.1229, found 205.1200. Ketone **44d** was also obtained in 27% yield (27.0 mg, 0.143 mmol).



44e

1-(4-Fluorophenyl)hex-5-en-1-one (44e).[198] Following the general procedure **H**, a solution of 5-bromo-1-pentene (1.14 mL, 9.66 mmol, 1.2 equiv) in THF (8 mL) was added drop wise to a stirring suspension of magnesium turnings (235 mg, 9.66 mmol, 1.2 equiv) and one small crystal of iodine in THF (7 mL) under argon atmosphere. After refluxing gently for 1 h, the reaction mixture was cooled to 0 °C and treated with a solution of 4-fluorobenzaldehyde (1.00 g, 8.05 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was then stirred at rt for 2 h. The aqueous work-up afforded the crude alcohol (1.75 g) as a yellow oil, which was used for the next oxidation step without further purification.

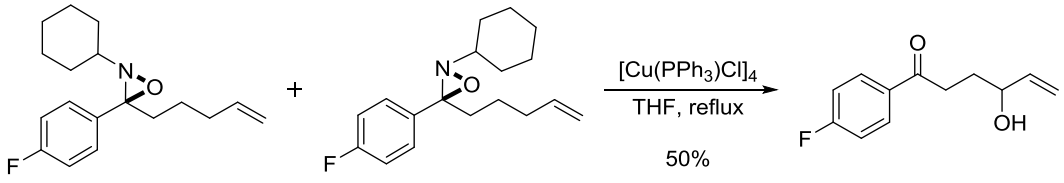
To a stirring solution of crude alcohol (1.75 g) in CH_2Cl_2 (50 mL) was added PCC (3.47 g, 16.1 mmol, 2 equiv) and the reaction mixture was stirred at rt for 2 h. The reaction mixture was filtered through Celite, rinsing with several portions of CH_2Cl_2, and the filtrate was concentrated under reduced pressure. Purification by chromatography on a silica gel (1% EtOAc/hexanes) afforded 1.25 g (6.51 mmol, 81% yield over 2 steps) of the corresponding ketone **44e** as a colorless oil. Ketone **44e**: R_f = 0.71 (15% EtOAc/hexanes); IR (neat) 1684, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (m, 2H), 2.06–2.12 (m, 2H), 2.88 (t, J = 7.3 Hz, 2H), 4.91–5.01 (m, 2H), 5.75 (m, 1H), 7.01–7.07 (m, 2H), 7.89–7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 33.1, 37.5, 115.3, 115.6 (d, J = 86.9 Hz, 2C), 130.64 (d, J = 36.7 Hz, 2C), 133.53 (d, J = 11.8 Hz, 1C), 138.0, 165.6 (d, J = 1010.8 Hz, 1C), 196.4; HRMS (EI) *m/z* calcd for $C_{12}H_{14}OF$ $[M + H]^+$ 193.1029, found 193.1021.



(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(4-fluorophenyl)-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*cis*-42eb) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-(4-fluorophenyl)-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*trans*-42eb). Following the general procedure **G**, 1-(4-fluorophenyl)hex-5-en-1-one **44e** (0.500 g, 2.60 mmol, 1.0 equiv), cyclohexylamine **45b** (0.446 mL, 3.90 mmol, 1.5 equiv), PTSA (24.7 mg, 0.130 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (30 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA

(0.539 g, 3.12 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.5–0.7% EtOAc/hexanes) afforded a mixture of oxaziridine diastereomers *cis*-**42eb** and *trans*-**42eb** and starting ketone **44e**, followed by the mixture of *cis*-**42eb** and *trans*-**42eb** as yellow oils (0.617 g, 2.13 mmol, 82% yield; *cis*-**42eb**:*trans*-**42eb** = ca. 2:1 by ^{1}H NMR). An analytical sample of the major diastereomer *cis*-**42eb** accompanied with 12% of the minor diastereomer *trans*-**42eb** was obtained for characterization during this purification. Major diastereomer *cis*-**42eb**: R_f = 0.67 (5% EtOAc/hexanes, run thrice); IR (neat) 2931, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74–0.85 (m, 1H), 0.98–1.18 (m, 2H), 1.18–1.29 (m, 3H), 1.40–1.52 (m, 3H), 1.53–1.59 (m, 1H), 1.65–1.75 (m, 3H), 1.83–1.87 (m, 1H), 1.93–2.07 (m, 2H), 2.33 (m, 1H), 4.88–4.95 (m, 2H), 5.69 (m, 1H), 7.04–7.10 (m, 2H), 7.36–7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.11, 24.18, 25.8, 28.6, 31.7, 33.7, 38.0, 60.9, 87.2, 115.0, 115.3 (d, J = 85.8 Hz, 2C), 129.65 (d, J = 32.3 Hz, 2C), 131.2 (d, J = 13.0 Hz, 1C), 138.3, 162.9 (d, J = 985.8 Hz, 1C); HRMS (ESI) *m/z* calcd for $C_{18}H_{25}FNO$ $[M + H]^+$ 290.1920, found 290.1887.

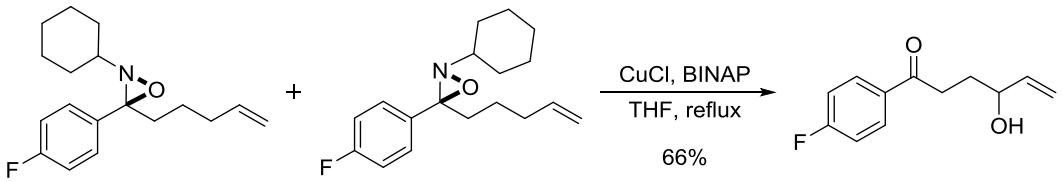
Minor diastereomer *trans*-**42eb**: R_f = 0.62 (5% EtOAc/hexanes, run thrice); ^{1}H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 2.26 (m, 1H), 2.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; diagnostic peaks only) δ 29.3, 61.3, 85.2.



42eb (cis:trans = 88:12) **43e**

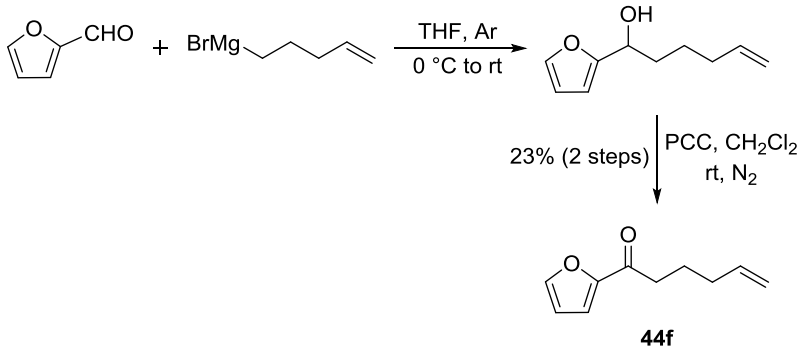
1-(4-Fluorophenyl)-4-hydroxyhex-5-en-1-one (43e; Table 19, entry 3). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (50.0 mg, 0.0346 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomers **42eb** (200 mg, 0.692 mmol,

1.0 equiv; cis:trans = ca. 88:12) in THF (8 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 72.0 mg (0.346 mmol, 50% yield) of the allylic alcohol **43e** as a colorless oil. Allylic alcohol **43e**: R_f = 0.34 (25% EtOAc/hexanes); IR (neat) 3411, 1681, 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88–1.97 (m, 1H), 2.00–2.08 (m, 1H), 2.05 (d, J = 4.4 Hz, 1H), 3.09 (t, J = 7.0 Hz, 2H), 4.21–4.26 (m, 1H), 5.13 (dt, J = 10.4, 1.3 Hz, 1H), 5.26 (dt, J = 17.2, 1.4 Hz, 1H), 5.90 (m, 1H), 7.09–7.14 (m, 2H), 7.97–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 34.4, 72.3, 115.1, 115.8 (d, J = 87.0 Hz, 2C), 130.9 (d, J = 36.8 Hz, 2C), 133.51 (d, J = 11.8 Hz, 1C), 140.8, 165.9 (d, J = 1012.8 Hz, 1C), 199.0; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}FO_2$ $[M + H]^+$ 209.0978, found 209.0991. Ketone **44e** was also obtained in 19% yield (25.0 mg, 0.130 mmol).



42eb (cis:trans = 58:42) **43e**

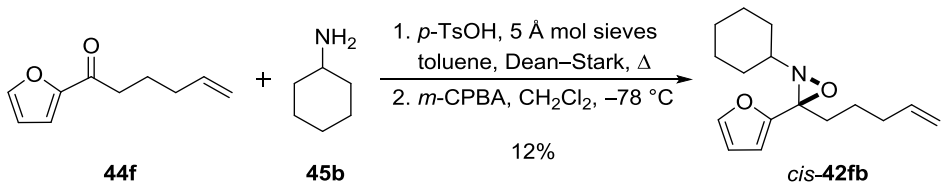
Following the general procedure **J**, CuCl (2.56 mg, 0.0259 mmol, 0.050 equiv) and *rac*-BINAP (16.1 mg, 0.0259 mmol, 0.050 equiv) in THF (9 mL) was reacted with a solution of oxaziridine diastereomers **42eb** (150 mg, 0.519 mmol, 1.0 equiv; cis:trans = ca. 58:42) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 71.0 mg (0.341 mmol, 66% yield) of **43e** as a yellow oil and 17.0 mg (0.0885 mmol, 17% yield) of **44e**.



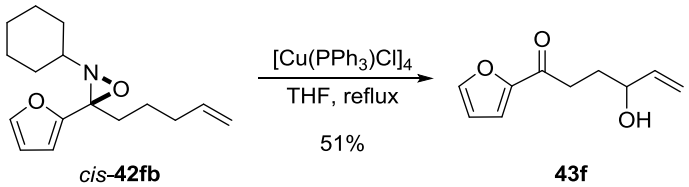
44f

1-(Furan-2-yl)hex-5-en-1-one (44f).[199] Following the general procedure **H**, a solution of 5-bromo-1-pentene (4.43 mL, 37.4 mmol, 1.2 equiv) in THF (25 mL) was added drop wise to a stirring suspension of magnesium turnings (0.910 g, 37.4 mmol, 1.2 equiv) and one small crystal of iodine in THF (25 mL). After refluxing gently for 1 h, the reaction mixture was cooled to 0 °C and treated with a solution of 2-furaldehyde (3.00 g, 31.2 mmol, 1.0 equiv) in THF (10 mL). The reaction mixture was then stirred at rt for 1 h. The aqueous work-up afforded the crude alcohol (5.24 g) as a brown oil, which was used for the next oxidation step without further purification.

To a stirring solution of crude alcohol (5.24 g) in CH_2Cl_2 (125 mL) was added Celite (12.0 g) followed by PCC (13.4 g, 62.4 mmol, 2 equiv), and the reaction mixture was stirred at rt for 12 h. The reaction mixture was filtered through Celite, rinsing with several portions of CH_2Cl_2, and the filtrate was concentrated under reduced pressure. Purification by chromatography on a silica gel (3% EtOAc/hexanes) afforded 1.20 g (7.31 mmol, 23% yield over 2 steps) of the corresponding ketone **44f** as a yellow oil. R_f = 0.47 (15% EtOAc/hexanes).

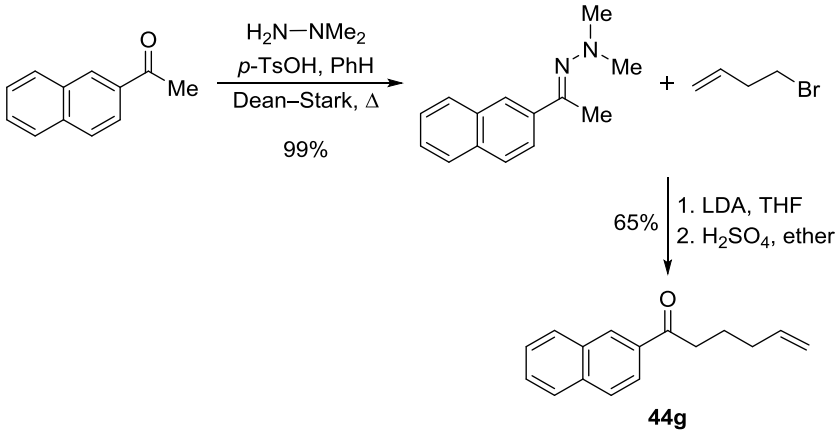


(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(furan-2-yl)-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*cis*-42fb). Following the general procedure **G**, 1-(furan-2-yl)hex-5-en-1-one **44f** (0.500 g, 3.04 mmol, 1.0 equiv), cyclohexylamine **45b** (0.523 mL, 4.57 mmol, 1.5 equiv), PTSA (28.9 mg, 0.152 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (30 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.631 g, 3.65 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.7–0.8% EtOAc/hexanes) afforded the oxaziridine *cis*-**42fb** as a yellow oil (0.100 g, 0.383 mmol, 12% yield; sample contains some minor impurities). Oxaziridine diastereomer *cis*-**42fb**: R_f = 0.55 (10% EtOAc/hexanes); IR (neat) 2931, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–0.99 (m, 1H), 1.12–1.18 (m, 2H), 1.19–1.25 (m, 2H), 1.33–1.41 (m, 1H), 1.45–1.57 (m, 3H), 1.58–1.64 (m, 1H), 1.72–1.80 (m, 2H), 1.87–1.91 (m, 1H), 2.01–2.10 (m, 3H), 2.32 (m, 1H), 4.90–4.99 (m, 2H), 5.74 (m, 1H), 6.38–6.40 (m, 2H), 7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.1, 24.4, 25.8, 28.6, 31.8, 33.7, 36.0, 61.4, 82.3, 110.3, 111.5, 115.0, 138.4, 143.5, 149.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{24}NO_2$ $[M + H]^+$ 262.1807, found 262.1796.



1-(Furan-2-yl)-4-hydroxyhex-5-en-1-one (43f; Table 19, entry 4). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (41.5 mg, 0.0287 mmol, 0.050 equiv) in THF (10 mL) was reacted with a solution of oxaziridine *cis*-**42fb** (150 mg, 0.574 mmol, 1.0 equiv) in

THF (5 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.6:1.0:0.4) afforded 53.0 mg (0.294 mmol, 51% yield) of the allylic alcohol **43f** as a pale yellow oil. Allylic alcohol **43f**: R_f = 0.11 (25% EtOAc/hexanes); IR (neat) 3420, 1666, 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86–1.95 (m, 1H), 1.97–2.05 (m, 1H), 2.09 (br s, 1H), 2.97 (t, J = 7.1 Hz, 2H), 4.22 (m, 1H), 5.12 (dt, J = 10.4, 1.3 Hz, 1H), 5.26 (dt, J = 17.2, 1.4 Hz, 1H), 5.88 (m, 1H), 6.51–6.53 (m, 1H), 7.20 (dd, J = 3.5, 0.6 Hz, 1H), 7.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 34.3, 72.3, 112.4, 115.2, 117.4, 140.7, 146.6, 152.8, 189.7; HRMS (ESI) *m/z* calcd for $C_{10}H_{13}O_3$ $[M + H]^+$ 181.0864, found 181.0867. Ketone **44f** was also obtained in 15% yield (14.0 mg, 0.0853 mmol).

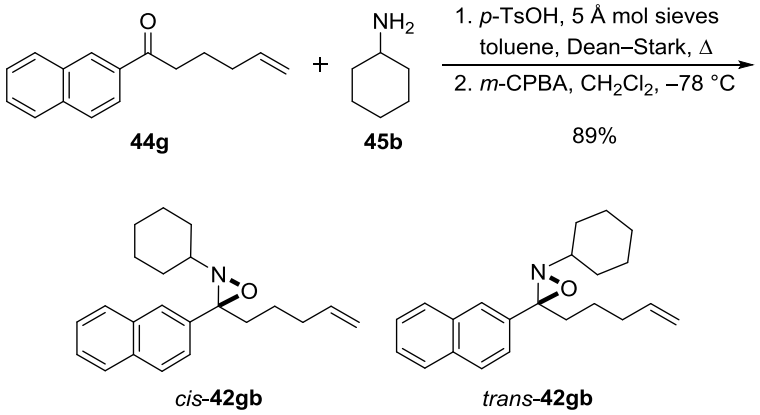


44g

1-(Naphthalen-2-yl)hex-5-en-1-one (44g). A solution of 2-acetonaphthone (5.00 g, 29.3 mmol, 1.0 equiv), *N,N*-dimethylhydrazine (5.29 g, 88.1 mmol, 3.0 equiv), and PTSA (279 mg, 1.46 mmol, 0.050 equiv) in benzene (35 mL) was refluxed for 18 h under nitrogen atmosphere with removal of water by a Dean–Stark apparatus. The reaction mixture was concentrated under reduced pressure and the residue was cooled to 0 °C. The yellow solid obtained was triturated with hexanes and filtered, washed with hexanes and dried under

vacuum to afford the corresponding hydrazone as a creamish-yellow solid (mp 47–50 °C) in 99% yield (6.15 g, 29.0 mmol).

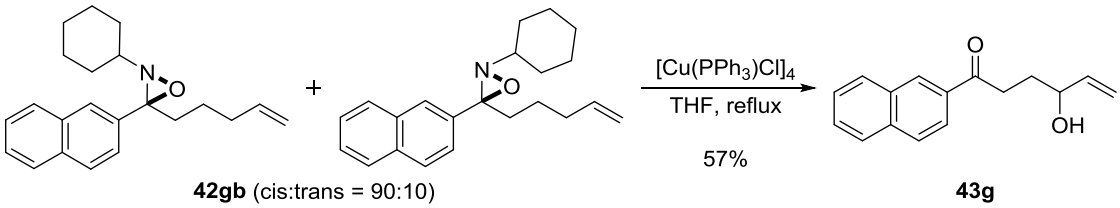
To a cooled 1.0 M LDA solution (23.3 mL, 23.3 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added the solution of hydrazone (4.50 g, 21.2 mmol, 1.0 equiv) in THF (35 mL) slowly over 25 min and was allowed to stir at 0 °C for 5 h. The reaction mixture was then cooled to –78 °C and a solution of 4-bromo-1-butene (3.43 g, 25.4 mmol, 1.2 equiv) in THF (10 mL) was added slowly over 20 min. The reaction was warmed to rt and stirred for 36 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ether (20 mL) and then treated with an ice-cold solution of dilute H_2SO_4 (20 mL) for 30 min to hydrolyze the hydrazone. The resulting solution was diluted with water and extracted with ether (2 × 20 mL) and the combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on a silica gel (4% EtOAc/hexanes) afforded the ketone **44g** as a cream-colored solid in 65% yield (3.10 g, 13.8 mmol; 95% brsm). Ketone **44g**: R_f = 0.74 (10% EtOAc/hexanes, run twice); mp 36–37 °C; IR (neat) 1678, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91(p, J = 7.3 Hz, 2H), 2.20 (q, J = 7.0 Hz, 2H), 3.08 (t, J = 7.3 Hz, 2H), 5.03 (d, J = 10.1 Hz, 1H), 5.09 (d, J = 17.1 Hz, 1H), 5.86 (m, 1H), 7.51–7.59 (m, 2H), 7.83–7.87 (m, 2H), 7.94 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 8.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 33.3, 37.8, 115.4, 124.0, 126.8, 127.8, 128.42, 128.47, 129.62, 129.65, 132.6, 134.4, 135.6, 138.1, 200.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}O$ $[M + H]^+$ 225.1279, found 225.1263.



(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(naphthalen-2-yl)-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*cis*-42gb) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-(naphthalen-2-yl)-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*trans*-42gb). Following the general procedure **G**, 1-(naphthalen-2-yl)hex-5-en-1-one **44g** (0.500 g, 2.23 mmol, 1.0 equiv), cyclohexylamine **45b** (0.382 mL, 3.34 mmol, 1.5 equiv), PTSA (21.2 mg, 0.115 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (25 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.461 g, 2.67 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.6% EtOAc/hexanes) afforded a mixture of oxaziridine diastereomers *cis*-**42gb** and *trans*-**42gb** and starting ketone **44g** as a colorless oil. Subsequent purification by chromatography on a silica gel (0.5–1% EtOAc/hexanes) afforded a mixture of *cis*-**42gb** and *trans*-**42gb**, which were separated into 2 fractions containing enrichment from each diastereomer (0.641 g, 1.99 mmol, 89% yield; *cis*-**42gb**:*trans*-**42gb** = ca. 1:1). A pure sample of the first *cis*-**42gb** and the second diastereomer *trans*-**42gb** for characterization was obtained during this purification. First diastereomer *cis*-**42gb**: R_f = 0.51 (5% EtOAc/hexanes, run thrice); IR (neat) 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66–0.77 (m, 1H), 0.94–1.17 (m, 2H), 1.21–1.33 (m, 2H), 1.35–1.39 (m, 1H), 1.41–1.57 (m, 4H), 1.67–1.71 (m, 1H), 1.76–1.84 (m, 2H), 1.88–1.92 (m, 1H), 1.95–2.08 (m, 2H), 2.48 (m, 1H), 4.87–4.95 (m, 2H), 5.69 (m, 1H), 7.50–7.56 (m, 3H), 7.85–7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 24.0, 24.1, 25.8, 28.7, 31.8, 33.8, 38.1, 60.9, 88.0, 115.0, 124.9,

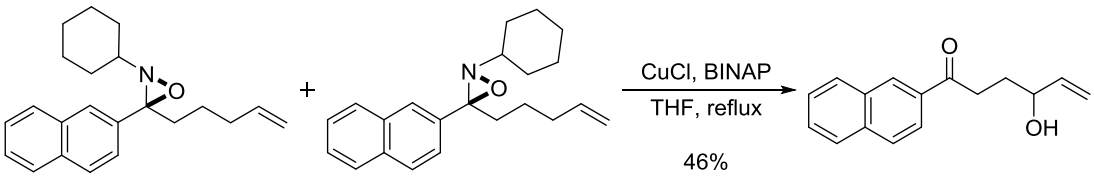
126.72, 126.78, 127.6, 127.9, 128.1, 128.5, 132.80, 132.85, 133.4, 138.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO$ $[M + H]^+$ 322.2171, found 322.2155.

Second diastereomer *trans*-**42gb**: R_f = 0.51 (5% EtOAc/hexanes, run thrice); IR (neat) 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.45 (m, 3H), 1.46–1.65 (m, 4H), 1.69–1.72 (m, 1H), 1.79–1.89 (m, 3H), 2.04–2.19 (m, 4H), 2.44 (m, 1H), 2.67 (m, 1H), 4.95–5.03 (m, 2H), 5.73 (m, 1H), 7.46–7.51 (m, 3H), 7.82–7.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.6, 24.8, 25.9, 29.0, 29.3, 32.1, 33.8, 61.3, 85.9, 115.4, 123.8, 125.4, 126.3, 127.8, 128.37, 128.39, 133.2, 133.3, 137.3, 137.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO$ $[M + H]^+$ 322.2171, found 322.2143.



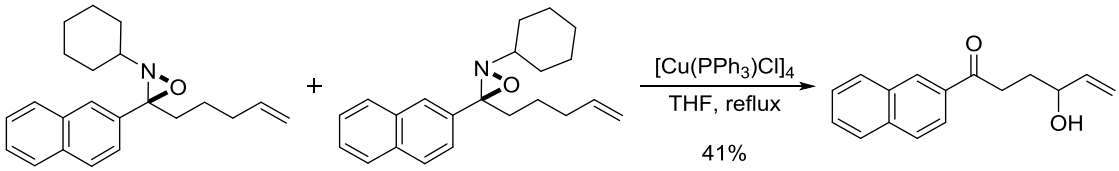
4-Hydroxy-1-(naphthalen-2-yl)hex-5-en-1-one (43g; Table 19, entries 5 and 6). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (33.7 mg, 0.0233 mmol, 0.045 equiv) in THF (10 mL) was reacted with a solution of oxaziridine diastereomers **42gb** (164 mg, 0.510 mmol, 1.0 equiv; cis:trans = ca. 90:10) in THF (5 mL). The reaction mixture was refluxed for 3 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 99.4:0.5:0.1) afforded 70.0 mg (0.291 mmol, 57% yield) of the allylic alcohol **43g** as a creamish-orange solid. Allylic alcohol **43g**: R_f = 0.15 (20% EtOAc/hexanes); mp 59–61 °C; IR (neat) 3410, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96–2.05 (m, 1H), 2.07–2.15 (m, 1H), 2.21 (br s, 1H), 3.26 (t, J = 7.0 Hz, 2H), 4.29 (br s, 1H), 5.15 (d, J = 10.4 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.94 (m, 1H), 7.52–7.61 (m, 2H), 7.85–7.88 (m, 2H), 7.95 (d, J = 7.9 Hz, 1H), 8.03 (dd, J = 8.6, 1.5 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 34.5, 72.4, 115.1, 124.0, 126.9, 127.9, 128.64, 128.66,

129.7, 129.9, 132.7, 134.4, 135.8, 140.9, 200.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}O_2$ [M + H]$^+$ 241.1229, found 241.1224. Ketone **44g** was also obtained in 19% yield (22.0 mg, 0.982 mmol).



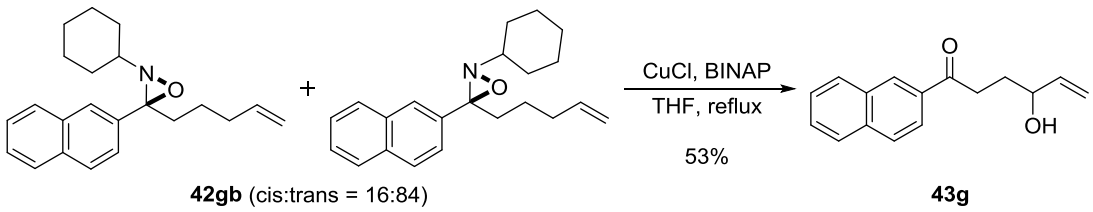
42gb (cis:trans = 90:10) **43g**

Following the general procedure **J**, CuCl (1.46 mg, 0.0147 mmol, 0.050 equiv) and *rac*-BINAP (9.20 mg, 0.0147 mmol, 0.050 equiv) in THF (8 mL) was reacted with a solution of oxaziridine diastereomers **42gb** (95.0 mg, 0.29 mmol, 1.0 equiv; cis:trans = ca. 90:10) in THF (2 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 33.0 mg (0.137 mmol, 46% yield; 57% brsm) of **43g** as a yellow oil and 7.00 mg (0.0312 mmol, 11% yield) of **44g**.



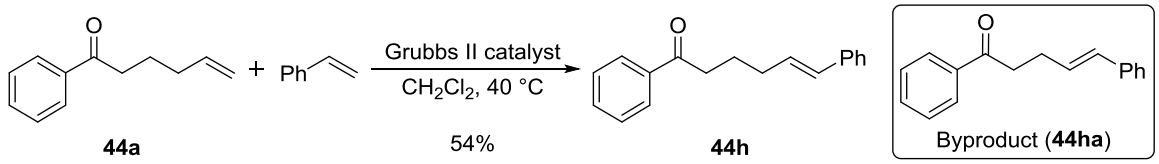
42gb (cis:trans = 16:84) **43g**

Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (33.7 mg, 0.0233 mmol, 0.042 equiv) in THF (10 mL) was reacted with a solution of oxaziridine diastereomers **42gb** (178 mg, 0.553 mmol, 1.0 equiv; cis:trans = ca. 16:84, accompanied with 2.5% of **44g**) in THF (5 mL). The reaction mixture was refluxed for 3 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 99.2:0.5:0.3) afforded 55.0 mg (0.229 mmol, 41% yield) of **43g** as an orange oil and 25.0 mg (0.111 mmol, 20% corrected yield) of **44g**.



42gb (cis:trans = 16:84) **43g**

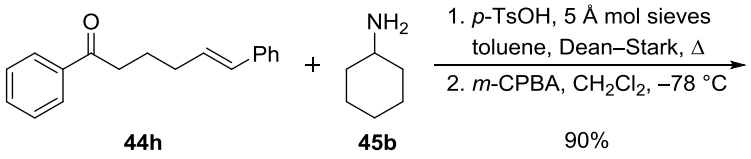
Following the general procedure **J**, CuCl (1.30 mg, 0.0132 mmol, 0.050 equiv) and *rac*-BINAP (8.22 mg, 0.0132 mmol, 0.050 equiv) in THF (8 mL) was reacted with a solution of oxaziridine diastereomers **42gb** (85.0 mg, 0.264 mmol, 1.0 equiv; cis:trans = ca. 16:84, accompanied with 2.5% of **44g**) in THF (2 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 34.0 mg (0.141 mmol, 53% yield; 73% brsm) of **43g** as a yellow oil and ca. 4.0 mg (ca. 6% corrected yield) of **44g**.

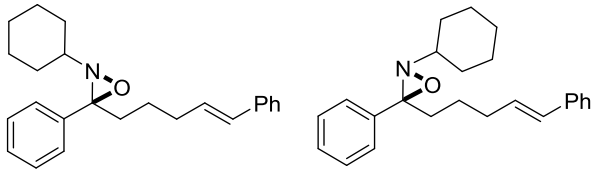


44a **44h**

(*E*)-1,6-Diphenylhex-5-en-1-one (44h). To a solution of Grubbs II catalyst[200] (0.195 g, 0.229 mmol, 0.04 equiv) in CH_2Cl_2 (20 mL) at rt under argon atmosphere was added a solution containing the mixture of 1-phenylhex-5-en-1-one **44a** (1.00 g, 5.74 mmol, 1.0 equiv) and styrene (1.97 mL, 17.2 mmol, 3.0 equiv) in CH_2Cl_2 (5 mL), and the reaction mixture was stirred at 40 °C for 4 h. The reaction mixture was concentrated under reduced pressure. Initial purification of crude residue by chromatography on a silica gel (0.5–0.6% EtOAc/hexanes) afforded a mixture of desired product **44h** and (*E*)-1,5-diphenylpent-4-en-1-one byproduct **44ha**[201] as a white solid (0.770 g, 3.08 mmol, 54% corrected yield for **44h** by ^{1}H NMR). Subsequent purification by chromatography on a silica gel (0.5% EtOAc/hexanes) followed by recrystallization from hexanes afforded a partial separation of the desired product **44h** as a white crystals. Ketone **44h**: R_f = 0.38 (5% EtOAc/hexanes);

mp 52–54 °C; IR (neat) 1682, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98 (m, 2H), 2.35 (q, J = 6.9 Hz, 2H), 3.03 (t, J = 7.2 Hz, 2H), 6.23–6.30 (m, 1H), 6.46 (d, J = 15.8 Hz, 1H), 7.24 (t, J = 7.1 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.39 (d, J = 7.3 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 8.00 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 32.4, 37.7, 126.0, 127.0, 128.0, 128.54, 128.59, 129.9, 130.7, 132.9, 137.0, 137.6, 200.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}O$ $[M + H]^+$ 251.1436, found 251.1424.



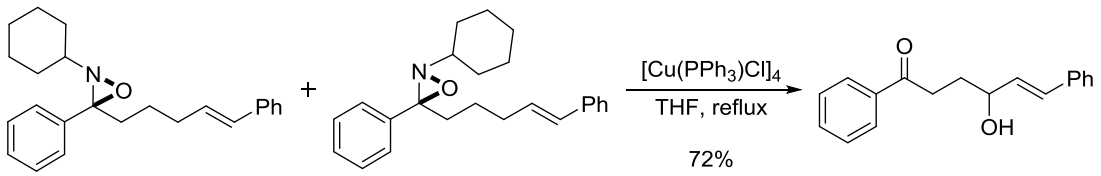


cis-**42hb** *trans*-**42hb**

(2*R*,3*S*,*E*)-*rel*-2-Cyclohexyl-3-phenyl-3-(5′-phenylpent-4′-en-1′-yl)-1,2-oxaziridine (*cis*-42hb) and (2*S*,3*S*,*E*)-*rel*-2-Cyclohexyl-3-phenyl-3-(5′-phenylpent-4′-en-1′-yl)-1,2-oxaziridine (*trans*-42hb). Following the general procedure **G**, (*E*)-1,6-diphenylhex-5-en-1-one **44h** (0.400 g, 1.60 mmol, 1.0 equiv), cyclohexylamine **45b** (0.274 mL, 2.40 mmol, 1.5 equiv), PTSA (15.2 mg, 0.0800 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.0 g) in toluene (30 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.331 g, 1.92 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL). Purification by chromatography on a silica gel (0.5–0.6% EtOAc/hexanes) afforded a mixture of major *cis*-**42hb** and minor *trans*-**42hb** diastereomers as a colorless oil (0.500 g, 1.44 mmol, 90% yield; *cis*-**42hb**:*trans*-**42hb** = ca. 60:40 by ^1H NMR). Subsequent purification of a small amount of the mixture of *cis*-**42hb** and *trans*-**42hb** by preparative TLC developing 13 times with 2% EtOAc/hexanes afforded a single band. The top and bottom portions of the band were

scraped from the plate and eluted separately with 100% CH_2Cl_2 through a short bed of silica gel. Evaporation of solvents for the top portion of the band afforded an analytical sample of *cis*-**42hb** for characterization and the bottom portion of the band afforded the mixture of *cis*-**42hb** and *trans*-**42hb**. Major diastereomer *cis*-**42hb**: R_f = 0.46 (5% EtOAc/hexanes, run twice); IR (neat) 2930, 2855, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73–0.84 (m, 1H), 0.98–1.19 (m, 2H), 1.19–1.29 (m, 1H), 1.31–1.39 (m, 2H), 1.43–1.59 (m, 4H), 1.68–1.83 (m, 3H), 1.85–1.89 (m, 1H), 2.12–2.22 (m, 2H), 2.42 (m, 1H), 6.07–6.14 (m, 1H), 6.30 (d, J = 15.8 Hz, 1H), 7.15–7.19 (m, 1H), 7.24–7.30 (m, 4H), 7.37–7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.1, 24.2, 25.8, 28.6, 31.8, 33.0, 38.1, 61.0, 87.7, 126.1, 127.0, 127.8, 128.2, 128.6, 128.8, 130.42, 130.44, 135.2, 137.8; HRMS (ESI) *m/z* calcd for $C_{24}H_{30}NO$ $[M + H]^+$ 348.2327, found 348.2357.

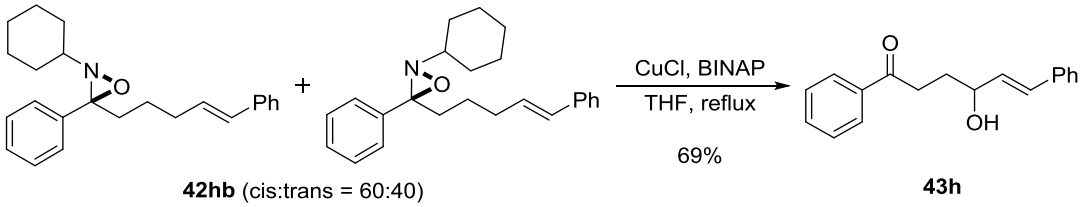
From a mixture of *cis*-**42hb** and *trans*-**42hb**: Minor diastereomer *trans*-**42hb**: R_f = 0.40 (5% EtOAc/hexanes, run twice); ^1H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 2.36 (m, 1H), 2.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; diagnostic peaks only) δ 29.1, 61.2, 85.8, 137.7, 139.9.



42hb (cis:trans = 60:40) **43h**

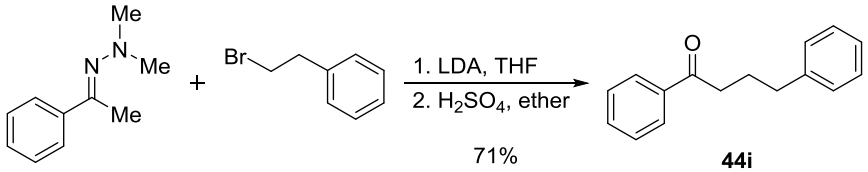
(*E*)-4-Hydroxy-1,6-diphenylhex-5-en-1-one (43h; Table 19, entry 8). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (31.2 mg, 0.0216 mmol, 0.050 equiv) in THF (10 mL) was reacted with a solution of oxaziridine diastereomers **42hb** (150 mg, 0.432 mmol, 1.0 equiv; cis:trans = 60:40) in THF (5 mL). Reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (0–1% acetone/CH_2Cl_2) afforded 83.0 mg (0.312 mmol, 72% yield) of the allylic alcohol **43h** as a creamish solid. Allylic alcohol **43h**:

R_f = 0.32 (25% EtOAc/hexanes); mp 59–61 °C; IR (neat) 3400, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.01–2.18 (m, 2H), 2.58 (d, J = 4.1 Hz, 1H), 3.16 (t, J = 7.0 Hz, 2H), 4.42 (m, 1H), 6.25 (dd, J = 15.9, 6.3 Hz, 1H), 6.61 (d, J = 15.8 Hz, 1H), 7.21–7.26 (m, 1H), 7.29–7.32 (m, 2H), 7.36–7.38 (m, 2H), 7.42–7.46 (m, 2H), 7.53–7.57 (m, 1H), 7.96–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 34.5, 72.1, 126.6, 127.8, 128.2, 128.7, 130.5, 132.1, 133.2, 136.7, 136.9, 200.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}O_2$ $[M + H]^+$ 267.1385, found 267.1392. Ketone **44h** was also obtained in 19% yield (21.0 mg, 0.0840 mmol).



42hb (cis:trans = 60:40) **43h**

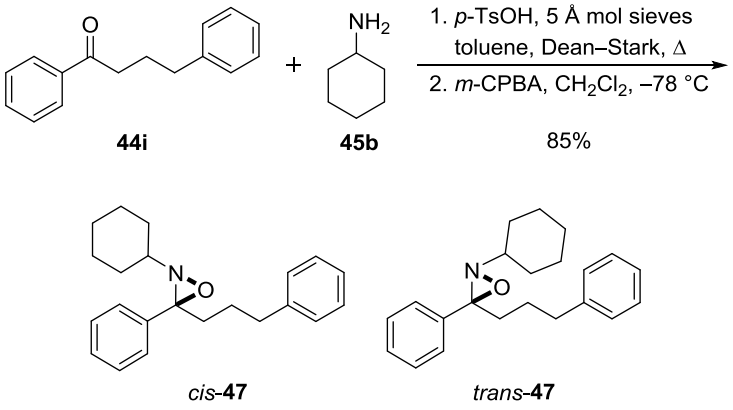
Following the general procedure **J**, CuCl (2.13 mg, 0.0216 mmol, 0.050 equiv) and *rac*-BINAP (13.4 mg, 0.0216 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomers **42hb** (150 mg, 0.432 mmol, 1.0 equiv; cis:trans = 60:40) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (0–1% acetone/CH_2Cl_2) afforded 79.0 mg (0.296 mmol, 69% yield) of **43h** as a yellow solid. Ketone **44h** was also obtained along with unidentified impurities.



44i

1,4-Diphenylbutan-1-one (44i). To a cooled 1.0 M LDA solution (15.6 mL, 15.6 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added a solution of acetophenone *N*,*N*-dimethylhydrazone (2.30 g, 14.1 mmol, 1.0 equiv) in THF (15 mL)

slowly over 15 min and was allowed to stir at 0 °C for 5 h. The reaction mixture was then cooled to –78 °C and a solution of (2-bromoethyl)benzene (2.49 mL, 18.4 mmol, 1.3 equiv) in THF (5 mL) was added slowly over 10 min. The reaction was warmed to rt and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ether (15 mL), and then treated with an ice-cold solution of dilute H_2SO_4 (15 mL) for 30 min to hydrolyze the hydrazone. The resulting solution was diluted with water and extracted with ether (2 × 15 mL), and the combined organic extracts were washed with water (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on a silica gel (0.25% EtOAc/hexanes) afforded the ketone **44i** in 71% yield (2.26 g, 10.0 mmol) as an off-white crystal. Ketone **44i**: R_f = 0.60 (5% EtOAc/hexanes, run twice); mp 54–56 °C; IR (neat) 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07–2.14 (m, 2H), 2.74 (t, J = 7.5 Hz, 2H), 2.99 (t, J = 7.3 Hz, 2H), 7.19–7.24 (m, 3H), 7.29–7.33 (m, 2H), 7.43–7.48 (m, 2H), 7.53–7.58 (m, 1H), 7.93–7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 35.3, 37.8, 126.1, 128.1, 128.5, 128.6, 128.7, 133.1, 137.1, 141.8, 200.2; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}O$ $[M]^+$ 224.1201, found 224.1195.

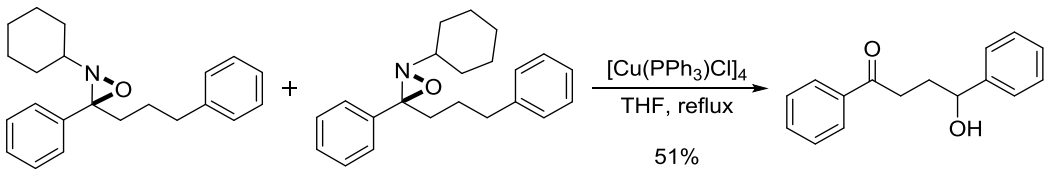


(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-phenyl-3-(3′-phenylpropyl)-1,2-oxaziridine (*cis*-47) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-phenyl-3-(3′-phenylpropyl)-1,2-oxaziridine (*trans*-47).

Following the general procedure **G**, 1,4-diphenylbutan-1-one **44i** (0.500 g, 2.23 mmol, 1.0 equiv), cyclohexylamine **45b** (0.382 mL, 3.34 mmol, 1.5 equiv), PTSA (21.2 mg, 0.111 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (30 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.462 g, 2.67 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.6% EtOAc/hexanes) afforded a mixture of oxaziridine diastereomers *cis*-**47** and *trans*-**47** as a colorless oil (0.610 g, 1.90 mmol, 85% yield; *cis*-**47**:*trans*-**47** = ca. 55:45). For a mixture of *cis*-**47** and *trans*-**47**: IR (neat) 2930, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75–0.86 (m, 1H), 1.00–1.21 (m, 2H), 1.21–1.36 (m, 5H), 1.46–1.62 (m, 6H), 1.65–1.78 (m, 7H), 1.79–1.90 (m, 4H), 1.97–2.00 (m, 1H), 2.04–2.11 (m, 1H), 2.31 (m, 1H), 2.39 (m, 1H), 2.50–2.57 (m, 2H), 2.59–2.65 (m, 2H), 2.66–2.74 (m, 1H), 7.08–7.12 (m, 4H), 7.14–7.20 (m, 2H), 7.21–7.26 (m, 4H), 7.27–7.33 (m, 2H), 7.33–7.42 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.13, 24.19, 24.3, 24.6, 25.7, 25.93, 25.95, 27.1, 28.7, 29.2, 29.4, 31.8, 32.1, 35.93, 35.98, 38.2, 60.9, 61.2, 85.7, 87.7, 125.9, 126.1, 126.2, 127.8, 128.2, 128.3, 128.4, 128.52, 128.55, 128.58, 128.7, 135.4, 140.0, 141.7, 142.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}NO$ $[M + H]^+$ 322.2171, found 322.2173.

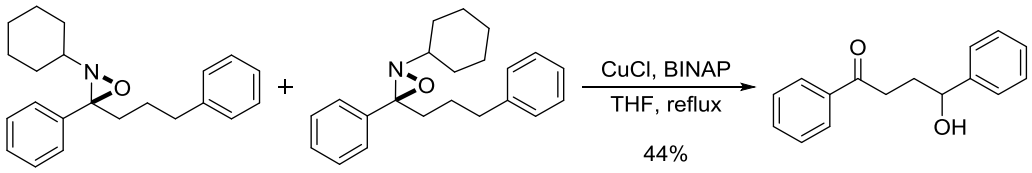
Major diastereomer *cis*-**47**: R_f = 0.43 (5% EtOAc/hexanes, run twice); ^1H NMR (400 MHz, $CDCl_3$; diagnostic peaks in the mixture) δ 2.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; diagnostic peaks in the mixture) δ 38.2, 60.9, 87.7.

Minor diastereomer *trans*-**47**: R_f = 0.40 (5% EtOAc/hexanes, run twice); ^1H NMR (400 MHz, $CDCl_3$; diagnostic peaks in the mixture) δ 2.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; diagnostic peaks in the mixture) δ 29.4, 61.2, 85.7.



47 (cis:trans = 55:45) **48**

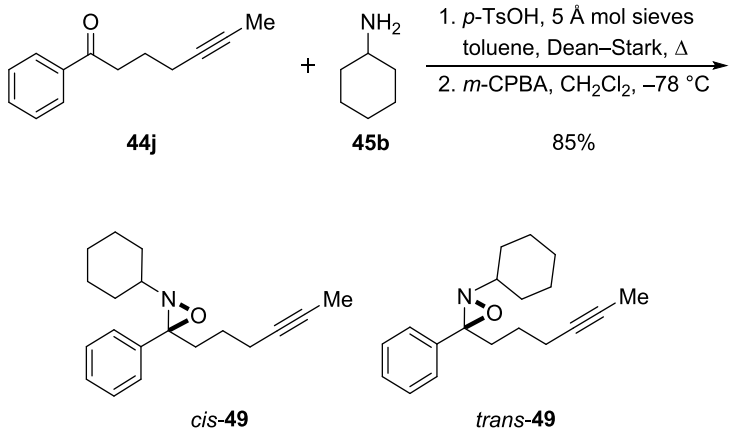
4-Hydroxy-1,4-diphenylbutan-1-one (48; Scheme 47).[202] Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (33.7 mg, 0.0233 mmol, 0.050 equiv) in THF (10 mL) was reacted with a solution of oxaziridine diastereomers **47** (150 mg, 0.467 mmol, 1.0 equiv; cis:trans = ca. 55:45) in THF (5 mL). The reaction mixture was refluxed for 3 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 99.3:0.5:0.2) afforded 57.0 mg (0.237 mmol, 51% yield) of the benzylic alcohol **48** as a white solid. Benzylic alcohol **48**: R_f = 0.15 (15% EtOAc/hexanes); mp 94–96 °C; IR (neat) 3420, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.14–2.27 (m, 2H), 2.49 (d, J = 3.6 Hz, 1H), 3.10 (t, J = 6.9 Hz, 2H), 4.83 (m, 1H), 7.26–7.29 (m, 1H), 7.32–7.39 (m, 4H), 7.42–7.46 (m, 2H), 7.53–7.56 (m, 1H), 7.92–7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.3, 34.9, 73.8, 125.9, 127.7, 128.3, 128.71, 128.76, 133.2, 137.1, 144.6, 200.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1229, found 241.1220. Ketone **44i** was also obtained in 21% yield (22.0 mg, 0.0982 mmol).



47 (cis:trans = 55:45) **48**

Following the general procedure **J**, CuCl (1.54 mg, 0.0155 mmol, 0.050 equiv) and *rac*-BINAP (9.69 mg, 0.0155 mmol, 0.050 equiv) in THF (9 mL) was reacted with a solution of oxaziridine diastereomers **47** (100 mg, 0.311 mmol, 1.0 equiv; cis:trans = ca. 55:45) in THF (3 mL). The reaction mixture was refluxed for 3 h. Purification by

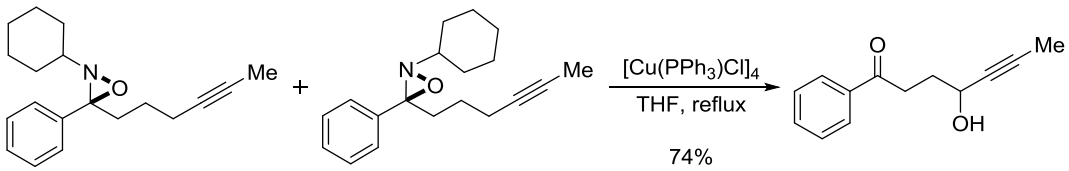
chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.8:1.0:0.2) afforded 33.0 mg (0.137 mmol, 44% yield) of **48** as a creamish-yellow solid and 11.0 mg (0.0491 mmol, 16% yield) of **44i**.



(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(hex-4′-yn-1′-yl)-3-phenyl-1,2-oxaziridine (*cis*-49) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-(hex-4′-yn-1′-yl)-3-phenyl-1,2-oxaziridine (*trans*-49). Following the general procedure **G**, 1-phenylhept-5-yn-1-one **44j**[203] (0.500 g, 2.68 mmol, 1.0 equiv), cyclohexylamine **45b** (0.461 mL, 4.03 mmol, 1.5 equiv), PTSA (25.5 mg, 0.134 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (30 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.556 g, 3.22 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.6–0.8% EtOAc/hexanes) afforded a mixture of oxaziridine diastereomers *cis*-**49** and *trans*-**49** as a colorless oil (0.640 g, 2.27 mmol, 85% yield; *cis*-**49**:*trans*-**49** = ca. 54:46 by ^{1}H NMR). An analytical sample of the major diastereomer *cis*-**49** accompanied with 8% of the minor diastereomer *trans*-**49** was obtained for characterization during this purification. Major diastereomer *cis*-**49**: R_f = 0.59 (5% EtOAc/hexanes, run thrice); IR (neat) 2931, 1447 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72–0.83 (m, 1H), 0.96–1.17 (m, 2H), 1.18–1.27 (m, 1H), 1.29–1.40 (m, 2H), 1.42–1.49 (m, 2H), 1.50–1.58 (m, 2H), 1.66–1.75 (m, 2H), 1.71 (t, *J* =

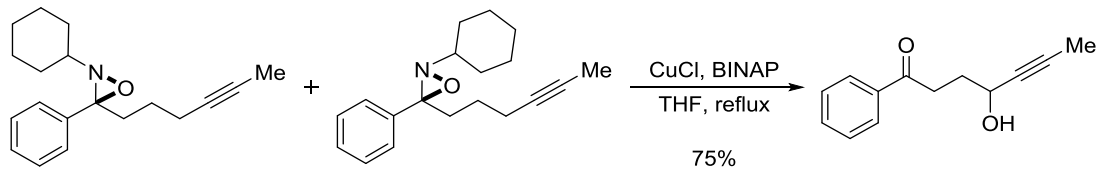
2.5 Hz, 3H), 1.80–1.88 (m, 2H), 2.07 (m, 2H), 2.41 (m, 1H), 7.34–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 18.9, 23.5, 24.0, 24.1, 25.8, 28.6, 31.7, 37.7, 60.9, 75.9, 78.7, 87.4, 127.8, 128.2, 128.7, 135.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}NO$ $[M + H]^+$ 284.2014, found 284.2032.

Minor diastereomer *trans*-**49**: R_f = 0.47 (5% EtOAc/hexanes, run thrice); ^{1}H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 2.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; diagnostic peaks only) δ 29.3, 61.2, 76.3, 78.3, 85.4.



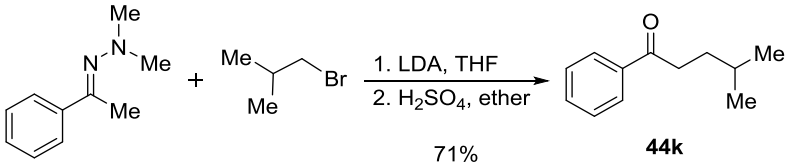
49 (cis:trans = 74:26) **50**

4-Hydroxy-1-phenylhept-5-yn-1-one (50; Scheme 47). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (51.0 mg, 0.0353 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomers **49** (200 mg, 0.706 mmol, 1.0 equiv; cis:trans = ca. 74:26) in THF (8 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 106 mg (0.524 mmol, 74% yield) of the propargylic alcohol **50** as a white crystals. Propargylic alcohol **50**: R_f = 0.26 (25% EtOAc/hexanes); mp 78–80 °C; IR (neat) 3405, 2232, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (d, J = 2.1 Hz, 3H), 2.06–2.19 (m, 2H), 2.46 (d, J = 5.2 Hz, 1H), 3.14–3.28 (m, 2H), 4.48–4.54 (m, 1H), 7.43–7.47 (m, 2H), 7.53–7.58 (m, 1H), 7.97–8.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.7, 32.1, 34.4, 62.0, 80.0, 81.7, 128.3, 128.7, 133.3, 137.0, 200.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2$ $[M + H]^+$ 203.1072, found 203.1051. Ketone **44j** was also obtained in 25% yield (33.0 mg, 0.177 mmol).



49 (cis:trans = 74:26) **50**

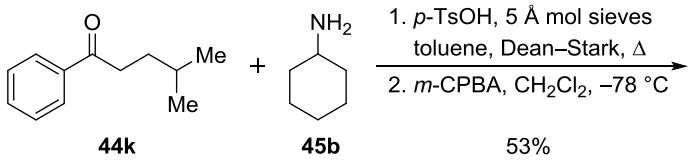
Following the general procedure **J**, CuCl (2.36 mg, 0.0238 mmol, 0.050 equiv) and *rac*-BINAP (14.8 mg, 0.0238 mmol, 0.050 equiv) in THF (9 mL) was reacted with a solution of oxaziridine diastereomers **49** (0.135 g, 0.477 mmol, 1.0 equiv; cis:trans = ca. 74:26) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 72.0 mg (0.356 mmol, 75% yield) of **50** as a pale yellow crystals and 7.00 mg (0.0376 mmol, 8% yield) of **44j**.

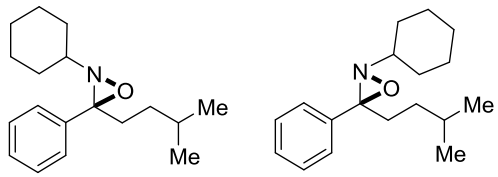


44k

4-Methyl-1-phenylpentan-1-one (44k).[204] To a cooled 1.0 M LDA solution (6.45 mL, 6.45 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added a solution of acetophenone *N*,*N*-dimethylhydrazone (0.950 g, 5.86 mmol, 1.0 equiv) in THF (10 mL) slowly over 15 min and was allowed to stir at 0 °C for 5 h. The reaction mixture was then cooled to –78 °C and a solution of 1-bromo-2-methylpropane (0.764 mL, 7.03 mmol, 1.2 equiv) in THF (5 mL) was added slowly over 10 min. The reaction was warmed to rt and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ether (15 mL), and then treated with an ice-cold solution of dilute H_2SO_4 (10 mL) for 30 min to hydrolyze the hydrazone. The resulting solution was diluted with water and extracted with ether (2 × 15 mL), and the combined organic extracts were

washed with water (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on a silica gel (0.5% EtOAc/hexanes) afforded the ketone **44k** as a colorless oil in 71% yield (0.730 g, 4.14 mmol). R_f = 0.74 (5% EtOAc/hexanes, run twice).

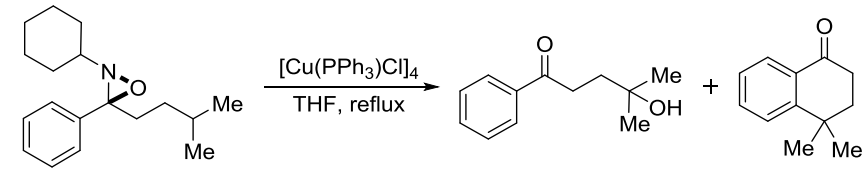




(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-isopentyl-3-phenyl-1,2-oxaziridine (*cis*-51) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-isopentyl-3-phenyl-1,2-oxaziridine (*trans*-51). Following the general procedure **G**, 4-methyl-1-phenylpentan-1-one **44k** (0.500 g, 2.84 mmol, 1.0 equiv), cyclohexylamine **45b** (0.487 mL, 4.26 mmol, 1.5 equiv), PTSA (27.0 mg, 0.142 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (30 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.588 g, 3.40 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL) for 45 min. The reaction was warmed to rt before quenching with saturated $Na_2S_2O_3$. Purification by chromatography on a silica gel (0.5% EtOAc/hexanes) afforded a partial separation of the major diastereomer *cis*-**51** containing ca. 22% of starting ketone **44k**, followed by the mixture of major and the minor *trans*-**51** diastereomers containing 10% of **44k** as a colorless oil (ca. 0.410 g, 1.50 mmol, 53% corrected yield; *cis*-**51**:*trans*-**51** = ca. 87:13 by ^{1}H NMR). Major diastereomer *cis*-**51** containing ca. 22% of **44k** was used for the subsequent reaction. Major diastereomer (*cis*-**51**, contains ca. 22% of **44k**): R_f =

0.75 (5% EtOAc/hexanes, run twice); IR (neat) 2930, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.71–0.79 (m, 1H), 0.79 (d, J = 6.6 Hz, 6H), 0.96–1.01 (m, 1H), 1.01–1.17 (m, 2H), 1.20–1.29 (m, 2H), 1.30–1.35 (m, 1H), 1.42–1.51 (m, 3H), 1.52–1.57 (m, 2H), 1.66–1.75 (m, 3H), 1.84–1.88 (m, 1H), 2.35 (m, 1H), 7.33–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 22.6, 24.11, 24.16, 25.8, 28.1, 28.6, 31.7, 32.7, 36.6, 60.9, 88.0, 127.8, 128.1, 128.6, 135.3; HRMS (ESI) *m/z* calcd for $C_{18}H_{28}NO$ $[M + H]^+$ 274.2171, found 274.2163.

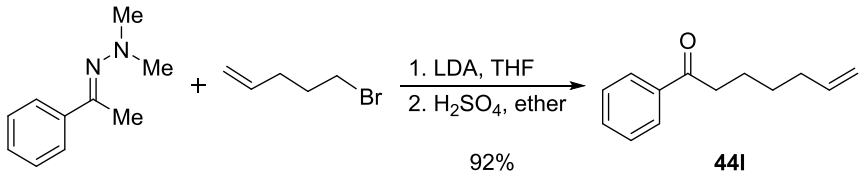
From a mixture of *cis*-**51** and *trans*-**51** containing 10% of **44k**: Minor diastereomer *trans*-**51**: R_f = 0.75 (5% EtOAc/hexanes, run twice); ^1H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 2.26 (m, 1H), 2.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; diagnostic peaks only) δ 61.2, 86.0.



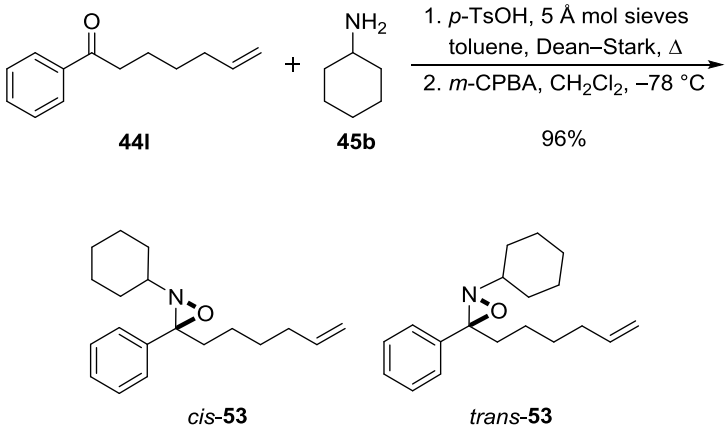
cis-**51** (contains ca. 22% of **44k**) **52a** (16%) **52b** (14%)

4-Hydroxy-4-methyl-1-phenylpentan-1-one (52a)[205] and 4,4-Dimethyl-3,4-dihydronaphthalen-1(2H)-one (52b; Scheme 47).[188] Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (23.7 mg, 0.0164 mmol, 0.050 equiv) in THF (7 mL) was reacted with a solution of oxaziridine *cis*-**51** (90.0 mg, 0.329 mmol, 1.0 equiv; containing ca. 22% of ketone **44k**) in THF (3 mL). The reaction mixture was refluxed for 2 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded ca. 19.0 mg (0.108 mmol, ca. 33% corrected yield) of **44k**, 8.00 mg (0.0459 mmol, 14% yield) of compound **52b** as a pale yellow oil (R_f = 0.71 (25% EtOAc/hexanes)), and 12.0 mg of tertiary alcohol **52a** containing an unidentified impurities. Alcohol **52a**

containing the impurities was further purified by chromatography on a silica gel (CH_2Cl_2:Et_3N, 99.9:0.1% to CH_2Cl_2:acetone:Et_3N, 97.4:2.5:0.1) to afford 10.0 mg (0.0520 mmol, 16% yield) of **52a** as a pale yellow oil (R_f = 0.18 (25% EtOAc/hexanes)).

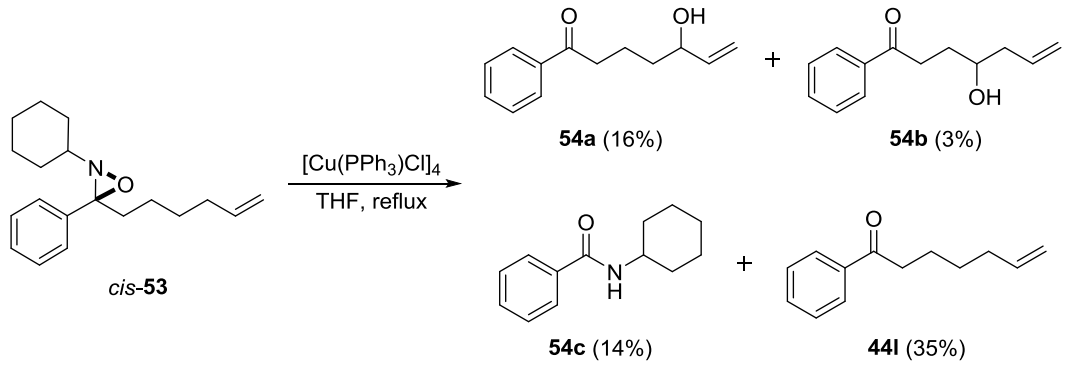


1-Phenylhept-6-en-1-one (44l).[196] To a cooled 1.0 M LDA solution (13.5 mL, 13.5 mmol, 1.1 equiv) in THF at 0 °C under nitrogen atmosphere was added the solution of hydrazone (2.00 g, 12.3 mmol, 1.0 equiv) in THF (15 mL) slowly over 15 min and was allowed to stir at 0 °C for 5 h. The reaction mixture was then cooled to –78 °C and a solution of 5-bromo-1-pentene (1.75 mL, 14.8 mmol, 1.2 equiv) in THF (5 mL) was added slowly over 10 min. The reaction was warmed to rt and stirred for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ether (20 mL), and then treated with an ice-cold solution of dilute H_2SO_4 (15 mL) for 30 min to hydrolyze the hydrazone. The resulting solution was diluted with water and extracted with ether (2 × 20 mL), and the combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on a silica gel (0.7–0.8% EtOAc/hexanes) afforded the ketone **44l** as a colorless oil in 92% yield (2.13 g, 11.3 mmol). R_f = 0.52 (5% EtOAc/hexanes, run twice).



(2*R*,3*S*)-*rel*-2-Cyclohexyl-3-(hex-5′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*cis*-53) and (2*S*,3*S*)-*rel*-2-Cyclohexyl-3-(hex-5′-en-1′-yl)-3-phenyl-1,2-oxaziridine (*trans*-53). Following the general procedure **G**, 1-phenylhept-6-en-1-one **44l** (0.500 g, 2.65 mmol, 1.0 equiv), cyclohexylamine **45b** (0.456 mL, 3.98 mmol, 1.5 equiv), PTSA (25.2 mg, 0.132 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (30 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.550 g, 3.19 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.6–0.7% EtOAc/hexanes) afforded a mixture of oxaziridine diastereomers *cis*-**53** and *trans*-**53** along with the partial separation of major diastereomer *cis*-**53** as colorless oils (0.720 g, 2.54 mmol, 96% yield; *cis*-**53**:*trans*-**53** = ca. 57:43 by ^{1}H NMR). Major diastereomer *cis*-**53**: R_f = 0.52 (5% EtOAc/hexanes, run twice); IR (neat) 1640, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72–0.83 (m, 1H), 0.97–1.16 (m, 2H), 1.16–1.28 (m, 2H), 1.29–1.40 (m, 4H), 1.42–1.51 (m, 2H), 1.52–1.58 (m, 1H), 1.67–1.76 (m, 3H), 1.84–1.88 (m, 1H), 1.93–1.98 (m, 2H), 2.33–2.40 (m, 1H), 4.85–4.95 (m, 2H), 5.71 (m, 1H), 7.34–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 24.1, 24.2, 25.8, 28.6, 29.0, 31.8, 33.7, 38.5, 60.9, 87.8, 114.5, 127.8, 128.2, 128.7, 135.3, 138.9; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}NO$ $[M + H]^+$ 286.2170, found 286.2163.

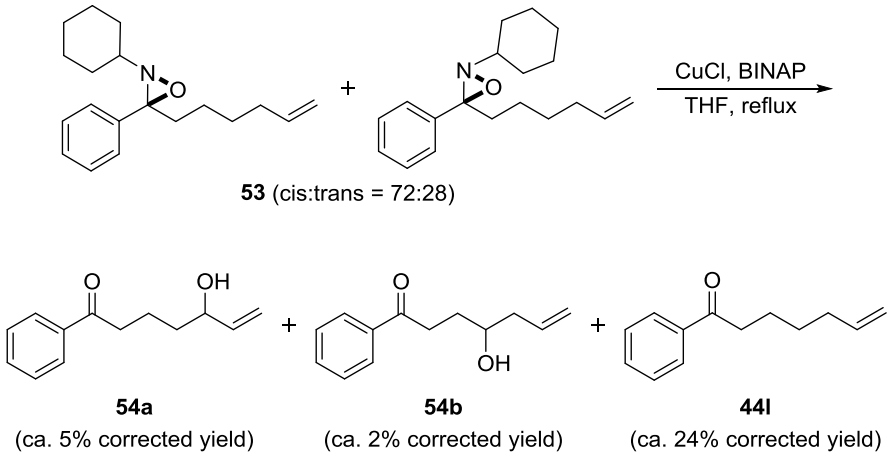
From a mixture of *cis*-**53** and *trans*-**53**: Minor diastereomer *trans*-**53**: R_f = 0.45 (5% EtOAc/hexanes, run twice); ^{1}H NMR (400 MHz, $CDCl_3$; diagnostic peaks only) δ 2.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; diagnostic peaks only) δ 29.6, 61.3, 85.8.



5-Hydroxy-1-phenylhept-6-en-1-one (54a), 4-Hydroxy-1-phenylhept-6-en-1-one (54b),[206] and *N*-Cyclohexylbenzamide (54c; Scheme 48).[207] Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (38.0 mg, 0.0263 mmol, 0.050 equiv) in THF (10 mL) was reacted with a solution of oxaziridine *cis*-**53** (150 mg, 0.526 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.6:1.0:0.4) afforded ca. 35.0 mg (0.186 mmol, ca. 35% yield) of a slightly impure **44l** as a colorless oil, 15.0 mg (0.0738 mmol, 14% yield) of amide **54c** as a white solid (R_f = 0.46 (25% EtOAc/hexanes)), and ca. 21.0 mg (0.102 mmol, ca. 16% yield for **54a** and ca. 3% yield for **54b** by ^{1}H NMR) of a slightly impure mixture of allylic alcohol **54a** and homoallylic alcohol **54b** as a pale yellow oil. Further purification of the mixture of **54a** and **54b** by preparative TLC developing two times with 7% EtOAc/hexanes gave two bands corresponding to **54a** and **54b**, which were scraped from the plate and eluted with 1% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Evaporation of solvents afforded analytical samples of **54a** and **54b** as colorless oils for characterization. Allylic alcohol **54a**: R_f = 0.26 (25%

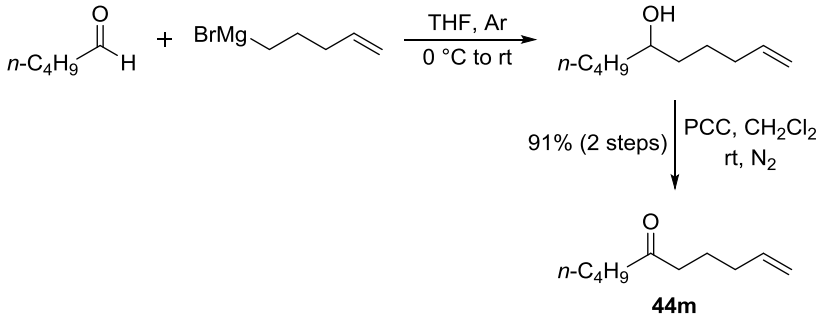
EtOAc/hexanes); IR (neat) 3403, 1679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–1.65 (m, 2H), 1.74 (br s, 1H), 1.80–1.90 (m, 2H), 3.02 (t, J = 7.4 Hz, 2H), 4.15 (q, J = 6.3 Hz, 1H), 5.12 (dt, J = 10.4, 1.3 Hz, 1H), 5.25 (dt, J = 17.2, 1.4 Hz, 1H), 5.88 (m, 1H), 7.44–7.47 (m, 2H), 7.54–7.57 (m, 1H), 7.95–7.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 36.6, 38.4, 73.0, 115.0, 128.2, 128.8, 133.2, 137.1, 141.1, 200.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2$ $[M + H]^+$ 205.1229, found 205.1237.

Homoallylic alcohol **54b** (sample obtained contains some minor impurities): R_f = 0.36 (25% EtOAc/hexanes); IR (neat) 3439, 1683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.80–1.87 (m, 1H), 1.95 (br s, 1H), 1.98–2.04 (m, 1H), 2.20–2.26 (m, 1H), 2.32–2.38 (m, 1H), 3.11–3.22 (m, 2H), 3.74 (m, 1H), 5.14–5.18 (m, 2H), 5.80–5.88 (m, 1H), 7.44–7.48 (m, 2H), 7.54–7.58 (m, 1H), 7.97–7.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.9, 35.1, 42.5, 70.3, 118.6, 128.3, 128.8, 133.3, 134.7, 137.0, 200.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2$ $[M + H]^+$ 205.1229, found 205.1227.



Following the general procedure **J**, CuCl (4.33 mg, 0.0438 mmol, 0.050 equiv) and *rac*-BINAP (27.3 mg, 0.0438 mmol, 0.050 equiv) in THF (15 mL) was reacted with a solution of oxaziridine diastereomers **53** (0.250 g, 0.877 mmol, 1.0 equiv; cis:trans = ca. 72:28) in THF (5 mL). The reaction mixture was refluxed for 1 h. Purification by

chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.6:1.0:0.4) afforded a mixture of unreacted oxaziridine diastereomers **53** and ketone **44l** (for oxaziridine diastereomers **53**: 26.0 mg recovered, ca. 10% corrected yield, *Z*:*E* = ca. 65:35 by ^{1}H NMR; for ketone **44l**: 39.0 mg, ca. 24% corrected yield by ^{1}H NMR), and an impure mixture of allylic alcohol **54a** and homoallylic alcohol **54b**. Further purification of the impure mixture of **54a** and **54b** by preparative TLC developing two times with 20% EtOAc/hexanes afforded two bands, one containing a mixture of **54a** and **54b** and other containing a mixture of **54a** and an unidentified byproduct, which were scraped from the plate and eluted with a solvent system of CH_2Cl_2:acetone:MeOH, 96:2:2 separately through a short bed of silica gel. Evaporation of solvents afforded a mixture of **54a** and **54b** and an impure sample of **54a** as a pale yellow oil (for **54a**: ca. 8.5 mg. 0.042 mmol, ca. 5% corrected yield by ^{1}H NMR; for **54b**: ca. 3.0 mg. 0.015 mmol, ca. 2% corrected yield by ^{1}H NMR).

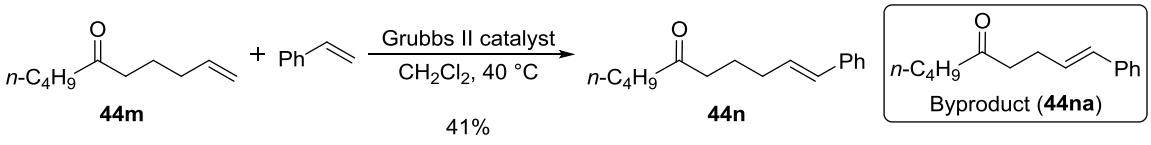


44m

Dec-9-en-5-one (44m).[208] Following the general procedure **H**, a solution of 5-bromo-1-pentene (2.47 mL, 20.8 mmol, 1.2 equiv) in THF (10 mL) was added drop wise to a stirring suspension of magnesium turnings (0.508 g, 20.8 mmol, 1.2 equiv) and two small crystals of iodine in THF (10 mL). After refluxing gently for 20 min, the reaction mixture was cooled to 0 °C and treated with a solution of valeraldehyde (1.50 g, 17.4 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was then stirred at rt for 1 h. The aqueous

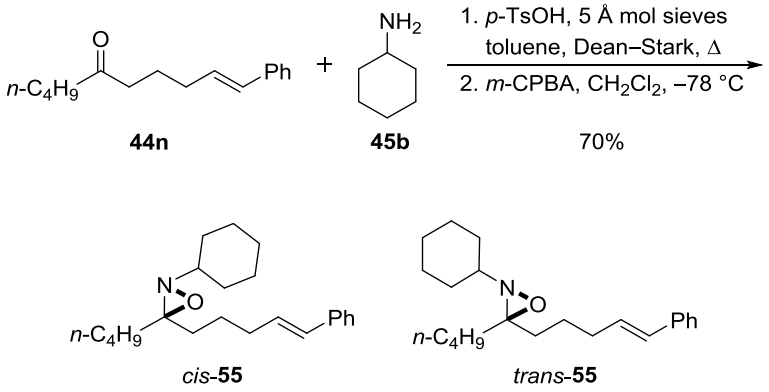
work-up afforded the crude alcohol (3.05 g) as colorless oil, which was used for the next oxidation step without further purification.

To a stirring solution of crude alcohol (3.05 g) in CH_2Cl_2 (50 mL) was added Celite (6.0 g) followed by PCC (5.63 g, 26.1 mmol, 1.5 equiv), and the reaction mixture was stirred at rt for 2 h. The reaction mixture was filtered through Celite, rinsing with several portions of ether, and the filtrate was concentrated under reduced pressure. Purification by chromatography on a silica gel (0.5–1% EtOAc/hexanes) afforded 2.44 g (15.8 mmol, 91% yield over 2 steps) of the corresponding ketone **44m** as a yellow oil. R_f = 0.57 (10% EtOAc/hexanes).



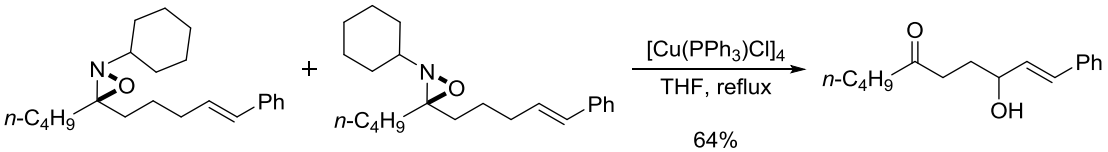
(*E*)-10-Phenyldec-9-en-5-one (44n). To a solution of Grubbs II catalyst (0.264 g, 0.311 mmol, 0.04 equiv) in CH_2Cl_2 (28 mL) at rt under argon atmosphere was added a solution containing a mixture of dec-9-en-5-one **44m** (1.20 g, 7.79 mmol, 1.0 equiv) and styrene (2.67 mL, 23.3 mmol, 3.0 equiv) in CH_2Cl_2 (7 mL), and the reaction mixture was stirred at 40 °C for 4.5 h. The reaction mixture was concentrated under reduced pressure. Initial purification of crude residue by chromatography on a silica gel (0.4% EtOAc/hexanes) afforded the mixture of desired product **44n** and byproduct (*E*)-1-phenylnon-1-en-5-one **44na** as a colorless oil (0.728 g, 3.16 mmol, 41% corrected yield for **44n** by ^{1}H NMR). Subsequent purification of the mixture of **44n** and **44na** (dissolved in DMSO) was carried out using the preparative HPLC. The product was purified in multiple batches. All the fractions containing the product were evaporated to dryness and the residue was diluted with ether (100 mL). The organic layer was washed with water (35 mL), dried

over Na_2SO_4, and concentrated. Pale yellow oil obtained was passed through a short bed of a silica gel using 100% CH_2Cl_2 to afford 480 mg of **44n** as a colorless oil. Ketone **44n**: R_f = 0.30 (5% EtOAc/hexanes); IR (neat) 2931, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.26–1.35 (m, 2H), 1.52–1.59 (m, 2H), 1.77 (m, 2H), 2.22 (dq, J = 7.5, 1.2 Hz, 2H), 2.38 (t, J = 7.4 Hz, 2H), 2.44 (t, J = 7.3 Hz, 2H), 6.14–6.21 (m, 1H), 6.39 (d, J = 15.8 Hz, 1H), 7.18–7.22 (m, 1H), 7.27–7.31 (m, 2H), 7.33–7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 23.3, 26.0, 32.4, 41.9, 42.6, 126.0, 127.0, 128.5, 129.9, 130.6, 137.6, 211.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}O$ $[M + H]^+$ 231.1749, found 231.1750.



(2*S*,3*R*,*E*)-*rel*-3-Butyl-2-cyclohexyl-3-(5′-phenylpent-4′-en-1′-yl)-1,2-oxaziridine (*cis*-55) and (2*R*,3*R*,*E*)-*rel*-3-Butyl-2-cyclohexyl-3-(5′-phenylpent-4′-en-1′-yl)-1,2-oxaziridine (*trans*-55). Following the general procedure **G**, (*E*)-10-phenyldec-9-en-5-one **44n** (0.450 g, 1.95 mmol, 1.0 equiv), cyclohexylamine **45b** (0.335 mL, 2.93 mmol, 1.5 equiv), PTSA (18.6 mg, 0.0978 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (35 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.405 g, 2.34 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.4–0.6% EtOAc/hexanes) afforded a mixture of oxaziridine diastereomers *cis*-**55** and *trans*-**55** as a pale yellow oil (0.449 g, 1.37 mmol, 70% yield; *cis*-**55**:*trans*-**55** = ca. 56:44 by ^1H NMR). For the mixture of *cis*-**55** and *trans*-**55**: R_f = 0.51 (5% EtOAc/hexanes,

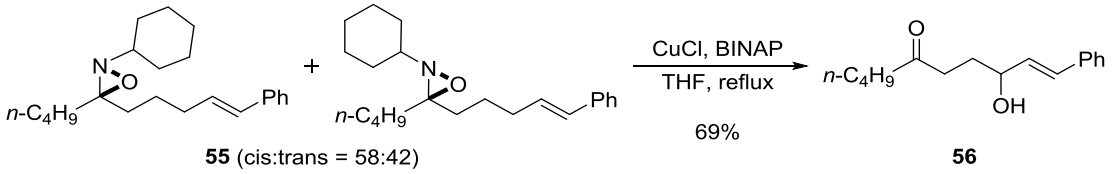
run thrice); IR (neat) 2929, 2856, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89–0.96 (m, 7H), 1.21–1.28 (m, 6H), 1.31–1.37 (m, 6H), 1.39–1.45 (m, 3H), 1.46–1.57 (m, 8H), 1.63–1.66 (m, 3H), 1.68–1.74 (m, 3H), 1.74–1.82 (m, 4H), 1.83–1.87 (m, 2H), 1.89–1.95 (m, 4H), 2.20–2.32 (m, 4H), 2.33–2.41 (m, 2H), 6.19 (m, 1H), 6.23 (m, 1H), 6.39 (d, J = 16.2 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 7.17–7.23 (m, 2H), 7.27–7.31 (m, 4H), 7.32–7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.13, 14.19, 23.0, 23.2, 24.35, 24.37, 24.4, 24.5, 24.6, 25.2, 25.9, 26.8, 27.5, 27.6, 27.9, 29.2, 29.3, 32.14, 32.16, 33.2, 36.3, 36.6, 60.44, 60.48, 85.90, 85.97, 126.1, 127.0, 127.1, 128.62, 128.67, 129.9, 130.42, 130.45, 130.8, 137.7, 137.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{34}NO$ $[M + H]^+$ 328.2640, found 328.2635.



55 (cis:trans = 58:42) **56**

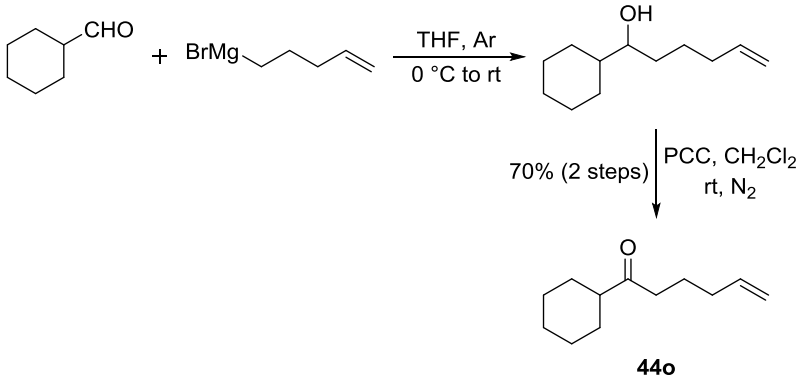
(*E*)-8-Hydroxy-10-phenyldec-9-en-5-one (56; Scheme 49). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (26.5 mg, 0.0183 mmol, 0.050 equiv) in THF (9 mL) was reacted with a solution of oxaziridine diastereomers **55** (120 mg, 0.366 mmol, 1.0 equiv; cis:trans = 58:42) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel twice (0–1% acetone/CH_2Cl_2) afforded the allylic alcohol **56** as a pale yellow oil containing ca. 10% of two unidentified byproducts (58.0 mg, 0.235 mmol, 64% corrected yield by ^1H NMR). Allylic alcohol **56**: R_f = 0.30 (25% EtOAc/hexanes); IR (neat) 3405, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.24–1.33 (m, 2H), 1.50–1.57 (m, 2H), 1.83–1.97 (m, 2H), 2.38–2.43 (m, 3H), 2.57 (t, J = 6.9 Hz, 2H), 4.31 (m, 1H), 6.18 (dd, J = 15.9, 6.3 Hz, 1H), 6.57 (d, J = 15.9 Hz, 1H), 7.21–7.25 (m, 1H), 7.28–7.32 (m, 2H), 7.35–7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 26.1, 30.9, 38.6, 42.8, 72.1, 126.6, 127.8, 128.7, 130.4, 132.0, 136.7,

212.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}O_2$ $[M + H]^+$ 247.1698, found 247.1699. Ketone **44n** was observed in trace amounts by ^1H NMR in a mixture of unidentified impurities.



55 (cis:trans = 58:42) **56**

Following the general procedure **J**, CuCl (1.81 mg, 0.0183 mmol, 0.050 equiv) and *rac*-BINAP (11.3 mg, 0.0183 mmol, 0.050 equiv) in THF (9 mL) was reacted with a solution of oxaziridine diastereomers **55** (120 mg, 0.366 mmol, 1.0 equiv; cis:trans = 58:42) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (0–1% acetone/CH_2Cl_2) afforded **56** as a yellow oil containing ca. 11% of two unidentified byproducts (62.0 mg, 0.252 mmol, 69% corrected yield by ^1H NMR). Ketone **44n** was observed in trace amounts by ^1H NMR in a mixture of unidentified impurities.

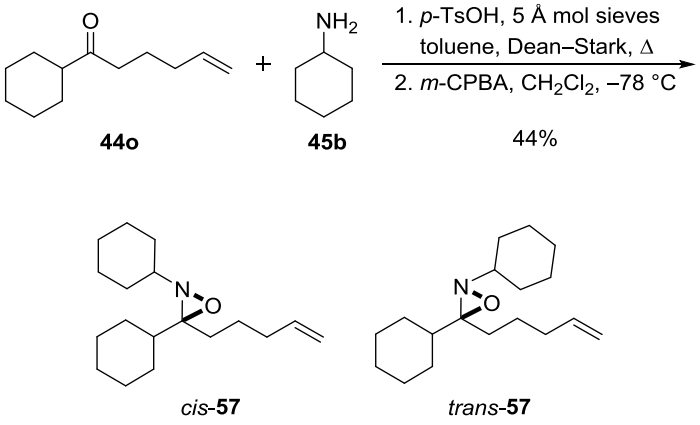


44o

1-Cyclohexylhex-5-en-1-one (44o).[209] Following the general procedure **H**, a solution of 5-bromo-1-pentene (1.90 mL, 16.0 mmol, 1.2 equiv) in THF (10 mL) was added drop wise to a stirring suspension of magnesium turnings (0.390 g, 16.0 mmol, 1.2 equiv) and two small crystals of iodine in THF (10 mL). After refluxing gently for 20 min, the reaction

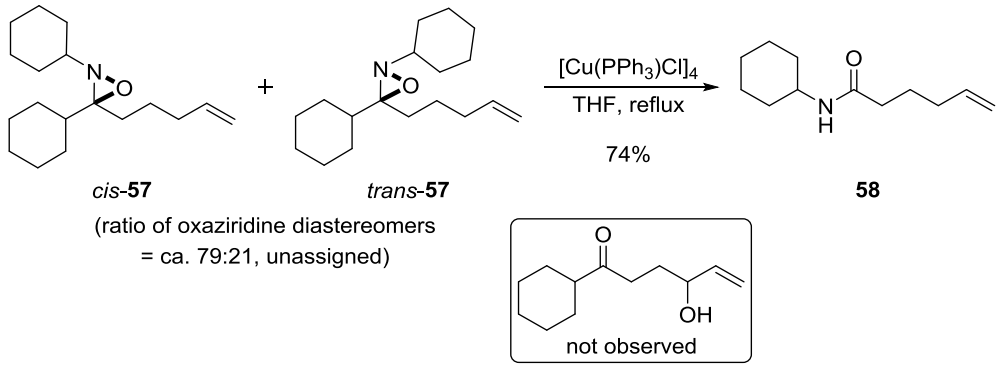
mixture was cooled to 0 °C and treated with a solution of cyclohexane carboxaldehyde (1.50 g, 13.3 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was then stirred at rt for 1 h. The aqueous work-up afforded the crude alcohol (2.31 g) as colorless oil, which was used for the next oxidation step without further purification.

To a stirring solution of crude alcohol (2.31 g) in CH_2Cl_2 (70 mL) was added Celite (6.0 g) followed by PCC (5.76 g, 26.7 mmol, 2.0 equiv), and the reaction mixture was stirred at rt for 75 min. The reaction mixture was filtered through Celite, rinsing with several portions of CH_2Cl_2, and the filtrate was concentrated under reduced pressure. Purification by chromatography on a silica gel (1% EtOAc/hexanes) afforded 1.68 g (9.33 mmol, 70% yield over 2 steps) of the corresponding ketone **44o** as a colorless oil. R_f = 0.62 (10% EtOAc/hexanes).



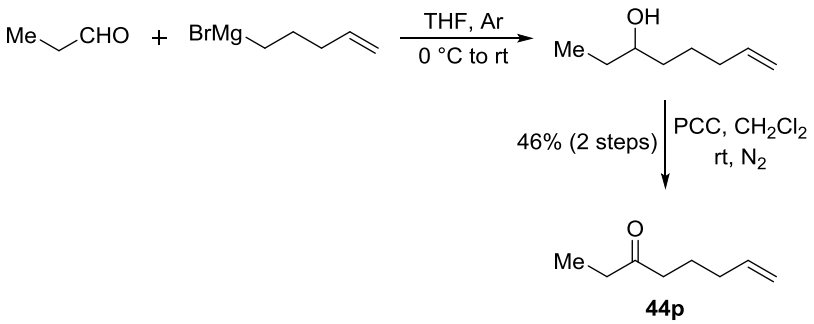
(2*R*,3*S*)-*rel*-2,3-Dicyclohexyl-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*cis*-57) and (2*S*,3*S*)-*rel*-2,3-Dicyclohexyl-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*trans*-57). Following the general procedure **G**, 1-cyclohexylhex-5-en-1-one **44o** (0.500 g, 2.77 mmol, 1.0 equiv), cyclohexylamine **45b** (0.476 mL, 4.16 mmol, 1.5 equiv), PTSA (26.3 mg, 0.138 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (30 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.573 g, 3.32 mmol, 1.2 equiv) in CH_2Cl_2

(20 mL) for 45 min. Purification by chromatography on a silica gel (0.5% EtOAc/hexanes) afforded a mixture of oxaziridine diastereomers *cis*-**57** and *trans*-**57** and ketone **44o** as a colorless oil. The ketone **44o** was removed from the mixture by vacuum distillation at ca. 65–67 °C and the mixture of two diastereomers *cis*-**57** and *trans*-**57** along with some decomposition products were left in the flask as an orange-colored residue. This residue was further purified by chromatography on a silica gel (2% ether/hexanes) to afford a mixture of *cis*-**57** and *trans*-**57** as a colorless oil (0.340 g, 1.22 mmol, 44% yield; ratio of two oxaziridine diastereomers = ca. 79:21 by ^{1}H NMR, unassigned). For the major diastereomer in a mixture of *cis*-**57** and *trans*-**57**: R_f = 0.68 (5% EtOAc/hexanes, run twice); IR (neat) 2927, 2853, 1450, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00–1.32 (m, 8H), 1.39–1.50 (m, 3H), 1.51–1.64 (m, 6H), 1.69–1.82 (m, 7H), 1.85–1.90 (m, 1H), 2.05–2.10 (m, 2H), 2.17–2.24 (m, 1H), 4.95–5.05 (m, 2H), 5.73–5.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.5, 25.2, 25.94, 25.99, 26.3, 26.4, 26.8, 28.1, 29.2, 32.0, 34.1, 44.7, 60.3, 87.4, 115.2, 138.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{32}NO$ $[M + H]^+$ 278.2484, found 278.2475.



***N*-Cyclohexylhex-5-enamide (58; Scheme 49).** Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (13.0 mg, 0.00902 mmol, 0.050 equiv) in THF (5 mL) was reacted with a solution of oxaziridine diastereomers *cis*-**57** and *trans*-**57** (50.0 mg, 0.180 mmol, 1.0 equiv;

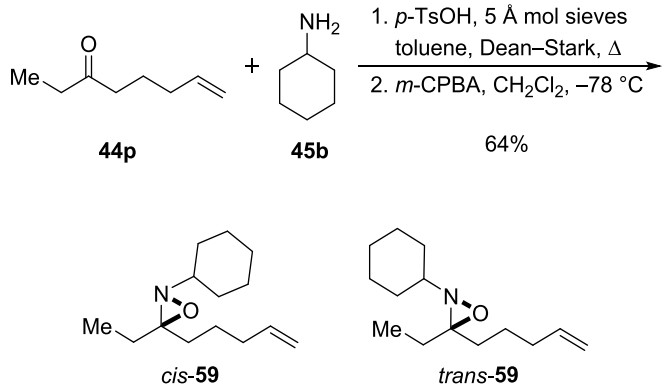
ratio of two diastereomers = ca. 79:21, unassigned) in THF (2 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.7:1.0:0.3) afforded 26.0 mg (0.133 mmol, 74% yield) of the amide **58** as a white solid instead of the allylic alcohol. Amide **58**: R_f = 0.27 (25% EtOAc/hexanes); mp 57–59 °C; IR (neat) 3284, 1638, 1546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04–1.19 (m, 3H), 1.30–1.41 (m, 2H), 1.58–1.64 (m, 1H), 1.66–1.76 (m, 4H), 1.88–1.92 (m, 2H), 2.05–2.14 (m, 4H), 3.76 (m, 1H), 4.95–5.04 (m, 2H), 5.28 (br s, 1H), 5.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.06, 25.08, 25.7, 33.3, 33.4, 36.3, 48.2, 115.4, 138.2, 171.9; HRMS (ESI) *m/z* calcd for $C_{12}H_{22}NO$ $[M + H]^+$ 196.1701, found 196.1702. Ketone **44o** was not recovered.



44p

Oct-7-en-3-one (44p).[210] Following the general procedure **H**, a solution of 5-bromo-1-pentene (3.67 mL, 31.0 mmol, 1.2 equiv) in THF (10 mL) was added drop wise to a stirring suspension of magnesium turnings (0.753 g, 31.0 mmol, 1.2 equiv) and two small crystals of iodine in THF (10 mL). After refluxing gently for 20 min, the reaction mixture was cooled to 0 °C and treated with a solution of propionaldehyde (1.50 g, 25.8 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was then stirred at rt for 1 h. The aqueous work-up afforded the crude alcohol (3.10 g) as a pale yellow oil, which was used for the next oxidation step without further purification.

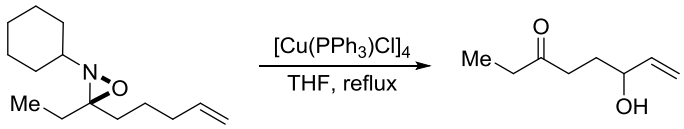
To a stirring solution of crude alcohol (3.10 g) in CH_2Cl_2 (50 mL) was added Celite (5.0 g) followed by PCC (8.35 g, 38.7 mmol, 1.5 equiv), and the reaction mixture was stirred at rt for 1.5 h. The reaction mixture was filtered through Celite, rinsing with several portions of ether, and the filtrate was concentrated under reduced pressure. Purification by chromatography on a silica gel (3% ether/hexanes) afforded 1.50 g (11.9 mmol, 46% yield over 2 steps) of the corresponding ketone **44p** as a yellow oil (significant amount of **44p** was lost during concentration and drying due to its volatile nature). Ketone **44p**: R_f = 0.47 (10% EtOAc/hexanes); IR (neat) 1713, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 1.62 (p, J = 7.4 Hz, 2H), 2.00 (q, J = 7.1 Hz, 2H), 2.33–2.38 (m, 4H), 4.89–4.97 (m, 2H), 5.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 23.0, 33.2, 36.0, 41.5, 115.2, 138.1, 211.5; HRMS (ESI) *m/z* calcd for $C_8H_{15}O$ $[M + H]^+$ 127.1123, found 127.1149.



(2*S*,3*R*)-*rel*-2-Cyclohexyl-3-ethyl-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*cis*-59) and (2*R*,3*R*)-*rel*-2-Cyclohexyl-3-ethyl-3-(pent-4′-en-1′-yl)-1,2-oxaziridine (*trans*-59). Following the general procedure **G**, oct-7-en-3-one **44p** (0.500 g, 3.97 mmol, 1.0 equiv), cyclohexylamine **45b** (0.680 mL, 5.95 mmol, 1.5 equiv), PTSA (37.7 mg, 0.198 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (35 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.820 g, 4.76 mmol, 1.2 equiv) in CH_2Cl_2

(25 mL). Purification by chromatography on a silica gel (0.5–1.0% EtOAc/hexanes) afforded partial separations of oxaziridine diastereomers *trans*-**59** and *cis*-**59** as colorless oils and the remaining was obtained as a mixture of *trans*-**59** and *cis*-**59** (0.570 g, 2.56 mmol, 64% yield; *cis*-**59**:*trans*-**59** = ca. 46:54 by ^{1}H NMR). Minor diastereomer *cis*-**59** (contains ca. 5% of *trans*-**59**): R_f = 0.58 (5% EtOAc/hexanes); IR (neat) 2931, 1451, 1389 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.6 Hz, 3H), 1.16–1.39 (complex, 4H), 1.42–1.52 (complex, 2H), 1.56–1.67 (complex, 4H), 1.70–1.92 (complex, 6H), 2.04–2.19 (m, 2H), 2.32 (tt, J = 10.4, 3.9 Hz, 1H), 4.97–5.06 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 24.4, 24.6, 24.7, 25.9, 27.0, 29.3, 29.8, 32.2, 34.0, 60.4, 86.6, 115.4, 138.1; HRMS (ESI) *m/z* calcd for $C_{14}H_{26}NO$ $[M + H]^+$ 224.2014, found 224.1996.

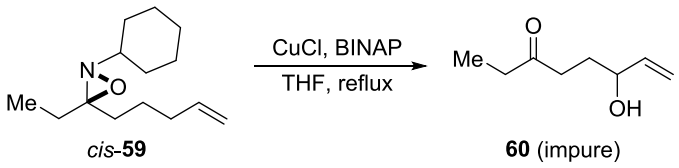
Major diastereomer *trans*-**59**: R_f = 0.68 (5% EtOAc/hexanes); IR (neat) 2931, 1451, 1384 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.6 Hz, 3H), 1.18–1.28 (complex, 2H), 1.28–1.53 (complex, 7H), 1.61–1.93 (complex, 7H), 2.01–2.11 (m, 2H), 2.35 (tt, J = 10.5, 3.9 Hz, 1H), 4.93–5.02 (m, 2H), 5.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 21.2, 23.9, 24.4, 24.6, 26.0, 29.4, 32.2, 34.0, 35.6, 60.5, 86.6, 115.0, 138.5; HRMS (ESI) *m/z* calcd for $C_{14}H_{26}NO$ $[M + H]^+$ 224.2014, found 224.2013.



trans-**59** **60** (impure)

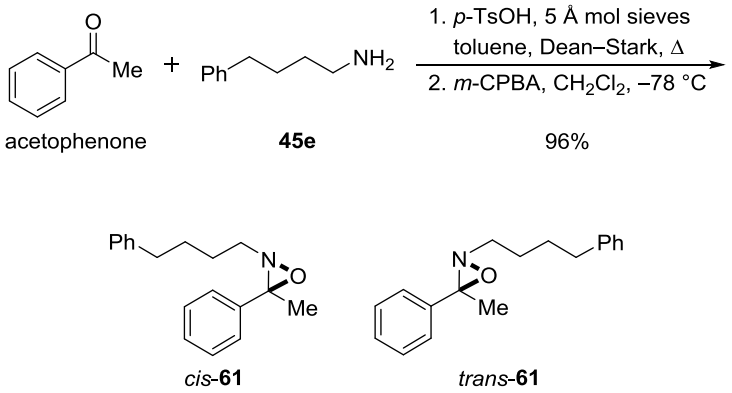
6-Hydroxyoct-7-en-3-one (60; Scheme 50). Following the general procedure **I**, $[Cu(PPh_3)Cl]_4$ (32.4 mg, 0.0224 mmol, 0.050 equiv) in THF (8 mL) was reacted with a solution of oxaziridine diastereomer *trans*-**59** (100 mg, 0.448 mmol, 1.0 equiv) in THF (2 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.8:1.0:0.2) afforded a small amount (ca. 25

mg) of supposedly impure product **60** as a pale yellow volatile oil. ^{1}H NMR showed characteristic peaks of product. However, the volatile nature of the product and the presence of ca. 25–35% of inseparable unidentified impurities/byproducts made further purification of the impure product unfeasible. Thus, analytical sample of pure product **60** was not obtained for complete spectroscopic analysis. Impure allylic alcohol **60** (contains ca. 25–35% of unidentified impurities/byproducts; most of the product peaks were overlapping with byproducts peaks): R_f = 0.23 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 1.70–1.81 (m, 2H, complete overlap with byproducts peaks), 2.17 (br d, J = 3.9 Hz, 1H), 2.44 (q, J = 7.3 Hz, 2H), 2.54 (t, J = 7.0 Hz, 2H), 4.13 (m, 1H), 5.10 (dt, J = 10.4, 1.4 Hz, 1H), 5.23 (dt, J = 17.2, 1.4 Hz, 1H), 5.83 (m, 1H).



cis-**59** **60** (impure)

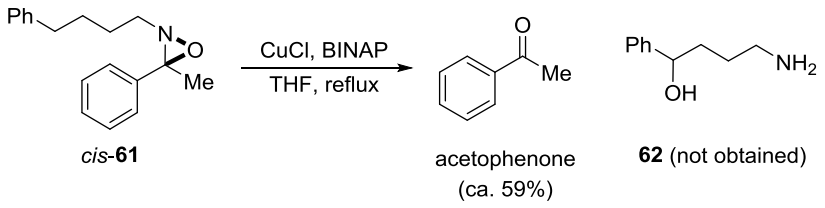
Following the general procedure **J**, CuCl (2.88 mg, 0.0291 mmol, 0.050 equiv) and *rac*-BINAP (18.1 mg, 0.0291 mmol, 0.050 equiv) in THF (8 mL) was reacted with a solution of oxaziridine diastereomer *cis*-**59** (130 mg, 0.583 mmol, 1.0 equiv) in THF (2 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.8:1.0:0.2) afforded a small amount of supposedly impure product **60** as a pale yellow volatile oil. ^{1}H NMR showed characteristic peaks of product, which matched with that obtained from the reaction with $[Cu(PPh_3)Cl]_4$ as mentioned above. Subsequent attempt to purify the impure product by preparative TLC was unsuccessful. Again, pure allylic alcohol **60** was not obtained for complete spectroscopic analysis.



(2*R*,3*S*)-*rel*-3-Methyl-3-phenyl-2-(4′-phenylbutyl)-1,2-oxaziridine (*cis*-61) and (2*S*,3*S*)-*rel*-3-Methyl-3-phenyl-2-(4′-phenylbutyl)-1,2-oxaziridine (*trans*-61). Following the general procedure **G**, acetophenone (0.500 g, 4.16 mmol, 1.0 equiv), 4-phenylbutylamine **45e** (0.986 mL, 6.24 mmol, 1.5 equiv), PTSA (39.6 mg, 0.208 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (35 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.861 g, 4.99 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL). Purification by chromatography on a silica gel (0.6–0.7% EtOAc/hexanes) afforded oxaziridine diastereomer *trans*-**61** with an inseparable impurity, followed by impure *cis*-**61** containing small amounts of *trans*-**61** and acetophenone as colorless oils (ca. 1.07 g, 4.01 mmol, 96% corrected yield; *cis*-**61**:*trans*-**61** = ca. 67:33 by ^{1}H NMR). Subsequent purification of a small amount of impure *trans*-**61** twice by preparative TLC developing two and seven times with 3% EtOAc/hexanes afforded a band corresponding to *trans*-**61**, which was scraped from the plate and eluted with 50% ether/hexanes through a short bed of silica gel. Evaporation of solvents afforded a slightly impure analytical sample of *trans*-**61** as a colorless oil for characterization. Similar purification of a small amount of impure *cis*-**61** containing small amounts of *trans*-**61** and acetophenone by preparative TLC developing four times with 3% EtOAc/hexanes afforded a band corresponding to *cis*-**61**, which was scraped from the plate and eluted with 50% ether/hexanes through a short bed of silica gel. Evaporation of solvents afforded a slightly impure analytical sample of *cis*-**61** as

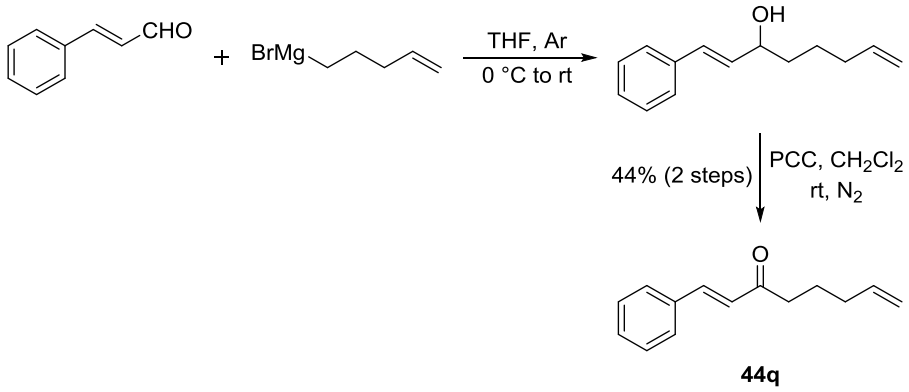
a colorless oil for characterization. Major diastereomer *cis*-**61**: R_f = 0.45 (5% EtOAc/hexanes, run twice); IR (neat) 2931, 1450, 1338 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56–1.67 (complex, 4H), 1.78 (s, 3H), 2.16–2.23 (m, 1H), 2.41–2.47 (m, 1H), 2.54–2.57 (m, 2H), 7.12–7.18 (m, 3H), 7.24–7.27 (m, 2H), 7.39 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 28.0, 29.2, 35.8, 55.5, 84.8, 125.9, 127.3, 128.40, 128.42, 128.6, 128.9, 136.4, 142.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1701, found 268.1693.

Minor diastereomer *trans*-**61**: R_f = 0.55 (5% EtOAc/hexanes, run twice); IR (neat) 2937, 1452, 1289 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76–1.84 (complex, 4H), 1.92 (s, 3H), 2.67–2.70 (m, 2H), 2.85–2.91 (m, 1H), 3.00–3.07 (m, 1H), 7.17–7.21 (m, 3H), 7.26–7.31 (m, 2H), 7.32–7.38 (m, 3H), 7.43–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 28.3, 29.4, 35.9, 54.7, 81.3, 125.9, 126.2 (2C), 128.5 (4C), 128.6 (2C), 128.8, 140.7, 142.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1701, found 268.1684.



cis-**61** acetophenone (ca. 59%) **62** (not obtained)

4-Amino-1-phenylbutan-1-ol (62; Scheme 51). Following the general procedure **J**, CuCl (2.77 mg, 0.0280 mmol, 0.050 equiv) and *rac*-BINAP (17.4 mg, 0.0280 mmol, 0.050 equiv) in THF (12 mL) was reacted with a solution of oxaziridine diastereomer *cis*-**61** (150 mg, 0.561 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was refluxed for 1 h. Purification by chromatography on a silica gel (0–5% MeOH/CH_2Cl_2) afforded acetophenone (eluted out at 100% CH_2Cl_2) in ca. 59% yield (ca. 40 mg). Desired amino alcohol product **62** could not be obtained during this purification.

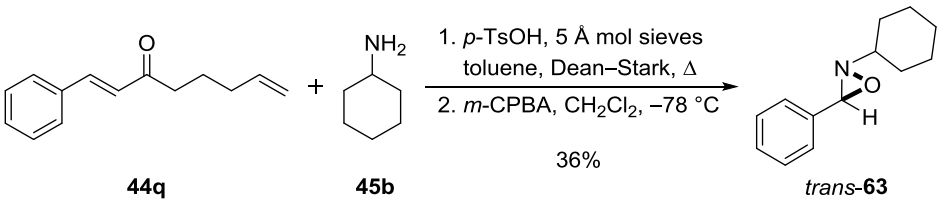


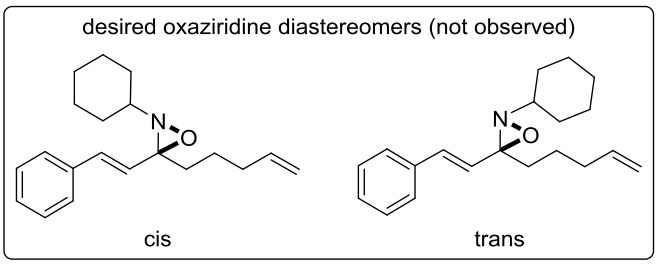
44q

(*E*)-1-Phenylocta-1,7-dien-3-one (44q).[211] Following the general procedure **H**, a solution of 5-bromo-1-pentene (1.61 mL, 13.6 mmol, 1.2 equiv) in THF (10 mL) was added drop wise to a stirring suspension of magnesium turnings (0.331 g, 13.6 mmol, 1.2 equiv) and two small crystals of iodine in THF (10 mL). After refluxing gently for 20 min, the reaction mixture was cooled to 0 °C and treated with a solution of *trans*-cinnamaldehyde (1.43 g, 11.3 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was then stirred at rt for 1 h. The aqueous work-up afforded the crude alcohol (2.50 g) as a pale yellow oil, which was used for the next oxidation step without further purification.

To a stirring solution of crude alcohol (2.50 g) in CH_2Cl_2 (50 mL) was added Celite (5.0 g) followed by PCC (4.89 g, 22.7 mmol, 2 equiv), and the reaction mixture was stirred at rt for 2 h. The reaction mixture was filtered through Celite, rinsing with several portions of CH_2Cl_2, and the filtrate was concentrated under reduced pressure. Purification by chromatography on a silica gel (1.0–1.5% EtOAc/hexanes) afforded impure enone **44q**. Subsequent purification of impure enone **44q** by chromatography on a silica gel (0.5–2.0% EtOAc/hexanes) afforded a small amount of impure enone followed by pure enone **44q** as a pale yellow oil (1.00 g, 5.00 mmol, 44% corrected yield over 2 steps by ^{1}H NMR). Enone **44q**: R_f = 0.56 (10% EtOAc/hexanes); IR (neat) 1689, 1663, 1610, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (m, 2H), 2.13 (m, 2H), 2.67 (t, J = 7.4 Hz, 2H), 4.98–5.08 (m, 2H), 5.81 (m, 1H), 6.74 (d, J = 16.2 Hz, 1H), 7.38–7.39 (m, 3H), 7.53–7.57 (m, 3H); ^{13}C

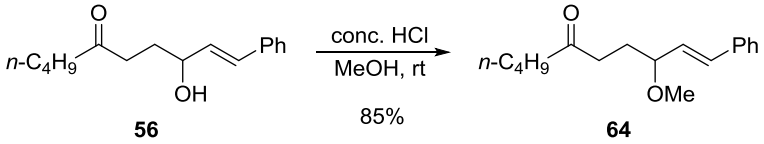
NMR (100 MHz, $CDCl_3$) δ 23.5, 33.3, 40.2, 115.4, 126.4, 128.4, 129.1, 130.6, 134.7, 138.2, 142.5, 200.4; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O$ $[M + H]^+$ 201.1279, found 201.1263.





(2*S*,3*S*)-*rel*-2-Cyclohexyl-3-phenyl-1,2-oxaziridine (*trans*-63; Scheme 52).[185,191] Following the general procedure **G**, (*E*)-1-phenylocta-1,7-dien-3-one **44q** (0.500 g, 2.50 mmol, 1.0 equiv), cyclohexylamine **45b** (0.428 mL, 3.75 mmol, 1.5 equiv), PTSA (23.8 mg, 0.125 mmol, 0.050 equiv), and activated 5 Å molecular sieves (3.50 g) in toluene (35 mL) was refluxed for 60 h, followed by oxidation with *m*-CPBA (0.517 g, 3.00 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). Purification by chromatography on a silica gel (0.4% EtOAc/hexanes) afforded impure oxaziridine *trans*-**63** as a yellow oil (0.185 g, 0.911 mmol, 36% corrected yield; ratio of *trans*-**63**:unidentified byproducts = ca. 84:16 by ^1H NMR) instead of the desired *cis*- and *trans*-oxaziridine diastereomers (shown in the box). A small amount of the impure oxaziridine *trans*-**63** was further purified by preparative TLC developing two times with 3% EtOAc/hexanes. The band corresponding to pure product was scraped from the plate and eluted with 50% ether/hexanes through a short bed of silica gel. Evaporation of solvents afforded an analytical sample of *trans*-**63** as a colorless oil for

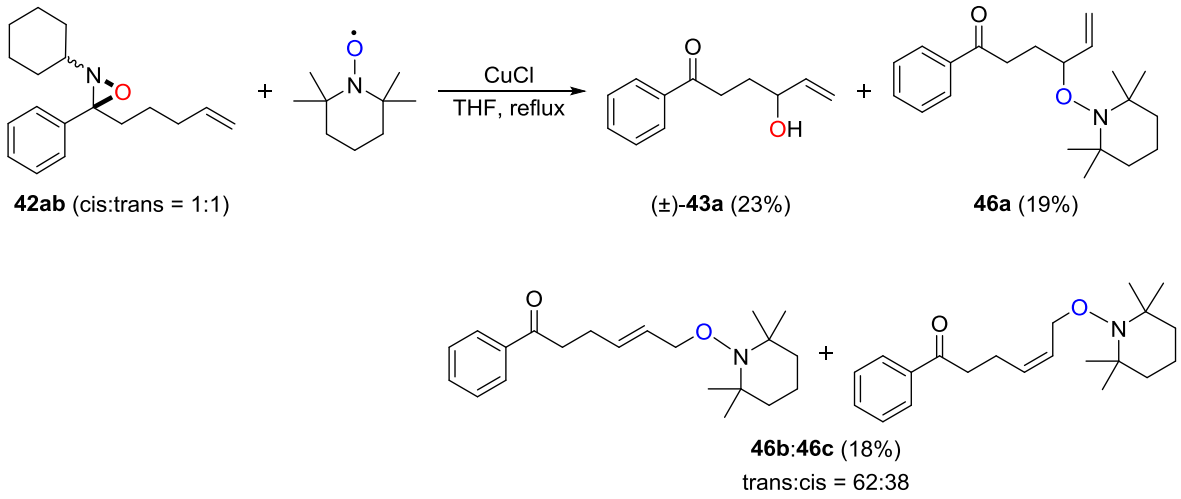
characterization. Oxaziridine diastereomer *trans*-**63**: R_f = 0.69 (5% EtOAc/hexanes, run twice); IR (neat) 2930, 2857, 1451, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.34 (complex, 3H), 1.40–1.50 (m, 1H), 1.54–1.66 (complex, 2H), 1.70–1.75 (m, 1H), 1.79–1.86 (complex, 2H), 2.04–2.12 (complex, 2H), 4.54 (s, 1H), 7.36–7.41 (m, 3H), 7.41–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 25.9, 29.4, 31.8, 70.4, 80.0, 127.6, 128.7, 130.1, 135.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO$ $[M + H]^+$ 204.1388, found 204.1380.



56 **64**

(*E*)-8-Methoxy-10-phenyldec-9-en-5-one (64; Scheme 54). To a solution of (*E*)-8-hydroxy-10-phenyldec-9-en-5-one **56** (20.0 mg, 0.0813 mmol, 1.0 equiv) in MeOH (1 mL) in an open flask at rt was added two small drops of concentrated HCl (37%) and the reaction mixture was stirred for 30 min. The reaction mixture was concentrated and the residue obtained was purified by chromatography on a silica gel (100% CH_2Cl_2) to afford 18.0 mg (0.0692 mmol, 85% yield) of the allylic ether **64** as a pale yellow oil. Allylic ether **64**: R_f = 0.62 (25% EtOAc/hexanes); IR (neat) 1712, 1364, 1108, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.29 (m, 2H), 1.54 (m, 2H), 1.84–1.97 (m, 2H), 2.39 (t, J = 7.5 Hz, 2H), 2.51 (t, J = 7.2 Hz, 2H), 3.30 (s, 3H), 3.73 (q, J = 6.8 Hz, 1H), 6.02 (dd, J = 16.0, 7.8 Hz, 1H), 6.53 (d, J = 15.9 Hz, 1H), 7.23–7.27 (m, 1H), 7.31–7.34 (m, 2H), 7.38–7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 26.2, 29.7, 38.5, 42.9, 56.5, 81.7, 126.7, 128.0, 128.8, 129.9, 132.7, 136.6, 211.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{25}O_2$ $[M + H]^+$ 261.1855, found 261.1832.

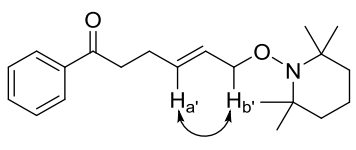
Procedure for the Radical-Trapping Experiment with TEMPO (Scheme 46)



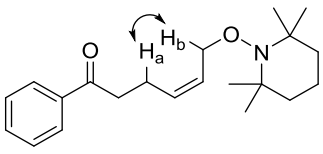
4-Hydroxy-1-phenylhex-5-en-1-one (43a), 1-Phenyl-4-((2,2,6,6-tetramethyl-piperidin-1-yl)oxy)hex-5-en-1-one (46a), *trans*-1-Phenyl-6-((2,2,6,6-tetramethylpiperi-din-1-yl)oxy)hex-4-en-1-one (*trans*-46b), and *cis*-1-Phenyl-6-((2,2,6,6-tetramethyl-piperidin-1-yl)oxy)hex-4-en-1-one (*cis*-46c). A flame-dried two-necked round bottom flask equipped with a reflux condenser was charged with CuCl (1.82 mg, 0.0184 mmol, 0.050 equiv) and THF (8 mL) under an argon atmosphere. The solution was degassed with argon and allowed to reflux for 30 min. A solution of TEMPO in THF (1 mL) followed by a solution of oxaziridine diastereomers **42ab** (100 mg, 0.369 mmol, 1.0 equiv; cis:trans = 1:1) in THF (3 mL) was added slowly by syringe to the resulting solution, and refluxing was continued for 1 h. The solvent was removed under reduced pressure and the crude mixture was purified by chromatography on a silica gel (100% CH_2Cl_2 to CH_2Cl_2:acetone:MeOH, 98.9:1.0:0.1 to 98.7:1.0:0.3) to afford 9.00 mg (0.0517 mmol, 14% yield) of **44a**, 45.0 mg of a mixture containing three radical-trapped products (**46a**, **46b**, and **46c**), and 16.0 mg (0.0842 mmol, 23% yield) of the allylic alcohol **43a** as an orange oil. Further purification of the mixture of **46a**, **46b**, and **46c** by chromatography on a silica gel (0.6–1.2% EtOAc/hexanes) afforded the internal radical-trapped product **46a** as a colorless oil (23.6 mg, 0.0717 mmol, 19% yield) and the mixture of terminal radical-trapped

products (*trans*-**46b** and *cis*-**46c**) as a colorless oil (21.4 mg, 0.0650 mmol, 18% yield, **46b**:**46c** = ca. 62:38). Internal radical-trapped product **46a**: R_f = 0.36 (5% EtOAc/hexanes); IR (neat) 1686, 1360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07–1.18 (m, 12H), 1.27–1.30 (m, 1H), 1.43–150 (m, 5H), 1.91–2.00 (m, 1H), 2.09–2.18 (m, 1H), 3.01 (t, J = 7.6 Hz, 2H), 4.24 (m, 1H), 5.08–5.13 (m, 2H), 5.85 (m, 1H), 7.43–7.47 (m, 2H), 7.53–7.57 (m, 1H), 7.94–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 20.60, 20.67, 28.8, 34.4, 34.6, 35.2, 40.4, 59.4, 60.3, 84.8, 116.4, 128.2, 128.7, 133.0, 137.2, 140.6, 200.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{32}NO_2$ $[M + H]^+$ 330.2433, found 330.2443.

Terminal radical-trapped products (*trans*-**46b** and *cis*-**46c**): R_f = 0.30 (5% EtOAc/hexanes); IR (neat) 1686, 1358 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08–1.17 (m, 24H), 1.29–1.32 (m, 2H, trans), 1.42–1.45 (m, 8H), 1.50–1.59 (m, 2H, cis), 2.46–2.53 (m, 4H), 3.02–3.10 (m, 4H), 4.22 (dd, J = 6.0, 1.1 Hz, 2H, trans), 4.36 (d, J = 5.2 Hz, 2H, cis), 5.55–5.66 (m, 3H), 5.72–5.80 (m, 1H), 7.43–7.47 (m, 4H), 7.53–7.57 (m, 2H), 7.93–7.97 (m, 4H); ^{13}C NMR for trans (100 MHz, $CDCl_3$) δ 17.3, 20.4, 27.1, 33.22, 38.2, 39.8, 59.8, 78.2, 126.9, 128.2, 128.7, 132.0, 133.2, 137.1, 199.7; ^{13}C NMR for cis (100 MHz, $CDCl_3$) δ 17.3, 20.3, 22.8, 33.29, 38.7, 39.85, 59.84, 73.4, 126.7, 128.2, 128.7, 131.1, 133.2, 137.0, 199.5; HRMS (ESI) for trans *m/z* calcd for $C_{21}H_{32}NO_2$ $[M + H]^+$ 330.2433, found 330.2439; HRMS (ESI) for cis *m/z* calcd for $C_{21}H_{32}NO_2$ $[M + H]^+$ 330.2433, found 330.2445.



trans-**46b**

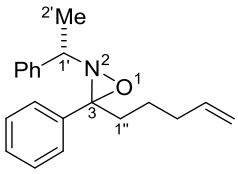
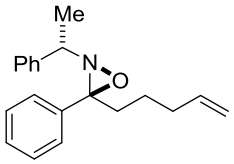
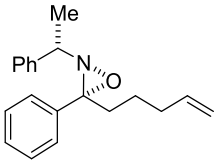
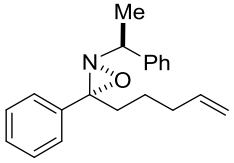
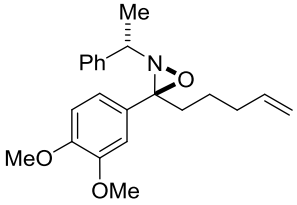
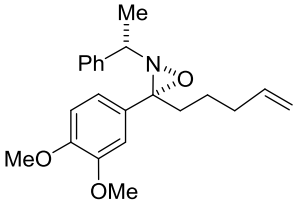
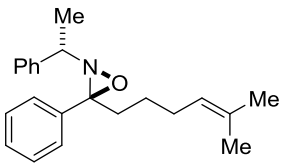


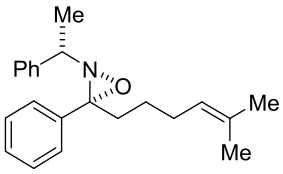
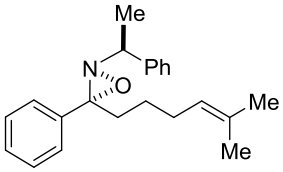
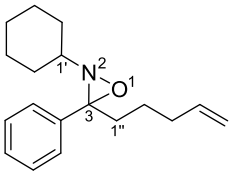
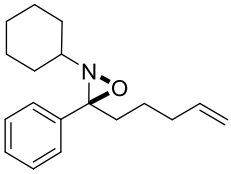
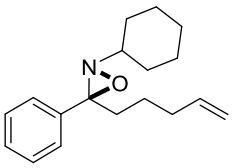
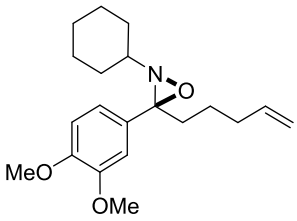
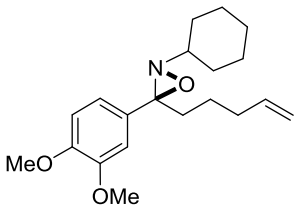
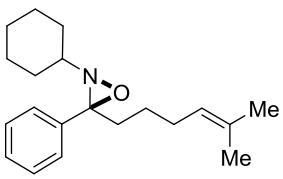
cis-**46c**

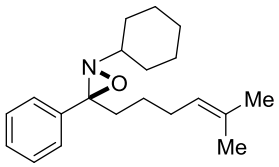
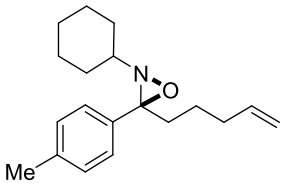
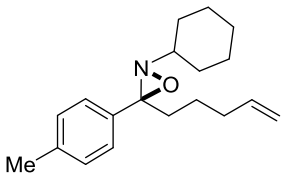
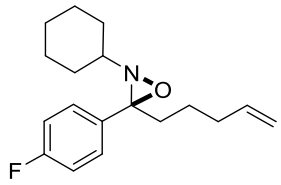
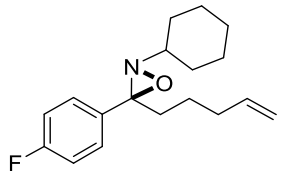
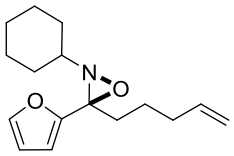
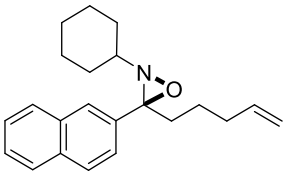
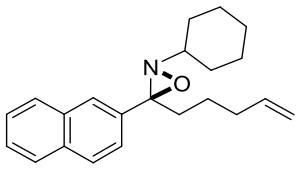
The trans and cis configuration were assigned based on NOESY signal observed between $H_{a'}$ and $H_{b'}$ for *trans*-radical-trapped product **46b** and between H_a and H_b for *cis*-radical-trapped product **46c**.

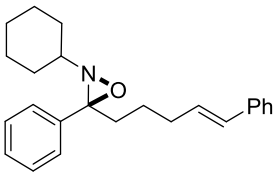
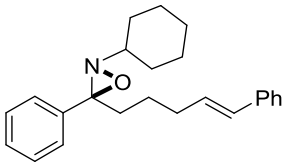
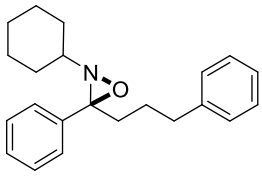
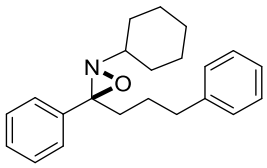
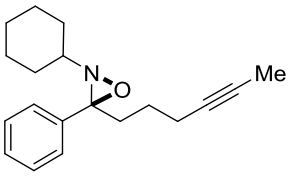
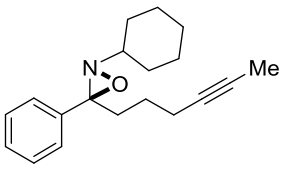
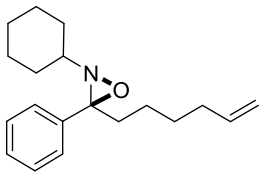
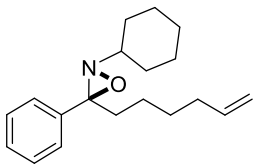
All oxaziridine stereostructures were assigned according to well-established chemical shift trends.[151b,161f,170a,181-182]

Table S26. Assignment of Oxaziridine Diastereomers Based on ^{1}H and ^{13}C NMR Shifts

compd no.	compd structure	^{1}H NMR (ppm)		^{13}C NMR (ppm)		
		1′-H	2′-H	3-C	1′-C	1″-C
						
42aa		2.99	1.48	88.4	62.8	37.9
42aa′		–	1.14	–	–	–
42aa″		–	1.62	–	–	–
42ba		3.01	1.47	88.2	62.7	37.9
42ba′		3.09	1.15	88.5	61.4	37.8
42ca		2.99	1.48	88.6	62.8	38.1

compd no.	compd structure	^{1}H NMR (ppm)		^{13}C NMR (ppm)		
		1′-H	2′-H	3-C	1′-C	1″-C
42ca′		3.19	–	87.8	61.7	–
42ca″		3.82	–	85.8	62.9	–
						
cis-**42ab**		2.36	–	87.7	61.0	38.1
trans-**42ab**		2.29	–	85.8	61.3	29.1
cis-**42bb**		2.31	–	87.5	60.7	38.1
trans-**42bb**		2.28	–	85.4	61.4	29.2
cis-**42cb**		2.35	–	87.8	60.9	38.3

compd no.	compd structure	^{1}H NMR (ppm)			^{13}C NMR (ppm)	
		1′-H	2′-H	3-C	1′-C	1″-C
trans-**42cb**		2.26	–	85.9	61.2	29.4
cis-**42db**		–	–	87.6	60.7	38.1
trans-**42db**		–	–	85.6	61.2	29.2
cis-**42eb**		2.33	–	87.2	60.9	38.0
trans-**42eb**		2.26	–	85.2	61.3	29.3
cis-**42fb**		2.32	–	82.3	61.4	36.0
cis-**42gb**		2.48	–	88.0	60.9	38.1
trans-**42gb**		2.44	–	85.9	61.3	29.3

compd no.	compd structure	^{1}H NMR (ppm)			^{13}C NMR (ppm)	
		1′-H	2′-H	3-C	1′-C	1″-C
cis-**42hb**		2.42	–	87.7	61.0	38.1
trans-**42hb**		2.36	–	85.8	61.2	29.1
cis-**47**		2.39	–	87.7	60.9	38.2
trans-**47**		2.31	–	85.7	61.2	29.4
cis-**49**		2.41	–	87.4	60.9	37.7
trans-**49**		-	–	85.4	61.2	29.3
cis-**53**		2.33–2.40	–	87.8	60.9	38.5
trans-**53**		–	–	85.8	61.3	29.6

Chapter 3

Synthesis and Cytotoxic Evaluation of Withalongolide A Analogues

3.1 Introduction

Classically defined withanolides are a group of naturally occurring C28 steroidal lactones assembled on an ergostane skeleton with either a C-22,26 δ-lactone ring or a C-23,26 γ-lactone ring (Figure 21). Most of the withanolides are highly oxygenated members of the Solanaceae family, which includes genera such as *Acnistus*, *Datura*, *Jaborosa*, *Lycium*, *Physalis*, *Vassobia*, and *Withania*.[212] Structurally complex and diverse withanolides with a C-17 δ-lactone side chain, as shown in Figure 21, can be further classified into withanolides with an unmodified skeleton (e.g., withaferin A **66**, withaperuvin B, and sominone) and those with a modified skeleton (e.g., withametelinone and physalin C).[212a,b] The occurrence of unmodified withanolides is more common in nature.[212b,c] Withanolides have attracted significant attention from several researchers as they exhibit numerous biological activities, including antimicrobial,[213] antineoplastic,[214] anti-neurodegenerative,[215] anti-inflammatory,[216] immunomodulating, antioxidant, anti-stress, cardiotonic, and insect antifeedant properties.[212a,b,217]

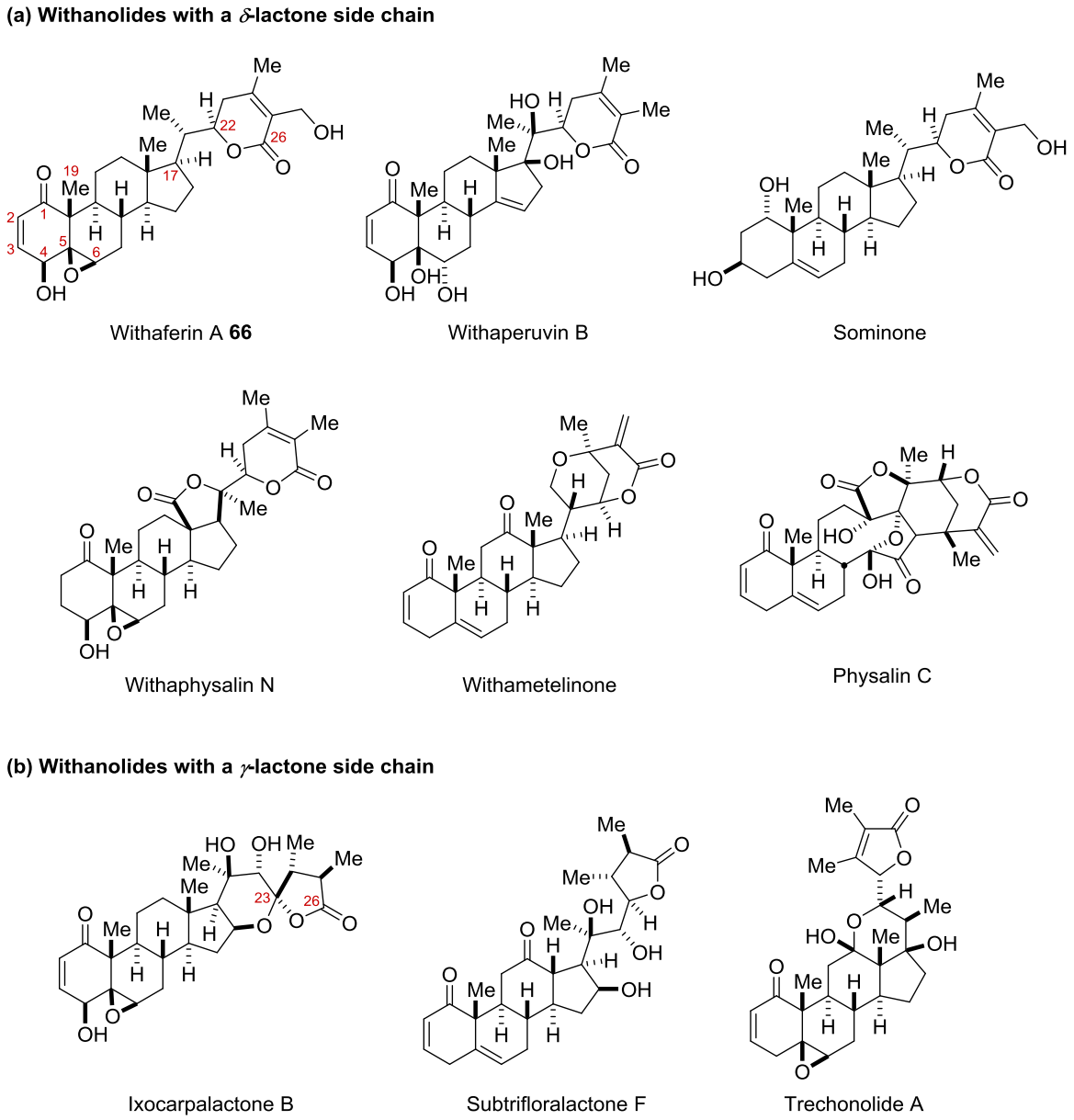


Figure 21. Representative examples of withanolides with a δ- and γ-lactone ring.

Withaferin A **66** was the first withanolide isolated by Lavie from *Withania somnifera* in 1965 and has become an iconic example for the entire class since then.[212a,b,218] Withaferin A **66** is the most studied withanolide and possesses a wide range of pharmacological activities such as antitumor, antimicrobial, antioxidant, anti-inflammatory, protective, and antiangiogenic effects.[212a,b,214d,219] The antitumor activity of **66** has been demonstrated both in vitro and in vivo against an array of tumor cells like breast, prostate,

lung, and head and neck squamous cell carcinoma (HNSCC).[212a,220] Such promising antitumor activity results from targeting multiple signaling pathways such as HSP90 and NF-κB, which may circumvent the development of resistance among cancer cells.[219a,c,221] The biological activities, especially the antitumor properties of **66** and other related unmodified withanolides, are thought to depend on the presence of structural features such as an α,β-unsaturated ketone in ring A, a 5β,6β-epoxide in ring B, and a 17β-oriented δ-lactone ring.[212,222]

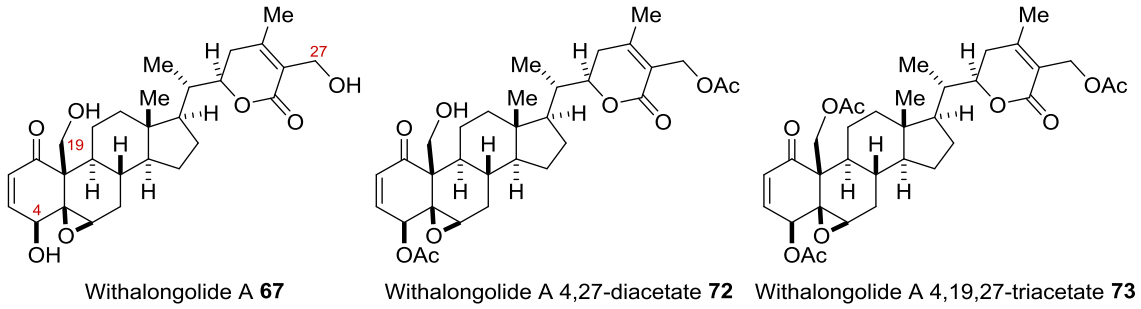


Figure 22. Withalongolide A and its di- and triacetates.

Recently, Timmermann and co-workers reported the isolation, structures, and cytotoxic activities of 14 new withanolides (named as withalongolides) from *Physalis longifolia* Nutt. (Solanaceae).[223] These withalongolides feature the presence of a rare C-19 hydroxy group. Withalongolide A (**67**, Figure 22; cf. **66** in Figure 21), a 19-hydroxywithaferin A, was the major withanolide isolated from the crude plant extract. Despite much structural similarity to **66**, withalongolide A **67** showed considerably decreased potency against the carcinoma and melanoma cell lines tested compared to **66**. However, the semisynthetic derivatives withalongolide A 4,27-diacetate **72** (IC_{50} = 0.098 μM) and withalongolide A 4,19,27-triacetate **73** (IC_{50} = 0.067 μM) (Figure 22) showed improved potency and selectivity against the melanoma cell line B16F10 over both the

parent compound **67** ($IC_{50} \geq 10$ μM) and **66** ($IC_{50} = 0.29$ μM).[223] This led us to initiate a study to examine preliminary SAR for analogues of compound **67**.[224]

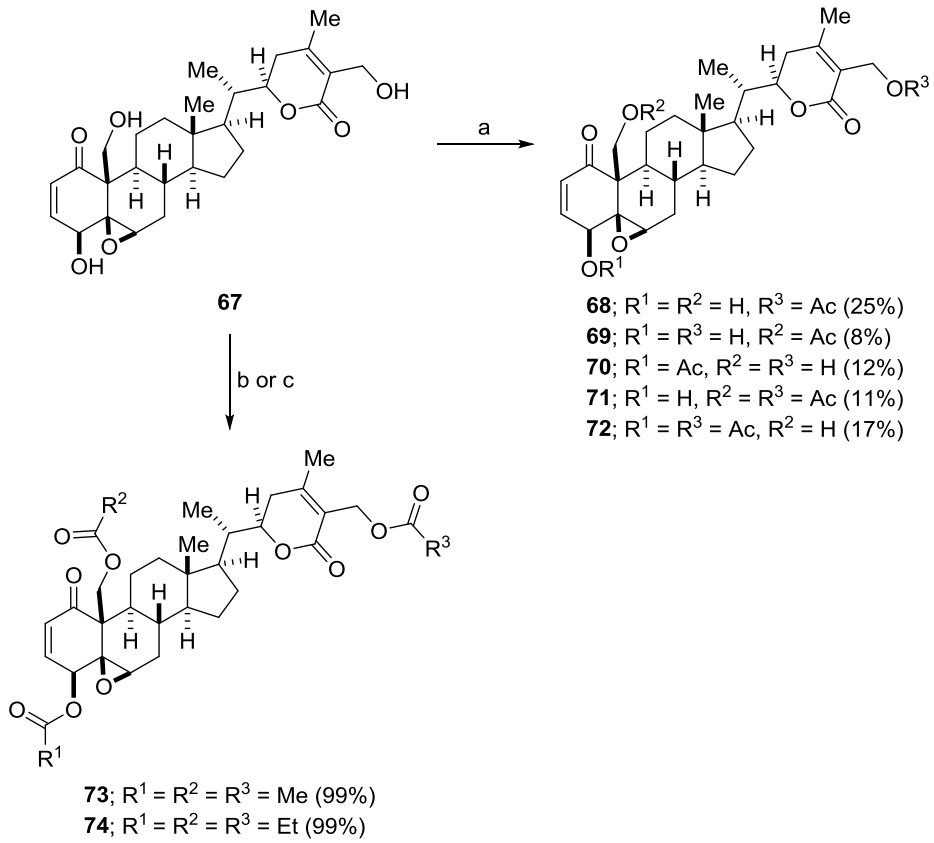
3.2 Results and Discussions

Semisynthesis

As previous authors have asserted the importance of 2-ene-1-one, a 5β,6β-epoxide, and a 17β-oriented δ-lactone for the antitumor activity of **66**,[212,222] we accordingly sought to minimize modifications at these positions. Moreover, since the di- and tri-acetate of **67** displayed significant selectivity against melanoma cell line B16F10 with potency in the nanomolar range, we first focused on examining the effects of modifying the free hydroxyl group of **67**.

Accordingly, we prepared a series of aliphatic esters of **67** (Scheme 46). After slight modifications of the standard acetylation procedures, it was possible to isolate mono- (**68**–**70**) and diacetylated analogues **71** and **72**[223a] from the same reaction along with some recovered **67** (acetic anhydride was added in two portions; see the Experimental Section for details). Triacetate **73**[223a] and withalongolide A 4,19,27-propionate **74** were obtained by treating **67** with appropriate anhydrides in the presence of pyridine and a catalytic amount of DMAP. On the other hand, reactions of **67** with both 2-chloroacetyl chloride and trifluoroacetic anhydride in pyridine led to complex mixtures and decomposition (Scheme 56a,b).

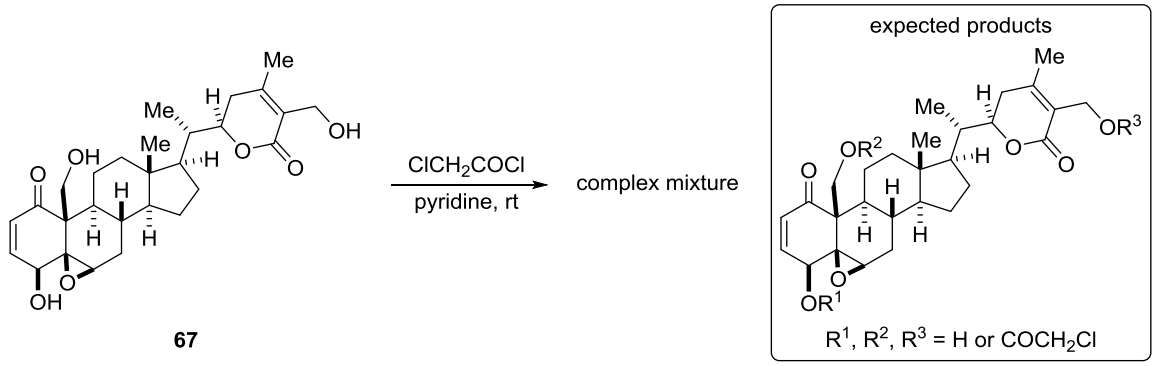
Scheme 55. Synthesis of Acetylated and Propionylated Analogues of Withalongolide A 67[a]



[a]Reagents and conditions: (a) For **68**–**72**: $(MeCO)_2O$, pyridine, rt, 73% combined yield; (b) for **73**: $(MeCO)_2O$, pyridine, DMAP, rt, 99%; (c) for **74**: $(EtCO)_2O$, pyridine, DMAP, rt, 99%.

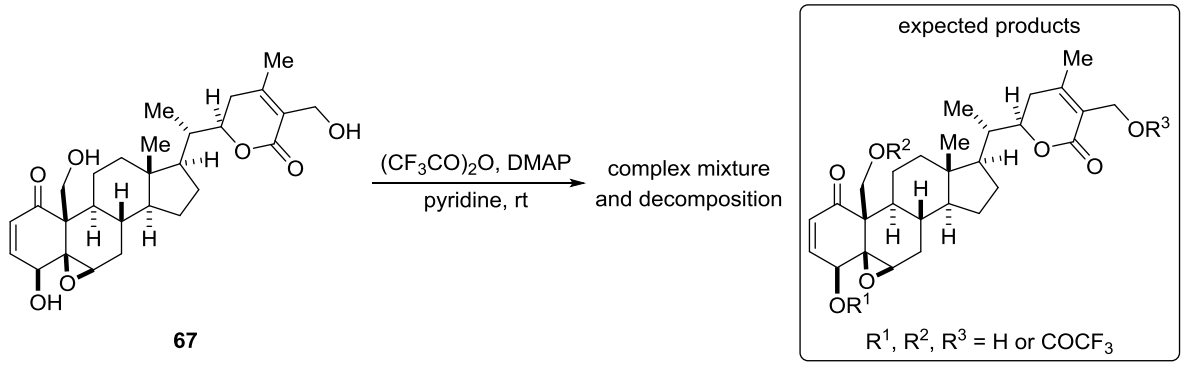
Scheme 56. Unsuccessful Synthesis of Haloacetylated and Benzoylated Analogues

(a) Acetylation reaction with 2-chloroacetyl chloride



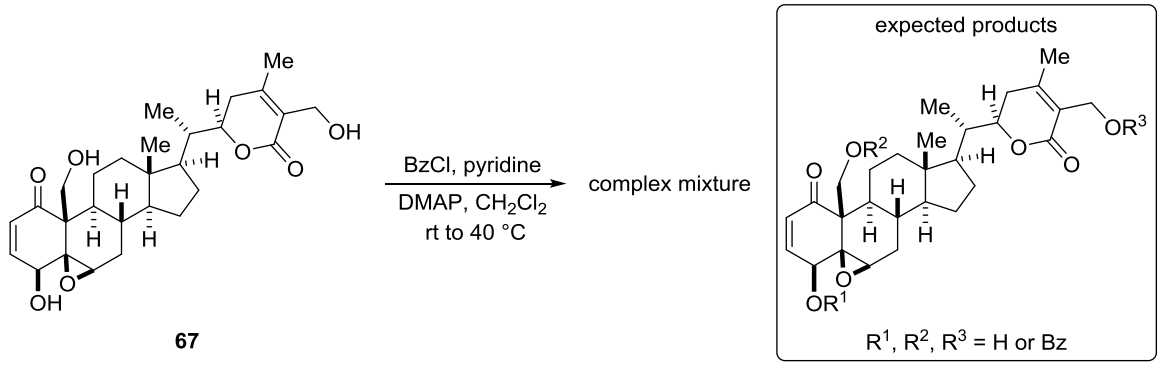
67

(b) Acetylation reaction with trifluoroacetic anhydride



67

(c) Benzoylation reaction with benzoyl chloride

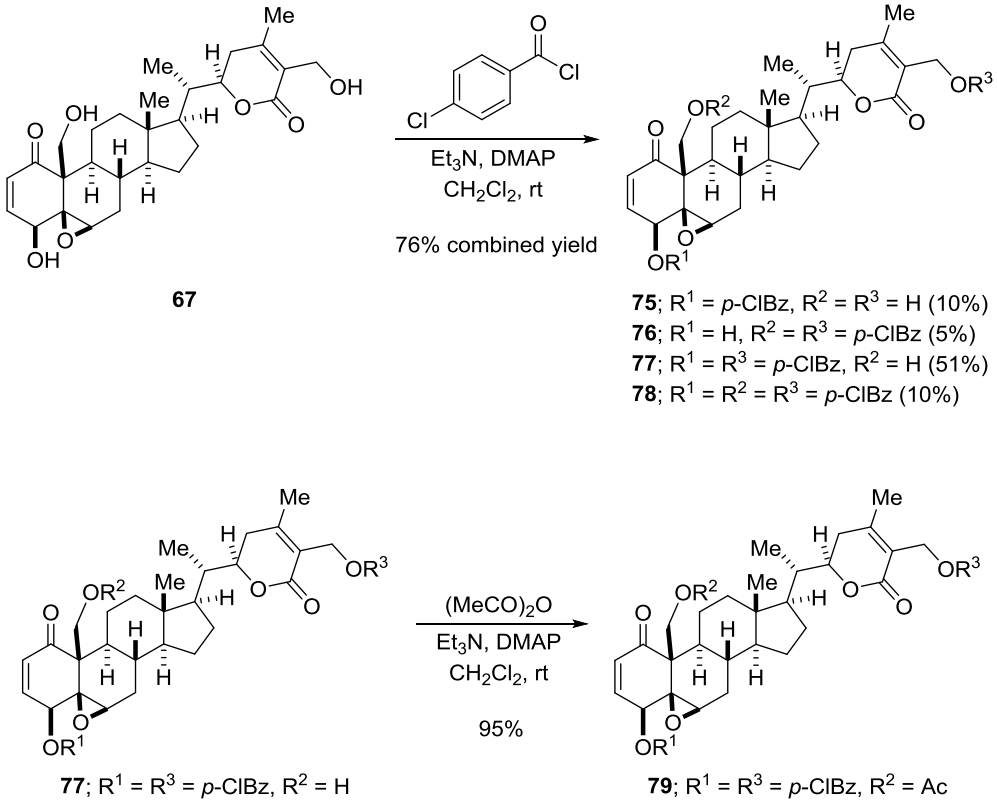


67

The second series of analogues entailed the synthesis of acetates and aromatic esters in assorted combinations along with carbamates. An initial attempt to make benzoylated analogues of **67** with benzoyl chloride (BzCl, PhCOCl) under typical acylation conditions (pyridine and DMAP) resulted in an incomplete reaction and the formation of a complex

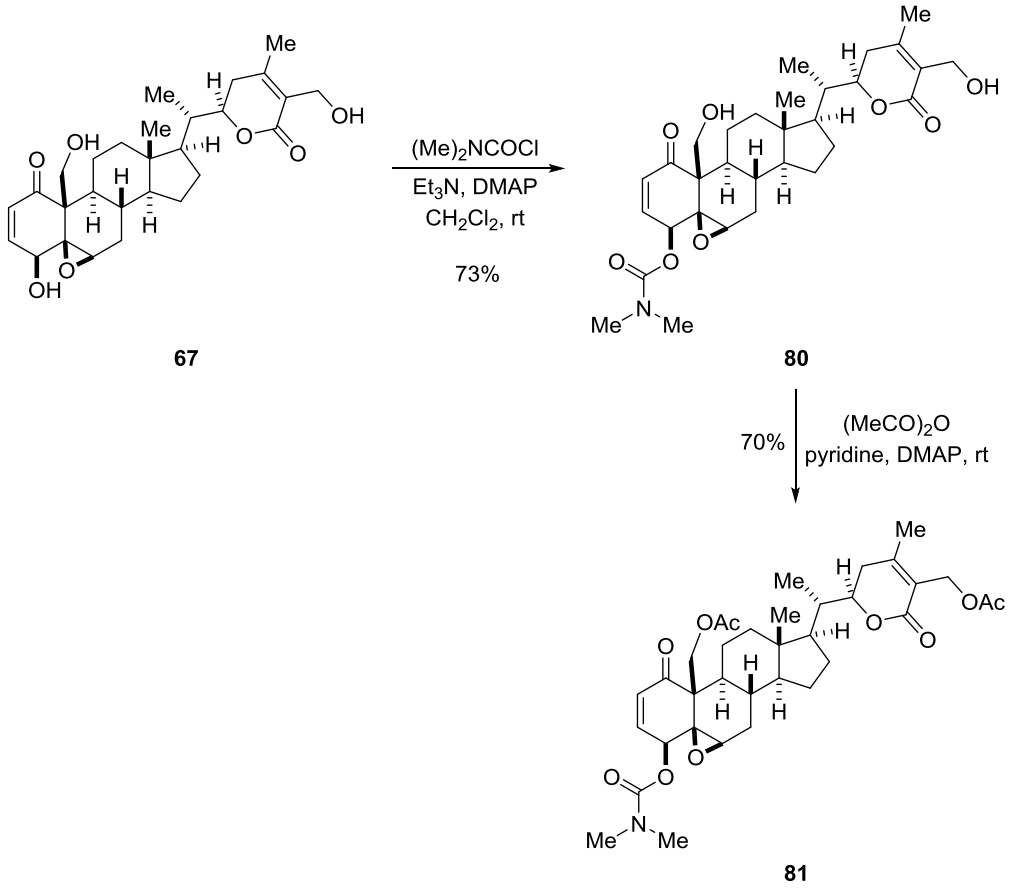
mixture (Scheme 56c). Gratifyingly, the reaction of **67** with *p*-chlorobenzoyl chloride in the presence of triethylamine (Et_3N) and DMAP afforded a mixture of *p*-chlorobenzoylated analogues from which mono- (**75**), di- (**76** and **77**), and tri-*p*-chlorobenzoate ester **78** were isolated (Scheme 57).[225] The free C-19 hydroxyl group of **77** was further acetylated with acetic anhydride to afford compound **79** (Scheme 57).

Scheme 57. Synthesis of *para*-Chlorobenzoylated Analogues of Withalongolide A 67



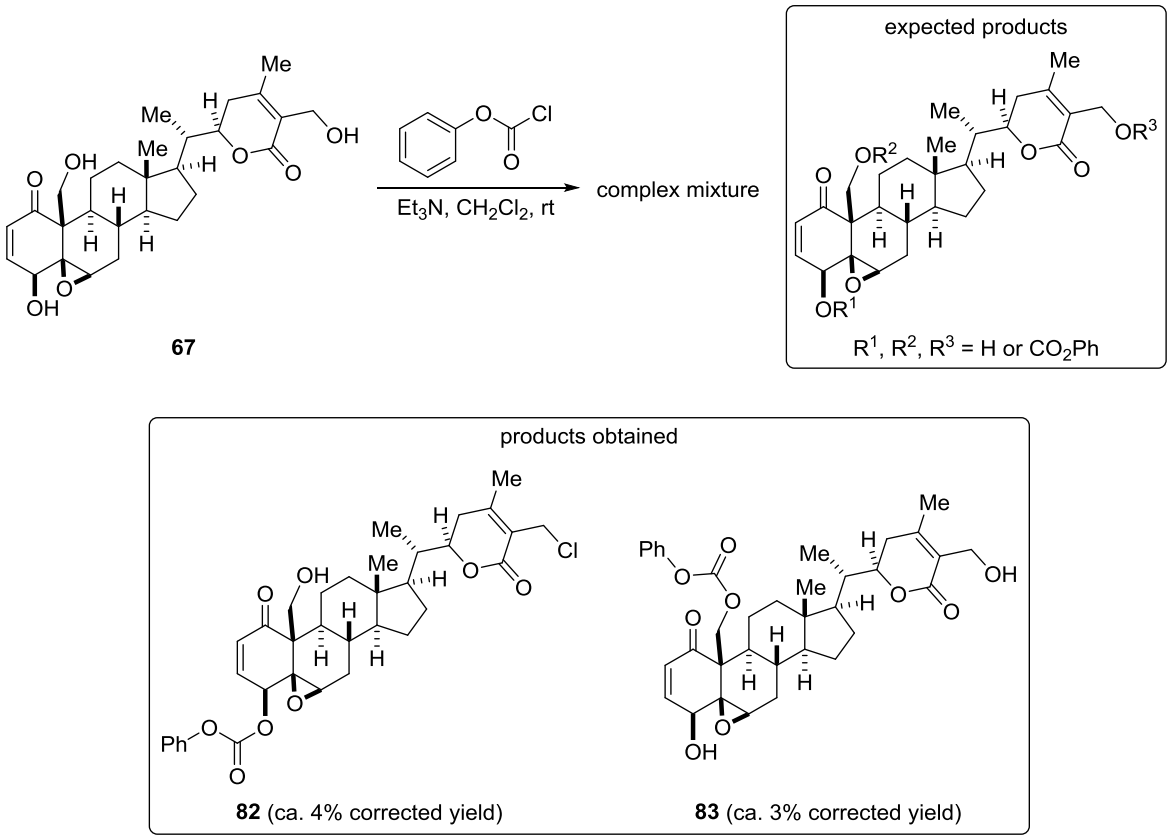
Carbamoylation only occurred at the C-4 hydroxyl even after treating **67** with excess dimethylcarbamoyl chloride, to afford monosubstituted dimethylcarbamate analogue **80** (Scheme 58). Subsequent acetylation of the remaining two hydroxyl groups with acetic anhydride delivered compound **81** in good yield (Scheme 58).

Scheme 58. Synthesis of Carbamate Analogues of Withalongolide A 67



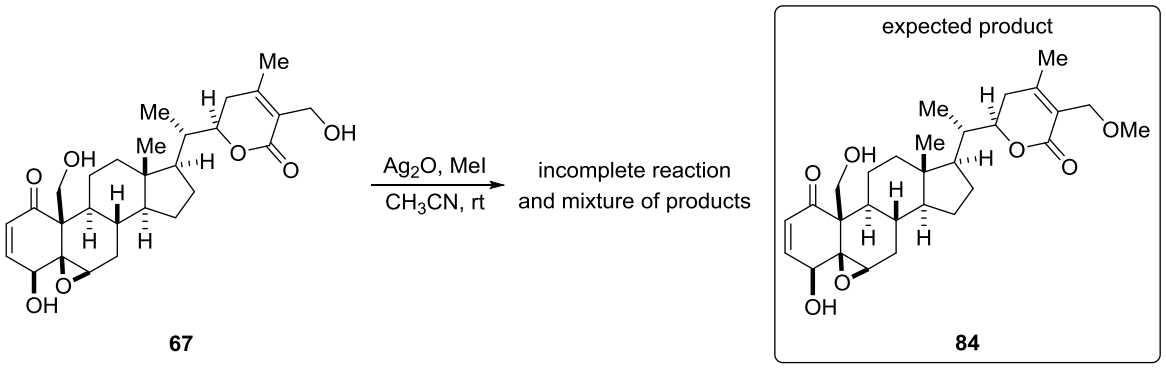
An effort to make carbonate analogues from phenylchloroformate under similar conditions that were employed for the synthesis of *p*-chlorobenzoylated analogues was unsuccessful. A multitude of products was obtained, some of which seemed to be unstable during preparative TLC purification (Scheme 59). However, it was possible to isolate a very small amount (ca. 2–3 mg) of impure samples of compounds **82** and **83** (Scheme 59; shown in the box). Compound **82** might have presumably formed from the nucleophilic substitution on the C-27 carbonate by a chlorine atom generated in situ from phenyl chloroformate.

Scheme 59. Failed Attempt for the Synthesis of Carbonate Analogues



Selective and mild etherification reaction of C-27 hydroxyl of **67** with methyl iodide in the presence of silver oxide (Ag_2O) resulted in an incomplete reaction and formation of more than two inseparable products (Scheme 60).[226] This experiment was not pursued further due to nonselectivity of the etherification reaction and the difficulty of separating the putative ether products.

Scheme 60. Fruitless Efforts towards the Synthesis of C-27 Methyl Ether Analogue 84



Jaborosalactones are withanolides isolated from *Jaborosa* species such as *Jaborosa integrifolia* and *Jaborosa leucotricha*. We synthetically prepared close derivatives of known jaborosalactones (see Figure 23) by chemically manipulating **73** as shown in Scheme 61. Thus, the palladium-catalyzed, formate-mediated reduction of triacetate **73** afforded a mixture of jaborosalactone derivatives **85**[227] and **86**[228] through C-4 deoxygenation of the acetate group.[229] The structure of the diacetate analogue of jaborosalactone V **85** was confirmed by single-crystal X-ray diffraction analysis (Figure 24).[227] Compound **86**, a C-19 acetate analogue of jaborosalactone B 27-acetate, was obtained via similar C-4 deoxygenation followed by subsequent epoxide ring-opening.[228] Analogue **87**, a C-19 acetate derivative of jaborosalactone E 27-acetate, was obtained by epoxide ring-opening of compound **85** using HCl solution in ether.[230] Besides being expected from a mechanistic perspective, the anti relationship of the C-5 chlorine and C-6 hydroxyl groups was assigned based on NMR data comparison with the literature values for jaborosalactone E and similar compounds.[230-231] Acetylation of a small amount of compound **87** showed a downfield shift of H-6 from δ 3.99 to 5.12 suggesting the presence of a hydroxyl group at C-6 (see the Experimental Section for details).[230] The C-6 free hydroxyl group of compound **86** was further acetylated to provide triacetylated analogue **88**.

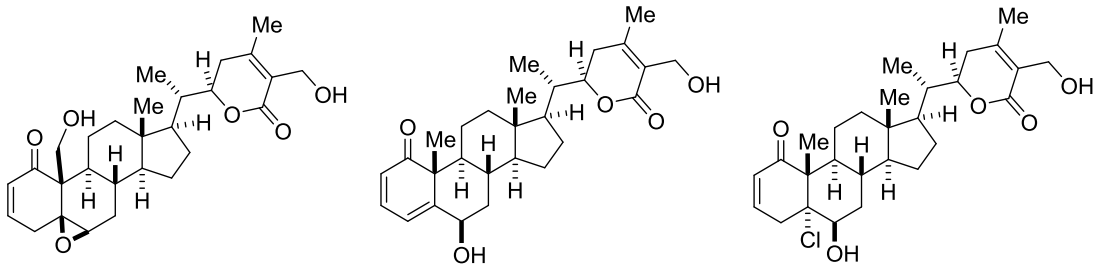
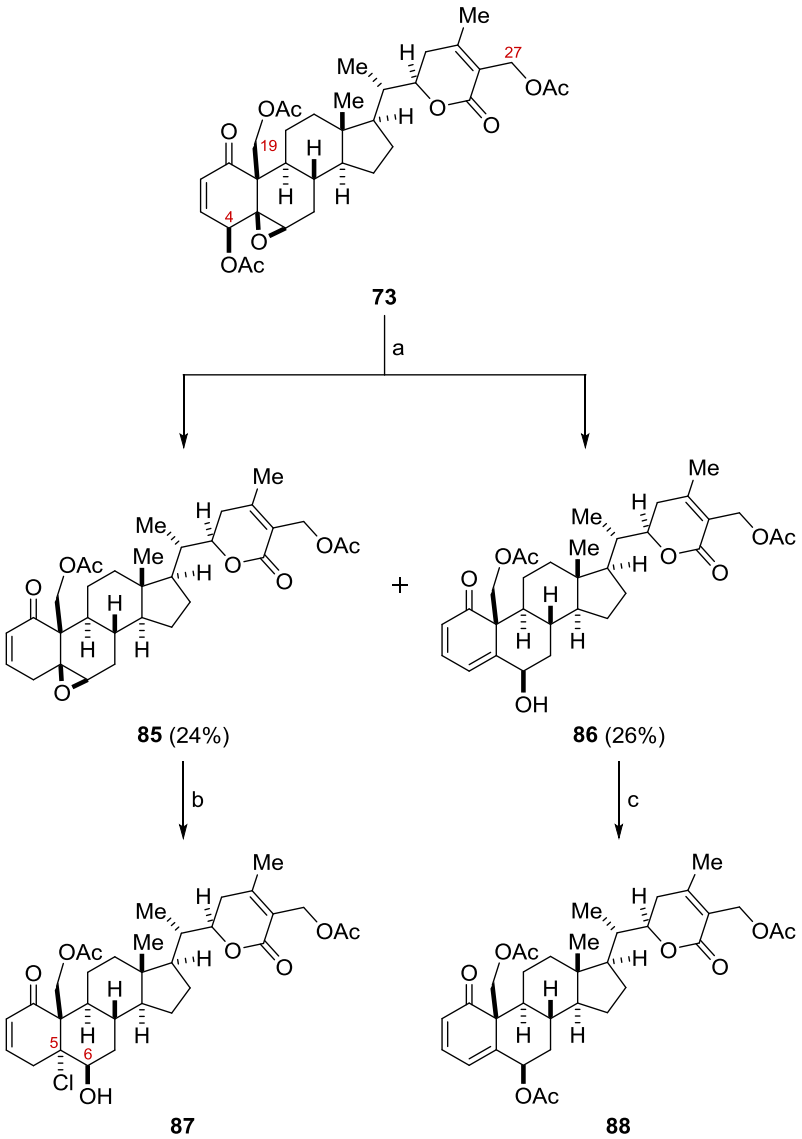


Figure 23. Chemical structures of jaborosalactones.

Scheme 61. Synthesis of Jaborosalactone Derivatives from Triacetate 73[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, HCO_2NH_4, dioxane, reflux, 50% combined yield; (b) HCl solution in ether, CH_2Cl_2, rt, 70%; (c) $(MeCO)_2O$, pyridine, DMAP, rt, 87%.

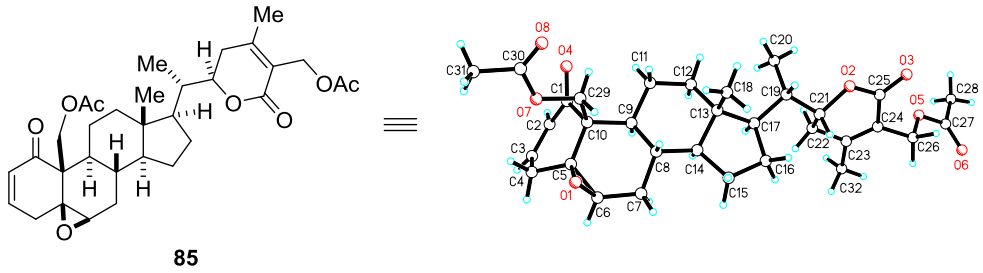
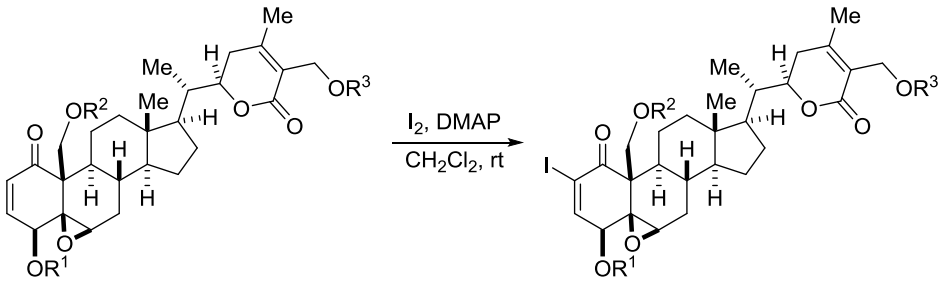


Figure 24. Single-crystal X-ray structure of analogue **85**.

The α,β-unsaturated ketone of withaferin A is a Michael acceptor.[221d] Therefore, we sought to modify the α,β-unsaturated ketone in order to modulate its reactivity. Initial efforts were focused toward making analogues with a minimal modification by keeping this important enone functionality intact. Thus, we directed our attention toward the synthesis of α-substituted aryl analogues of the ring A enone of **67**. Compound **67** and its triacetate analogue **73** were subjected to α-iodination conditions using iodine and DMAP to afford their corresponding α-iodoenone analogues **89** and **90** (Scheme 62).[232] However, an attempt to execute Suzuki cross-coupling of the α-iodoenone moiety in **90** with 4-acetylphenylboronic acid[233] to obtain α-aryl analogue **91** met with no success; only decomposition of **90** was observed (Scheme 63).

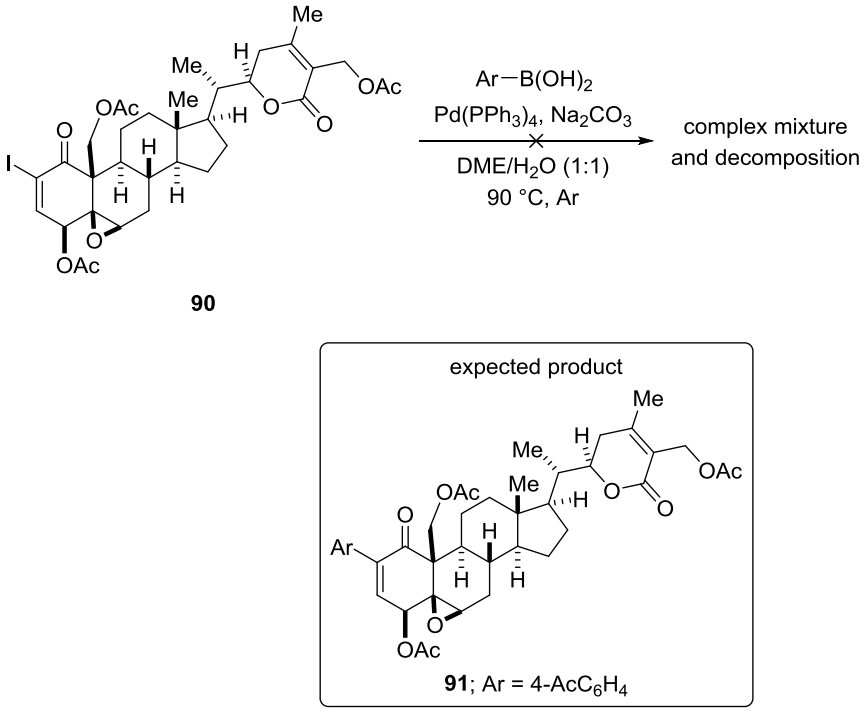
Scheme 62. Synthesis of α-Iodoenone Derivatives



67; $R^1 = R^2 = R^3 = H$
73; $R^1 = R^2 = R^3 = Ac$

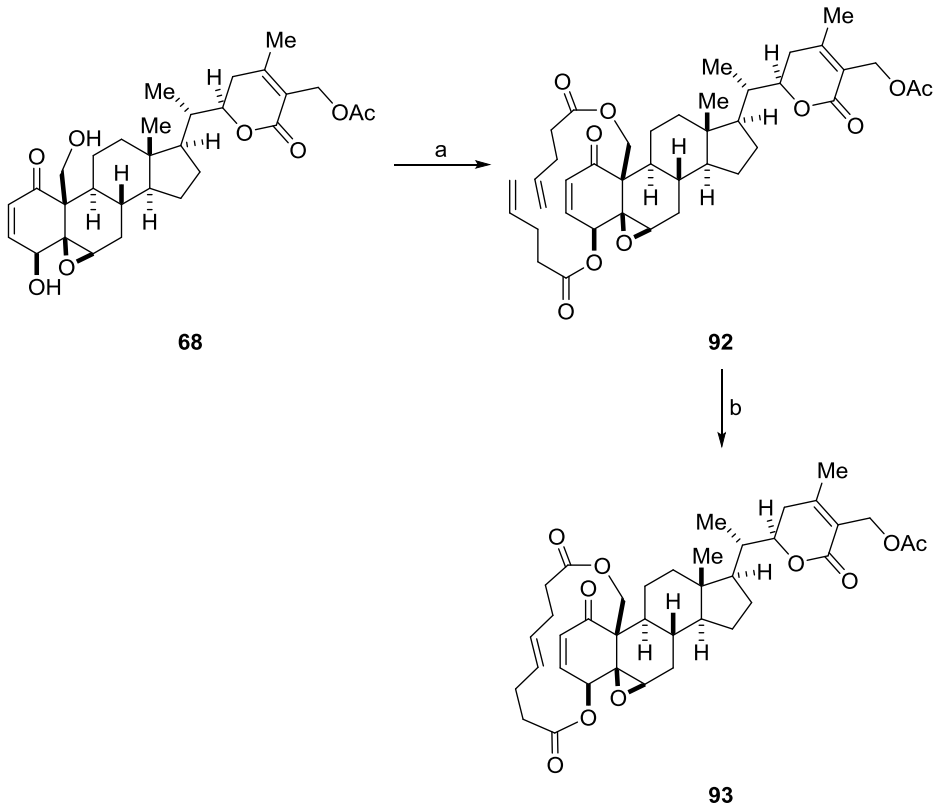
89; $R^1 = R^2 = R^3 = H$ (40%)
90; $R^1 = R^2 = R^3 = Ac$ (71%)

Scheme 63. Failed Suzuki Cross-Coupling of 90 with 4-Acetylphenylboronic acid



An additional analogue was prepared via ring-closing macrocyclization[234] to afford a rare steroidal macrocycle (Scheme 64).[235] Initial bis-acylation of withalongolide monoacetate **68** with 4-pentenoyl chloride in the presence of Et_3N and DMAP afforded a complex mixture of products. Pleasingly, the bis-acylation reaction of **68** with 4-pentenoic anhydride in the presence of pyridine and DMAP afforded **92** in excellent yield. Subsequent ring-closing metathesis with Grubbs II catalyst exclusively afforded the 14-membered macrocycle **93** with *E*-configuration.[236]

Scheme 64. Synthesis of Steroidal Macrocycle 93 from Withalongolide Monoacetate 68[a]



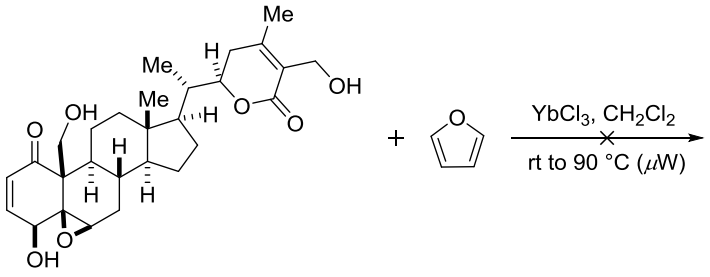
[a]Reagents and conditions: (a) $(H_2C{=}CHCH_2CH_2CO)_2O$, pyridine, DMAP, rt, 92%; (b) Grubbs II catalyst, CH_2Cl_2, 37 °C, 87%.

Other Attempted Analogue Syntheses

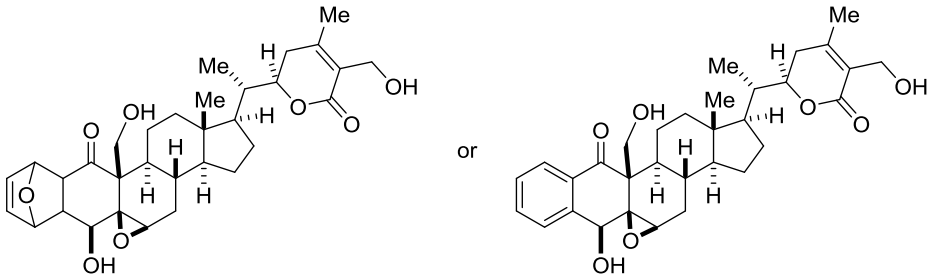
The complexity of **67** and its vulnerability to various reaction conditions made syntheses of many designed analogues unfeasible. For example, preliminary efforts to transform the α,β-unsaturated ketone of **67** into fused A-ring analogues **94** and **95** through Diels–Alder reaction of the $\Delta^{2,3}$-olefin with dienes, such as furan and Danishefsky′s diene, met with failure (Scheme 65). The Diels–Alder reaction of a small amount of **67** with furan under Lewis acid ($YbCl_3$)[237] conditions did not lead to the desired product **94**. Likewise, the reaction of **67** with Danishefsky′s diene at elevated temperature afforded a complex mixture.

Scheme 65. Unsuccessful Diels–Alder Reaction of 67 with Dienes

(a) Diels–Alder reaction with furan

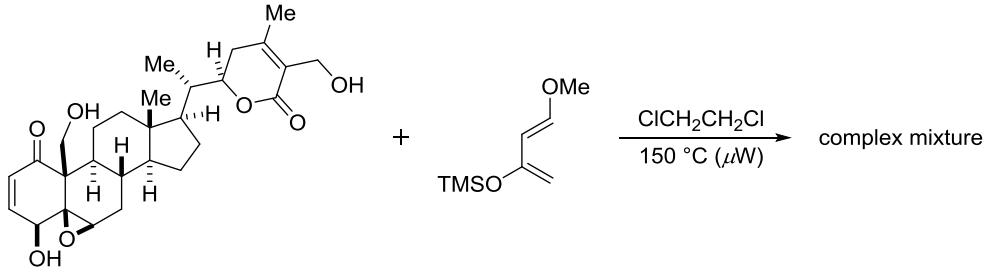


67



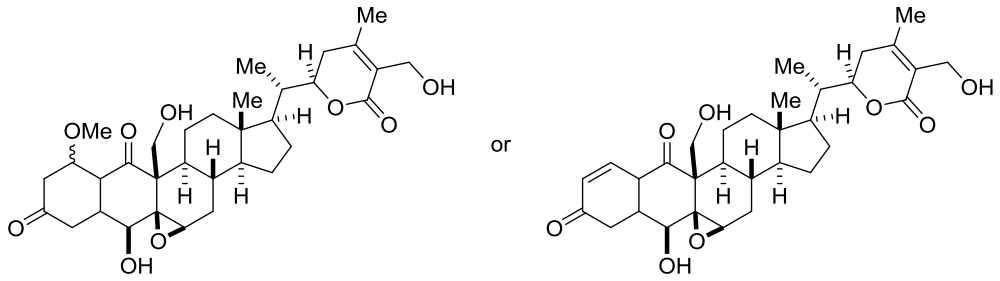
94a (not observed) **94b** (not observed)

(b) Diels–Alder reaction with Danishefsky's diene



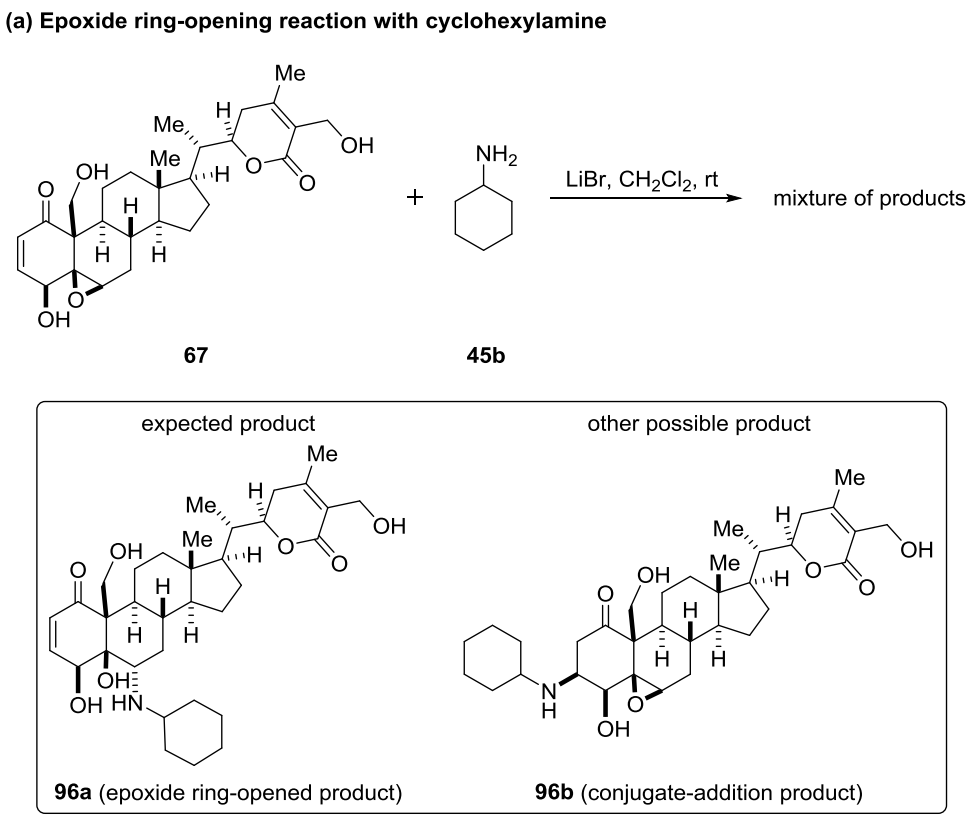
67

possible expected products



95a **95b**

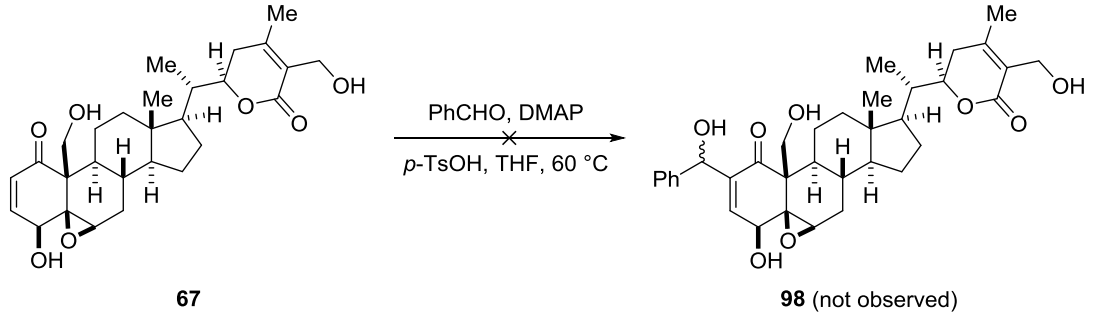
Scheme 66. Failed Efforts toward the Epoxide Ring-Opening Reactions of 67



With an intention to access additional analogues through selective epoxide ring-opening reaction of **67** with various nucleophiles, an initial attempt was made to open the epoxide ring in **67** with cyclohexylamine **45b** in the presence of lithium bromide (LiBr).[238] However, a mixture of inseparable products was observed from this reaction (Scheme 66a). ^{1}H NMR and mass analysis of this mixture of inseparable products and a crude reaction

mixture suggests the presence of conjugate-addition product **96b** in the mixture. Such conjugate addition of secondary amines to withaferin A has been reported.[239] Similar epoxide ring-opening reaction of **67** with iodine (I_2) in the presence of thiophenol (PhSH)[240] provided a complex mixture of impurities/byproducts and unreacted **67** (Scheme 66b). The possibility of the conjugate addition of thiophenol to enone also exists in this case. On the other hand, the Baylis–Hilman reaction of **67** with benzaldehyde in the presence of DMAP failed to give any product **98** (Scheme 67).

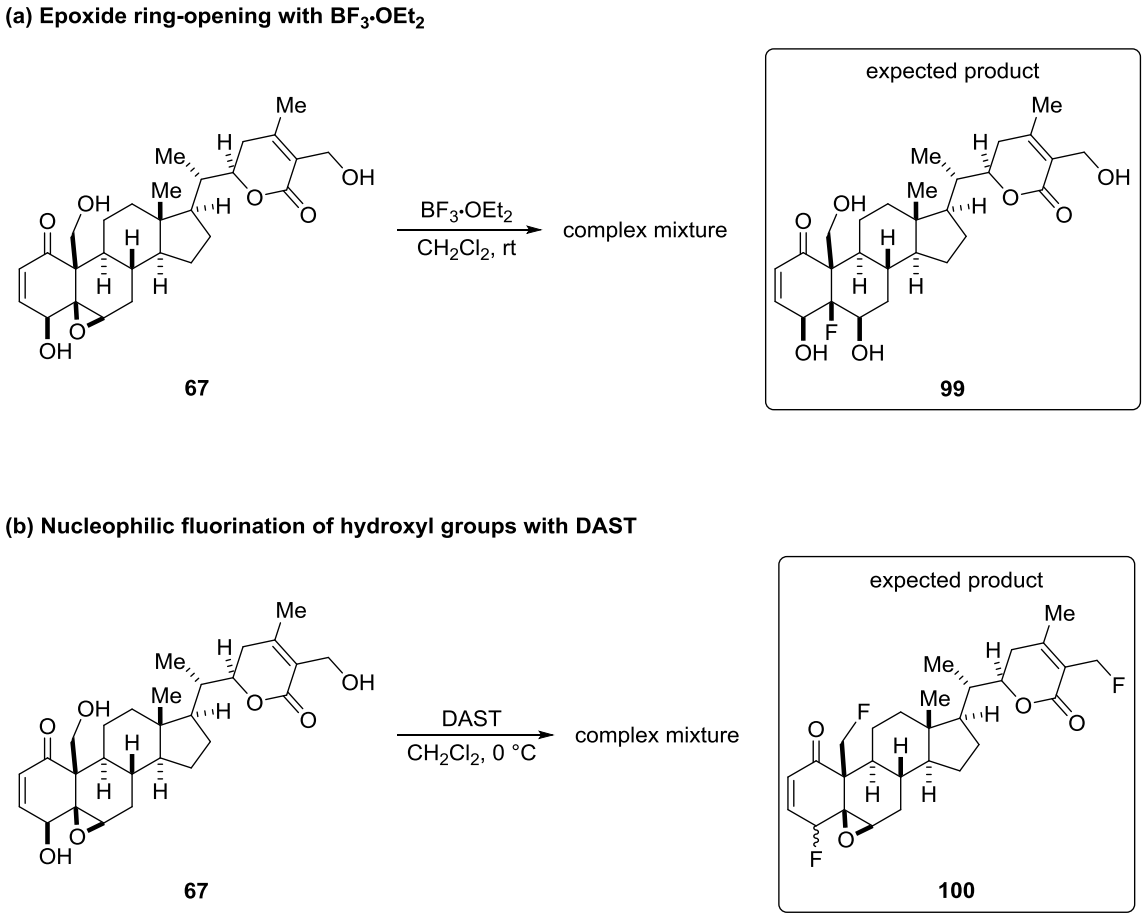
Scheme 67. Unsuccessful Baylis–Hilman Reaction of 67



67 **98** (not observed)

Incorporation of fluorine into a molecule can have a dramatic effect on the pharmacokinetic properties of the molecule such as increase in lipophilicity.[241] Also, the substitution of a hydrogen or hydroxyl group for a fluorine can have a dramatic effect on the potency of the compound through conformational changes.[241] Hence, we tried to introduce fluorine in **67** either through epoxide ring-opening or nucleophilic fluorination of alcohols to obtain analogues **99** or **100**, respectively (Scheme 68). The epoxide ring-opening reaction of **67** with $BF_3{\cdot}OEt_2$ led to a complex mixture and an incomplete reaction.[242] Similarly, the nucleophilic fluorination of hydroxyl groups in **67** with DAST led to a complex mixture.[243]

Scheme 68. Unsuccessful Attempts to Incorporate Fluorine in 67

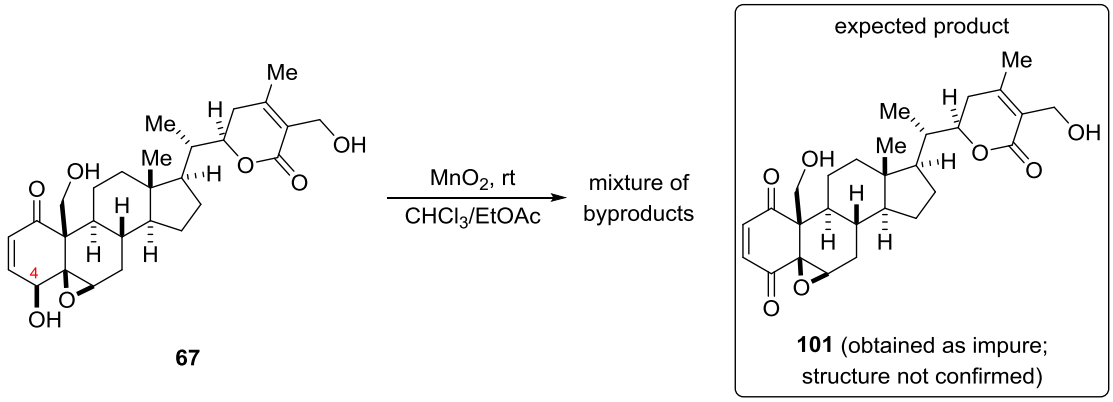


Oxidation of primary and secondary alcohols of **67** to aldehydes and ketone can provide a handle for additional chemical manipulations in order to access useful analogues (Scheme 69). Initially, we followed the reported allylic oxidation of C-4 alcohol with activated manganese(IV) oxide (MnO_2)[244] on withalongolide A **67** (Scheme 69a). Unfortunately, the reaction afforded a mixture of products from which a very small amount (ca. 1 mg) of an impure sample of 1,4-dione product **101** was obtained (^{1}H NMR and mass analysis of the impure sample showed the presence of **101**). The quantity of **101** was not enough to obtain complete spectroscopic data and determine the structure conclusively. Changing the oxidation conditions to manganese(III) acetate and DDQ[245] showed no

apparent formation of **101** by TLC analysis (Scheme 69b). Using a harsh oxidant like PDC led to decomposition and formation of a complex mixture (Scheme 69c).

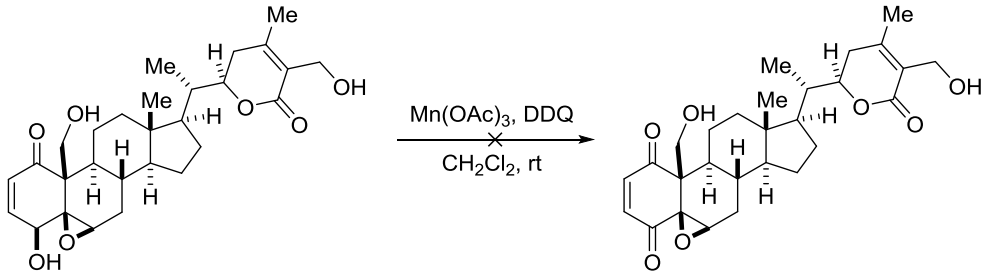
Scheme 69. Unsuccessful Oxidation Reactions of 67

(a) Allylic oxidation with MnO_2



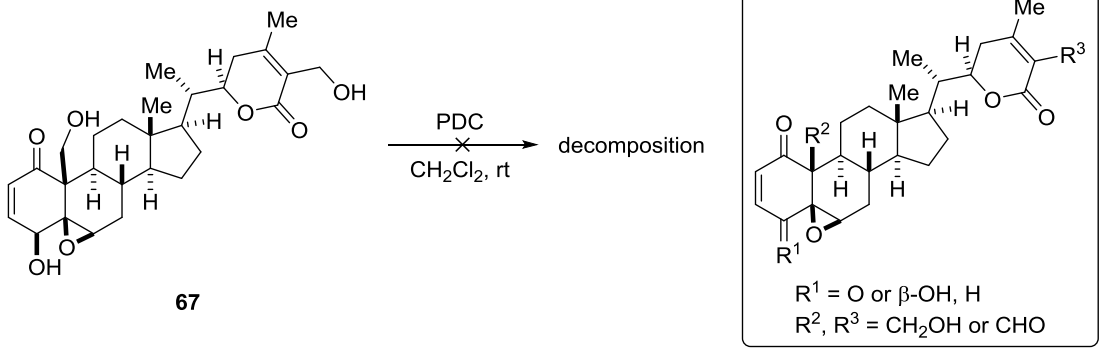
67

(b) Allylic oxidation with $Mn(OAc)_3$ and DDQ



67 **101** (not observed)

(c) Oxidation with pyridinium dichromate (PDC)



67

Cytotoxic Evaluation (carried out in the laboratory of Dr. Mark Cohen)

All synthesized analogues of **67**, along with **66** as a positive control were tested for their cytotoxic activity against four cancer cell lines: head and neck squamous cell carcinoma (HNSCC, JMAR), breast cancer cells (MDA-MB-231), melanoma (SKMEL-28), and colon cancer cells (DRO81-1), in addition to normal fetal lung fibroblast (MRC-5) cells (Table 20). Compound **67** was less potent than **66**, as previously reported.[223a] Acetylation of **67** resulted in more potent analogues with diacetates (**71** and **72**) and triacetate **73** exhibiting enhanced cytotoxic activity than the monoacetylated analogues (**68**, **69**, and **70**). Notably, diacetate **72** was found to be selectively cytotoxic towards DRO81-1 with an IC_{50} value of 0.0580 μM.[223a] The tripropionylated analogue **74** was also active with IC_{50} values in the range of 0.130–1.00 μM. The increased cytotoxic potency of the di- and triacetate analogues of **67** could be due to increased lipophilicity leading to enhanced cell permeability.[225,246]

Although the mono-*p*-chlorobenzoylated derivative **75** and C-19,27-dibenzoylated analogue **76** were active, the C-4,27-dibenzoylated analogue **77** and tribenzoylated compound **78** were not (Table 20). Compounds **80** and **81** exhibited higher cytotoxic activity than **67**, with compound **81** displaying 3–5 times increased cytotoxicity against breast cancer and melanoma cells compared to **66**. Compound **81** also demonstrated modest selectivity towards DRO81-1 cells with an IC_{50} value of 0.0865 μM, similar to analogue **72**.

Jaborosalactone V diacetate **85** was found to be equipotent to **66**, suggesting that C-4 hydroxyl group is not crucial for activity (Table 20).[212b,c] Compound **87**, containing a 5α,6β-chlorohydrin, was slightly less potent than the 5β,6β-epoxy analogue **85**, with IC_{50} values in the range of 0.800–2.16 μM against melanoma and carcinoma cells. The cytotoxic activity was abolished in epoxide-lacking analogues **86** and **88**.[212b,c]

Table 20. Cytotoxicity Activity (IC_{50} Values in μM) of Withalongolide A Analogues against Five Cell Lines[a]

compd	JMAR	MDA-MB-231	SKMEL-28	DRO81-1	MRC-5
66	1.00	0.540	1.00	0.780	2.70
67	3.10	1.50	1.60	1.70	5.30
68	1.22	0.415	0.705	1.05	2.30
69	3.06	1.15	1.23	0.780	1.80
70	2.48	0.890	1.22	0.570	1.20
71	0.515	0.205	0.230	0.155	0.490
72	0.600	0.635	0.170	**0.0580**	0.295
73	0.655	0.655	0.110	0.110	0.310
74	1.00	0.365	0.285	0.130	0.615
75	1.72	1.40	2.25	1.85	2.55
76	4.64	2.62	1.11	1.90	2.35
77	>10	>10	>10	>10	>10
78	>10	>10	>10	>10	>10
79	>10	>10	>10	>10	>10
80	2.09	0.610	0.515	0.585	1.75
81	0.970	0.175	0.205	**0.0865**	0.510
85	1.22	0.790	0.710	1.10	2.05
86	>10	>10	>10	>10	>10
87	2.16	0.800	1.17	1.35	3.15
88	>10	>10	>10	>10	>10
89	>10	>10	9.11	5.25	9.10
90	0.830	0.210	0.275	0.115	0.475
92	1.44	0.625	0.470	0.580	0.865
93	0.965	0.245	0.205	0.225	0.360

[a]Analogues **77**, **78**, **79**, **86**, and **88** were inactive with $IC_{50} \geq 10$ μM for all cell lines tested.

Even though the 2-iodoenone analogue **90** displayed comparable cytotoxicity to its parent compound **73**, compound **89** showed very weak activity compared to **67** (Table 20). Interestingly, macrocycle **93** exhibited increased potency compared to its acyclic analogue **92** across all cell lines tested with IC_{50} values in the range of 0.205–0.965 μM.[234] Most of the active analogues were moderately selective towards cancer cells compared to normal fibroblast cells.

3.3 Conclusions

Our initial goal to synthesize complex and varied derivatives of withalongolide A **67** proved challenging as the highly oxygenated, intricate steroidal framework was vulnerable to various chemistries. This prevented us from attaining the synthesis of several designed analogues. However, in our efforts to contribute toward the development of anticancer-related therapeutics, we accessed a series of cytotoxic agents based on the natural product **67** through the developed chemistry. Overall, we prepared 20 new semisynthetic analogues of this fascinating class of cytotoxic agents and evaluated their cytotoxic activity. Many of these analogues were more potent than the parent compound and the SAR profile was in good agreement with those previously reported for withanolides having similar structures.[212,225] The selectivity of analogues **72** and **81** towards colon cancer cells (DRO81-1) is intriguing and further efforts are underway to study these analogues as potential anticancer agents.

3.4 Experimental Section

General Information. All reactions were performed under nitrogen atmosphere either in capped vials or oven-dried glassware. All chemicals were used as received from commercial source without further purification. Commercial anhydrous pyridine was used. Methylene chloride, ACN, and THF were dried by passage through neutral alumina columns using a commercial solvent purification system prior to use. TLC was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Preparative TLC was carried out using glass-backed TLC plates (silica gel GF with UV 254 nm, 1000 microns). Pasteur pipette with a cotton plug or SPE phase separator tabless (6 mL) was used for filtration/elution during preparative TLC purification. Visualization was accomplished with UV light and Seebach's stain or aqueous $KMnO_4$ by heating. Flash chromatography was either carried out on a standard grade silica gel (40–63 μm particle size, 230 × 400 mesh) with compressed nitrogen as a source of positive pressure or on a CombiFlash Rf system using a 4 g normal-phase silica flash column. IR spectra were acquired as thin films or solids. All NMR spectra (^{1}H, ^{13}C, APT, COSY, HSQC, HMBC, and NOESY) were recorded on either a 400 MHz or a 500 MHz with a dual carbon/proton cryoprobe instrument. All NMR samples were recorded in $CDCl_3$ that was passed through basic alumina. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent (δ 7.26 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR). Coupling constants are given in Hertz (Hz). HRMS data were collected with a LCT Premier time-of-flight mass spectrometer and an electrospray ion source. Reaction mixtures were concentrated under nitrogen gas using a sample concentrator. Melting points were determined in open capillary tubes either using a semi-automated or an automated melting point apparatus, were taken on solids rather than crystals, and were uncorrected. Single-

crystal X-ray analyses were performed using Cu Kα radiation (λ = 1.54178 Å) with either Bruker APEX2 or Platinum 135 CCD detector. X-rays were provided by a Bruker MicroStar microfocus rotating anode equipped with Helios multilayer optics.

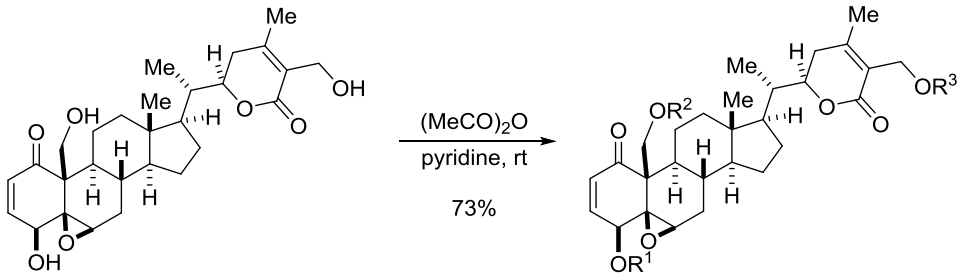
Cytotoxicity Assay. Cell viability was determined by a colorimetric CellTiter96® AQueous 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) cell proliferation assay (Promega) to manufacturer′s specifications. In brief, each compound was dissolved in DMSO and serially diluted in media. Cells were seeded in 90 μL of media in 96-well microtiter plates at 1×10^3 cells/well save for MRC5 (3×10^3 cells/well) and incubated overnight. Treatment was carried out in triplicate by the addition of 10 μL/well of the serial dilutions for a final drug concentration range of 0.039–10 μM plus control and incubated for 72 hours. 20 μL of MTS reagent was added to each well, incubated at 37 °C for approximately 1.5 hours, and then read at a wavelength of 490 nm on a BioTek Synergy 2 plate reader. Values were normalized to media alone for the lower limit and untreated cells for the upper limit.

Cell Culture. The colon cancer cell line DRO81-1 was a gift from Dr. G. Juillard (University of California, Los Angeles, CA) and was propagated in Roswell Park Memorial Institute media (RPMI 1640) supplemented with 10% heat-inactivated fetal bovine serum (FBS), 1% L-glutamine, 1% penicillin/streptomycin, 1X Hyclone MEM-vitamin solution, 1X MEM non-essential amino acid solution, and 0.11 mg/mL sodium pyruvate. The HNSCC cell lines JMAR was a gift from Dr. Jeffrey Myers (University of Texas, M.D. Anderson Cancer Center, Houston, TX). The breast cancer cell line MDA-MB-231 along with the human melanoma cell line SKMEL-28 and the fetal fibroblast cell line MRC-5

were purchased via ATCC (Manassas, VA). JMAR and MRC5 cell lines were propagated with Dulbecco′s Modified Eagle′s Media (DMEM) and supplemented with 10% heat-inactivated fetal bovine serum, 1% L-glutamine, 1% penicillin/streptomycin, 1X MEM-vitamin solution, and 1X MEM non-essential amino acid solution. The remaining cell lines were grown in similar DMEM but with 5% heat-inactivated FBS. All cell lines were expanded in T-75 flasks and incubated in a humidified environment containing 5% CO_2 at 37 °C. Cells were harvested for the cytotoxicity assay when they were approximately 80% confluent.

Experimental Procedures

The extraction and isolation of withalongolide A **67** is already described.[223] Synthesized compounds were named based on the nomenclature system used for withanolides in the literature.[212a,b,225,231a,247]



67

68; $R^1 = R^2 = H$, $R^3 = Ac$ (25%)
69; $R^1 = R^3 = H$, $R^2 = Ac$ (8%)
70; $R^1 = Ac$, $R^2 = R^3 = H$ (12%)
71; $R^1 = H$, $R^2 = R^3 = Ac$ (11%)
72; $R^1 = R^3 = Ac$, $R^2 = H$ (17%)

(4*S*,20*S*,22*R*)-27-Acetyloxy-4*β*,19-dihydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 27-acetate 68), (4*S*,20*S*,22*R*)-19-Acetyloxy-4*β*,27-dihydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 19-acetate 69), (4*S*,20*S*,22*R*)-4*β*-Acetyloxy-19,27-dihydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 4-acetate 70), (4*S*,20*S*,22*R*)-19,27-Diacetyloxy-4*β*-hydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 19,27-diacetate 71), and (4*S*,20*S*,22*R*)-4*β*,27-Diacetyloxy-19-hydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 4,27-diacetate 72; Scheme 55).[223a] To a vial flushed with nitrogen gas at rt was added withalongolide A **67** (60.0 mg, 0.123 mmol, 1.0 equiv), pyridine (0.40 mL), and acetic anhydride (13.8 mg, 0.135 mmol, 1.1 equiv). The vial was capped and the reaction mixture was stirred at rt for 2 h after which an additional amount of acetic anhydride (13.8 mg, 0.135 mmol, 1.1 equiv) was added and stirring was continued for another 1 h. The reaction mixture was quenched with ethanol and volatile residues were removed under reduced pressure. The crude pale yellow residue obtained was dissolved in CH_2Cl_2 and was subjected to preparative TLC purification developing four times with 3% MeOH/CH_2Cl_2. Bands corresponding to products were scraped from the plate and eluted with 6% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Evaporation of solvents under reduced pressure provided impure products, which were further subjected to

similar but separate preparative TLC purifications developing two to four times with 2.5% MeOH/CH_2Cl_2 for each product. Subsequent evaporation of solvents afforded **68** (16.0 mg, 25%; colorless solid), **69** (5.0 mg, 8%; colorless oil), **70** (8.0 mg, 12%; colorless solid), **71** (8.0 mg, 11%; colorless oil), and **72** (12.0 mg, 17%; pale yellow solid). Withalongolide A **67** (10.0 mg, 17%) was recovered during the initial preparative TLC purification.

Withalongolide A 27-acetate **68**: R_f = 0.37 (4% MeOH/CH_2Cl_2, run twice); mp 184–188 °C; IR (neat) 3330 (br), 2940, 1736, 1706, 1677, 1380, 1232, 1026, 910, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.84–1.00 (m, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.02–1.16 (m, 3H), 1.29–1.44 (m, 3H), 1.49–1.56 (m, 1H), 1.58–1.71 (m, 2H), 1.77 (br s, 1H), 1.92–2.02 (m, 4H), 2.04 (s, 3H), 2.05 (s, 3H), 2.18–2.22 (m, 1H), 2.50 (dd, J = 17.7, 13.3 Hz, 1H), 3.25 (s, 1H), 3.64 (d, J = 6.0 Hz, 1H), 3.77 (d, J = 9.7 Hz, 1H), 4.32 (d, J = 9.7 Hz, 1H), 4.38 (dt, J = 13.2, 3.4 Hz, 1H), 4.84 (1/2 AB, J = 11.8 Hz, 1H), 4.88 (1/2 AB, J = 11.9 Hz, 1H), 6.23 (d, J = 10.0 Hz, 1H), 7.01 (dd, J = 10.0, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 13.5, 20.8, 21.1, 22.2, 24.3, 27.4, 30.2, 30.5, 31.2, 38.9, 39.7, 42.6, 44.0, 52.0, 54.3, 56.8, 58.1, 61.7, 62.00, 62.01, 68.4, 78.3, 122.0, 133.0, 145.3, 157.2, 165.5, 171.1, 200.2; HRMS (ESI) *m/z* calcd for $C_{30}H_{40}O_8Na$ $[M + Na]^+$ 551.2621, found 551.2625.

Withalongolide A 19-acetate **69**: R_f = 0.40 (4% MeOH/CH_2Cl_2, run twice); IR (neat) 3444 (br), 2939, 1736, 1687, 1396, 1233, 1042, 913, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.73 (s, 3H), 0.86–0.92 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.98–1.03 (m, 1H), 1.05–1.17 (m, 3H), 1.26–1.39 (m, 2H), 1.52–1.71 (m, 4H), 1.95–2.02 (m, 4H), 2.03 (s, 3H), 2.08 (s, 3H), 2.16–2.21 (m, 1H), 2.49 (dd, J = 17.3, 13.5 Hz, 1H), 2.85 (br s, 1H), 3.15 (s, 1H), 3.49 (br s, 1H), 3.71 (d, J = 6.0 Hz, 1H), 4.21 (d, J = 10.9 Hz, 1H), 4.32–4.43 (m, 3H), 5.04 (d, J = 11.0 Hz, 1H), 6.23 (d, J = 10.0 Hz, 1H), 7.05 (dd, J = 10.0, 6.0 Hz, 1H); ^{13}C

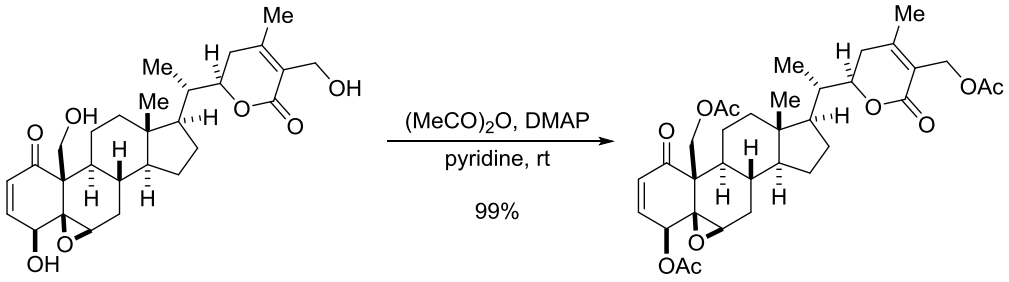
NMR (125 MHz, $CDCl_3$) δ 11.8, 13.5, 20.2, 21.2, 22.3, 24.4, 27.4, 30.0, 30.7, 31.1, 38.9, 39.6, 42.7, 44.4, 51.4, 52.0, 56.7, 57.6, 60.7, 61.4, 64.2, 69.4, 78.8, 125.9, 132.4, 144.8, 152.9, 167.1, 170.6, 198.4; HRMS (ESI) *m/z* calcd for $C_{30}H_{40}O_8Na$ $[M + Na]^+$ 551.2621, found 551.2629.

Withalongolide A 4-acetate **70**: R_f = 0.47 (4% MeOH/CH_2Cl_2, run twice); mp 185–189 °C; IR (neat) 3524 (br), 2940, 1743, 1696, 1686, 1396, 1229, 1018, 916, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (s, 3H), 0.82–0.96 (m, 2H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.04–1.18 (m, 3H), 1.27–1.41 (m, 2H), 1.57–1.70 (m, 2H), 1.82–1.91 (m, 2H), 1.95–2.02 (m, 4H), 2.02 (s, 3H), 2.09 (s, 3H), 2.16–2.21 (m, 1H), 2.48 (dd, *J* = 17.3, 13.5 Hz, 1H), 2.87 (dd, *J* = 10.0, 2.8 Hz, 2H), 3.22 (s, 1H), 4.10 (t, *J* = 10.9 Hz, 1H), 4.32–4.43 (m, 4H), 4.75 (d, *J* = 6.0 Hz, 1H), 6.24 (d, *J* = 9.9 Hz, 1H), 7.03 (dd, *J* = 9.9, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 13.5, 20.2, 21.0, 21.9, 24.3, 27.5, 30.0, 30.4, 31.4, 38.9, 39.7, 43.0, 44.6, 52.0, 52.2, 57.0, 57.6, 59.8, 61.1, 65.6, 71.7, 78.9, 125.9, 134.4, 140.1, 152.9, 167.1, 170.0, 198.8; HRMS (ESI) *m/z* calcd for $C_{30}H_{40}O_8Na$ $[M + Na]^+$ 551.2621, found 551.2620.

Withalongolide A 19,27-diacetate **71**: R_f = 0.57 (4% MeOH/CH_2Cl_2, run twice); IR (neat) 3448 (br), 2940, 1736, 1710, 1678, 1380, 1232, 1033, 915, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.73 (s, 3H), 0.86–0.93 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.99–1.19 (m, 4H), 1.26–1.40 (m, 2H), 1.52–1.73 (m, 4H), 1.96–2.03 (m, 4H), 2.05 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.16–2.21 (m, 1H), 2.51 (dd, *J* = 17.6, 13.3 Hz, 1H), 3.15 (s, 1H), 3.49 (d, *J* = 4.9 Hz, 1H), 3.70 (t, *J* = 5.2 Hz, 1H), 4.21 (d, *J* = 10.9 Hz, 1H), 4.40 (dt, *J* = 13.2, 3.4 Hz, 1H), 4.86 (1/2 AB, *J* = 11.8 Hz, 1H), 4.89 (1/2 AB, *J* = 11.8 Hz, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 6.23 (d, *J* = 10.0 Hz, 1H), 7.05 (dd, *J* = 10.0, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 13.5, 20.8, 21.1, 21.2, 22.3, 24.3, 27.4, 30.3, 30.7, 31.1, 38.9, 39.6, 42.7, 44.4, 51.4, 52.0, 56.7, 58.2, 60.7, 61.4, 64.2, 69.4, 78.3, 122.1, 132.3, 144.8, 157.1, 165.4,

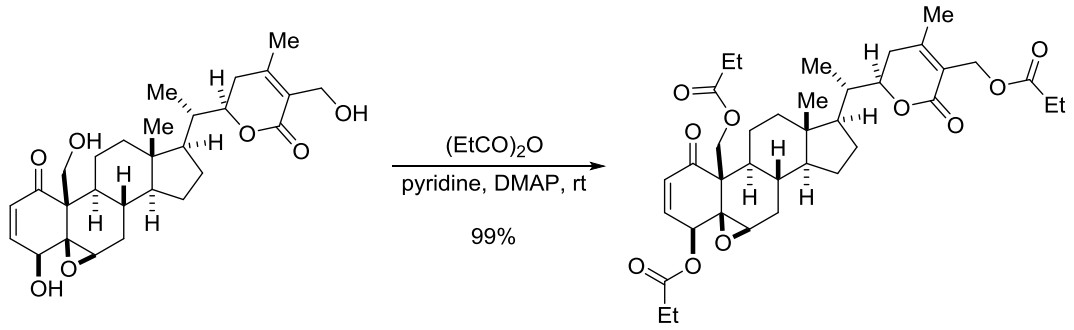
170.6, 171.1, 198.4; HRMS (ESI) *m/z* calcd for $C_{32}H_{42}O_9Na$ $[M + Na]^+$ 593.2727, found 593.2726.

Withalongolide A 4,27-diacetate **72**: R_f = 0.70 (4% MeOH/CH_2Cl_2, run twice); mp 202–205 °C.



67 73

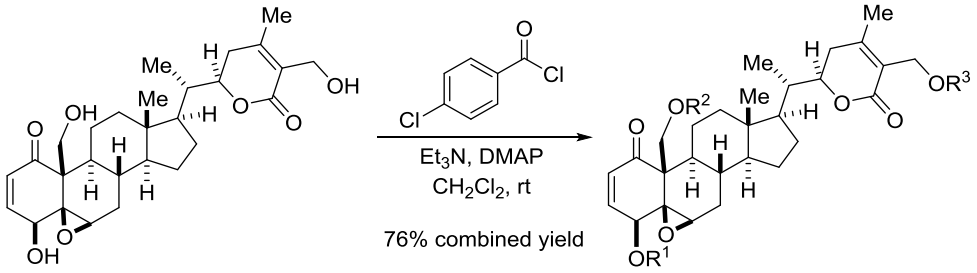
(4*S*,20*S*,22*R*)-4*β*,19,27-Triacetyloxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 4,19,27-triacetate 73; Scheme 55).[223a] A solution of withalongolide A **67** (300 mg, 0.617 mmol, 1.0 equiv), pyridine (3.0 mL), acetic anhydride (3.0 mL), and DMAP (15.1 mg, 0.123 mmol, 0.2 equiv) was stirred at rt under argon atmosphere for 2 h. The reaction mixture was quenched with ethanol and volatile residues were removed under reduced pressure. The crude yellow oil was purified by chromatography on a silica gel (1.0% MeOH/CH_2Cl_2) and the semisolid residue obtained was triturated with a hexanes:ether mixture. Vacuum filtration and drying afforded **73** as a creamish solid (375 mg, 99%). Withalongolide A 4,19,27-triacetate **73**: R_f = 0.71 (4% MeOH/CH_2Cl_2, run twice).



67 **74**

(4*S*,20*S*,22*R*)-4*β*,19,27-Tripropionyloxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 4,19,27-tripropionate 74; Scheme 55). A solution of withalongolide A **67** (4.5 mg, 0.00926 mmol, 1.0 equiv), pyridine (0.050 mL), propionic anhydride (0.020 mL), and a small pellet of DMAP (ca. 1–2 mg) was stirred at rt under nitrogen atmosphere for 2 h. The reaction mixture was quenched with ethanol and volatile residues were removed under reduced pressure. The crude pale yellow residue obtained was purified by preparative TLC developing two times with 2% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **74** as a colorless semisolid (6.0 mg, 99%). Withalongolide A 4,19,27-tripropionate **74**: R_f = 0.38 (2% MeOH/CH_2Cl_2); IR (neat) 2978, 2942, 1736, 1710, 1677, 1462, 1349, 1179, 1082, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (s, 3H), 0.85–0.92 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H), 1.01–1.06 (m, 1H), 1.08–1.19 (m, 11H), 1.23–1.28 (m, 2H), 1.35–1.42 (m, 1H), 1.60–1.73 (m, 3H), 1.78–1.85 (m, 1H), 1.97–2.03 (m, 4H), 2.07 (s, 3H), 2.13–2.17 (m, 1H), 2.29–2.47 (m, 6H), 2.51 (dd, J = 17.8, 13.4 Hz, 1H), 3.13 (s, 1H), 4.36–4.42 (m, 2H), 4.81 (d, J = 5.9 Hz, 1H), 4.87 (1/2 AB, J = 11.8 Hz, 1H), 4.90 (1/2 AB, J = 11.9 Hz, 1H), 5.10 (d, J = 11.6 Hz, 1H), 6.23 (d, J = 9.9 Hz, 1H), 7.02 (dd, J = 9.9, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1, 9.21, 9.28, 11.8, 13.5, 20.8, 22.5, 24.4, 27.50, 27.54, 27.6, 27.9, 30.3, 30.9, 31.0, 39.0, 39.6, 42.9, 44.9, 51.1, 52.0, 56.6, 58.1, 59.1, 59.5, 64.4, 71.1, 78.3, 122.2, 133.4, 141.1, 157.0, 165.4,

173.9, 174.0, 174.5, 198.4; HRMS (ESI) *m/z* calcd for $C_{37}H_{51}O_{10}$ $[M + H]^+$ 655.3482, found 655.3494.



67

75; R^1 = *p*-ClBz, R^2 = R^3 = H (10%)
76; R^1 = H, R^2 = R^3 = *p*-ClBz (5%)
77; R^1 = R^3 = *p*-ClBz, R^2 = H (51%)
78; R^1 = R^2 = R^3 = *p*-ClBz (10%)

(4*S*,20*S*,22*R*)-4*β*-*p*-Chlorobenzoyloxy-19,27-dihydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 4-*p*-chlorobenzoate 75), (4*S*,20*S*,22*R*)-19,27-Di-*p*-chlorobenzoyloxy-4*β*-hydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 19,27-di-*p*-chlorobenzoate 76), (4*S*,20*S*,22*R*)-4*β*,27-Di-*p*-chlorobenzoyloxy-19-hydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 4*β*,27-di-*p*-chlorobenzoate 77), and (4*S*,20*S*,22*R*)-4*β*,19,27-Tri-*p*-chlorobenzoyloxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 4,19,27-tri-*p*-chlorobenzoate 78; Scheme 57). To a solution of withalongolide A **67** (60.0 mg, 0.123 mmol, 1.0 equiv), Et_3N (0.50 mL), and DMAP (15.1 mg, 0.123 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) at rt under nitrogen atmosphere was added *p*-chlorobenzoyl chloride (32.3 mg, 0.185 mmol, 1.5 equiv), and the reaction mixture was stirred for 0.5 h after which an additional amount of *p*-chlorobenzoyl chloride (10.8 mg, 0.0617 mmol, 0.5 equiv) was added and stirring was continued for another 0.5 h. Volatile residues were removed under reduced pressure. The crude pale yellow residue obtained was dissolved in 4% MeOH/CH_2Cl_2 and was subjected to preparative TLC purification developing one time with 2% MeOH/CH_2Cl_2. Bands

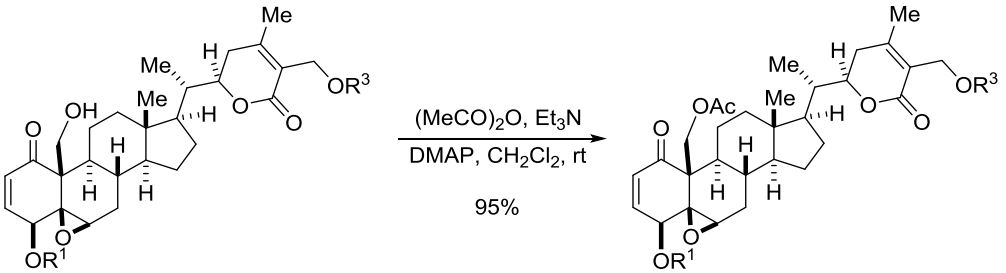
corresponding to products were scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Evaporation of solvents provided impure products **75**, **76**, **77**, and **78**. Impure products (**75**, **76**, and **78**) were further subjected to separate preparative TLC purifications developing one time (for **78**) to six times (for **75** and **76**) with 1% MeOH/CH_2Cl_2 for each product. Bands corresponding to products were scraped from the plate and eluted with 2–7% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Subsequent evaporation of solvents afforded **75** (7.7 mg, 10%; colorless solid), **76** (5.0 mg, 5%; off-white semisolid), and **78** (11.0 mg, 10%; off-white solid). Impure product **77** was triturated with ether twice to remove grease impurities. The ether layers were decanted to afford a sample of pure **77** as a colorless solid after drying under vacuum (48.0 mg, 51%). Withalongolide A 4-*p*-chlorobenzoate **75**: R_f = 0.37 (2% MeOH/CH_2Cl_2); mp >250 °C (dec.); IR (neat) 3587, 3541, 2933, 2869, 1719, 1706, 1684, 1593, 1397, 1266, 1092, 1012, 907, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (s, 3H), 0.86–0.92 (m, 1H), 0.97–1.06 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 1.08–1.19 (m, 3H), 1.32–1.42 (m, 2H), 1.58–1.71 (m, 2H), 1.85–1.93 (m, 2H), 1.95–2.03 (m, 4H), 2.03 (s, 3H), 2.19–2.24 (m, 1H), 2.50 (dd, J = 17.3, 13.5 Hz, 1H), 2.85 (br s, 1H), 2.92 (dd, J = 10.2, 2.4 Hz, 1H), 3.31 (s, 1H), 4.18 (t, J = 10.9 Hz, 1H), 4.32–4.41 (m, 2H), 4.42 (dt, J = 13.3, 3.4 Hz, 1H), 4.52 (dd, J = 11.5, 1.8 Hz, 1H), 5.04 (d, J = 6.0 Hz, 1H), 6.30 (d, J = 9.9 Hz, 1H), 7.13 (dd, J = 9.8, 6.0 Hz, 1H), 7.41–7.44 (m, 2H), 7.90–7.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 13.5, 20.2, 22.1, 24.3, 27.5, 30.0, 30.4, 31.5, 39.0, 39.7, 43.1, 44.7, 52.0, 52.4, 57.0, 57.7, 60.0, 61.2, 65.7, 72.3, 78.9, 125.9, 127.6, 129.3, 131.4, 134.7, 140.0, 140.4, 152.9, 165.1, 167.2, 198.9; HRMS (ESI) *m/z* calcd for $C_{35}H_{42}ClO_8$ $[M + H]^+$ 625.2568, found 625.2565.

Withalongolide A 19,27-di-*p*-chlorobenzoate **76**: R_f = 0.40 (2% MeOH/CH_2Cl_2); IR (neat) 3468, 2924, 2861, 1702, 1670, 1594, 1270, 1104, 1014, 908, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.72 (s, 3H), 0.90–0.96 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 1.07–1.21 (m, 4H), 1.25–1.41 (m, 3H), 1.59–1.71 (m, 3H), 2.00–2.06 (m, 3H), 2.10–2.18 (m, 2H), 2.13 (s, 3H), 2.55 (dd, J = 17.7, 13.3 Hz, 1H), 3.15 (s, 1H), 3.31 (br s, 1H), 3.79 (d, J = 5.8 Hz, 1H), 4.41 (dt, J = 13.2, 3.4 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 5.13 (s, 2H), 5.16 (d, J = 11.5 Hz, 1H), 6.24 (d, J = 10.0 Hz, 1H), 7.04 (dd, J = 10.0, 5.8 Hz, 1H), 7.37–7.42 (m, 4H), 7.94–7.99 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 13.5, 20.9, 23.0, 24.3, 27.4, 30.4, 30.9, 31.0, 39.0, 39.6, 42.8, 44.7, 51.2, 52.1, 56.6, 58.8, 60.6, 61.8, 65.4, 69.6, 78.3, 122.1, 128.61, 128.64, 128.9, 129.0, 131.32, 131.36, 132.0, 139.7, 139.8, 144.2, 157.4, 165.4, 165.8, 166.0, 198.7; HRMS (ESI) *m/z* calcd for $C_{42}H_{45}Cl_2O_9$ $[M + H]^+$ 763.2441, found 763.2443.

Withalongolide A 4β,27-di-*p*-chlorobenzoate **77**: R_f = 0.65 (2% MeOH/CH_2Cl_2); mp >250 °C; IR (neat) 3573, 2968, 2941, 1710, 1673, 1591, 1398, 1263, 1080, 1047, 1013, 906, 757, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.76 (s, 3H), 0.85–0.91 (m, 1H), 0.99–1.04 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 1.06–1.18 (m, 3H), 1.31–1.42 (m, 2H), 1.57–1.72 (m, 2H), 1.84–1.92 (m, 2H), 1.97–2.06 (m, 4H), 2.12 (s, 3H), 2.18–2.22 (m, 1H), 2.54 (dd, J = 17.7, 13.3 Hz, 1H), 2.92 (dd, J = 10.4, 3.0 Hz, 1H), 3.31 (s, 1H), 4.17 (t, J = 11.0 Hz, 1H), 4.41 (dt, J = 13.2, 3.4 Hz, 1H), 4.51 (dd, J = 11.6, 3.0 Hz, 1H), 5.03 (d, J = 6.0 Hz, 1H), 5.12 (s, 2H), 6.29 (d, J = 9.9 Hz, 1H), 7.12 (dd, J = 9.9, 6.0 Hz, 1H), 7.36–7.39 (m, 2H), 7.40–7.42 (m, 2H), 7.89–7.92 (m, 2H), 7.93–7.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 13.5, 20.9, 22.0, 24.3, 27.5, 30.36, 30.39, 31.4, 38.9, 39.6, 43.0, 44.6, 52.0, 52.3, 56.9, 58.8, 60.0, 61.1, 65.6, 72.2, 78.4, 122.0, 127.5, 128.6, 128.8, 129.2, 131.31,

131.34, 134.6, 139.6, 139.9, 140.3, 157.4, 165.0, 165.3, 165.7, 198.8; HRMS (ESI) *m/z* calcd for $C_{42}H_{45}Cl_2O_9$ $[M + H]^+$ 763.2441, found 763.2417.

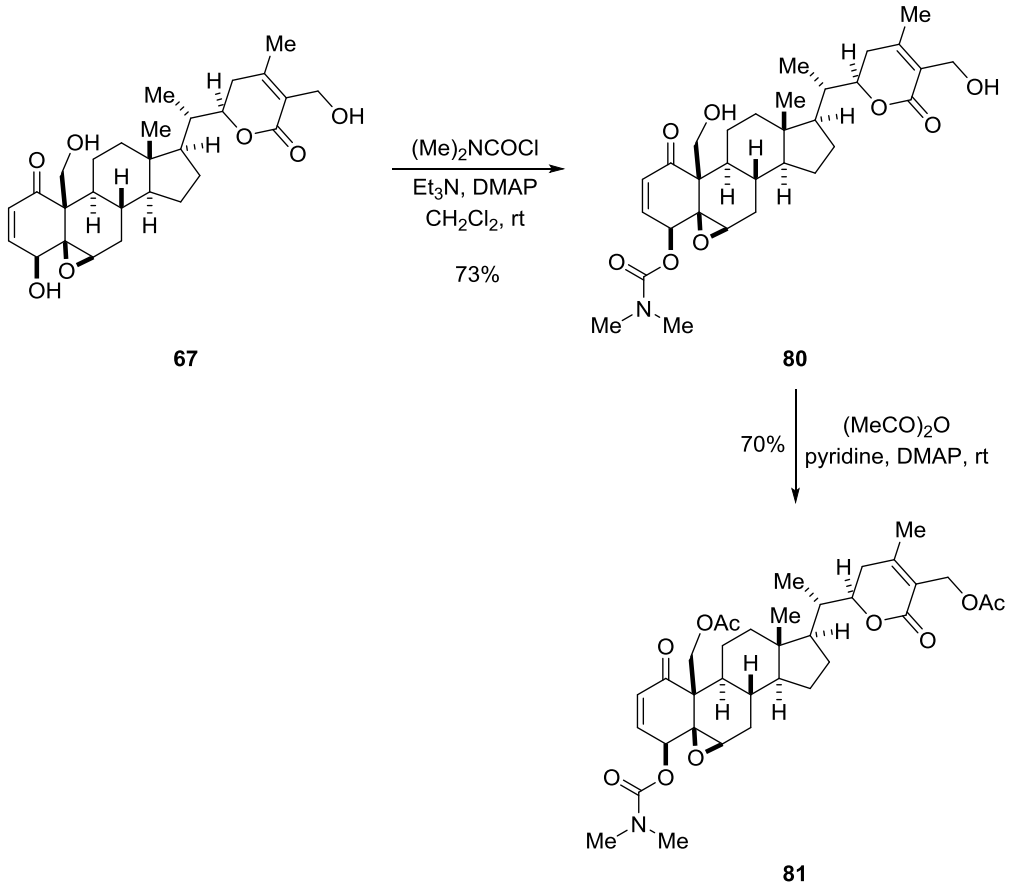
Withalongolide A 4,19,27-tri-*p*-chlorobenzoate **78**: R_f = 0.87 (2% MeOH/CH_2Cl_2); IR (neat) 2942, 1715, 1678, 1593, 1400, 1268, 1091, 1014, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.63 (s, 3H), 0.92–0.98 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 1.07–1.22 (m, 3H), 1.26–1.38 (m, 3H), 1.57–1.73 (m, 3H), 1.80–1.87 (m, 1H), 1.96–2.06 (m, 3H), 2.11–2.16 (m, 1H), 2.13 (s, 3H), 2.19–2.23 (m, 1H), 2.54 (dd, J = 17.7, 13.3 Hz, 1H), 3.30 (d, J = 1.5 Hz, 1H), 4.41 (dt, J = 13.1, 3.4 Hz, 1H), 4.89 (d, J = 11.7 Hz, 1H), 5.04 (d, J = 11.8 Hz, 1H), 5.13 (s, 2H), 5.15 (d, J = 5.7 Hz, 1H), 6.32 (d, J = 10.0 Hz, 1H), 7.13 (dd, J = 10.0, 5.7 Hz, 1H), 7.29–7.32 (m, 2H), 7.34–7.40 (m, 4H), 7.86–7.89 (m, 2H), 7.93–7.96 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 13.5, 20.9, 23.4, 24.4, 27.4, 30.3, 30.9, 31.1, 38.9, 39.6, 42.8, 44.9, 51.3, 52.1, 56.3, 58.8, 59.5, 59.9, 65.7, 71.7, 78.3, 122.1, 127.5, 128.5, 128.6, 128.8, 128.9, 129.0, 131.2, 131.3, 131.4, 133.3, 139.6, 139.8, 140.2, 141.0, 157.4, 165.4, 165.80, 165.85, 198.5; HRMS (ESI) *m/z* calcd for $C_{49}H_{48}Cl_3O_{10}$ $[M + H]^+$ 901.2313, found 901.2291.



77; $R^1 = R^3$ = *p*-ClBz **79**; $R^1 = R^3$ = *p*-ClBz

(4*S*,20*S*,22*R*)-19-Acetyloxy-4*β*,27-di-*p*-chlorobenzoyloxy-5*β*,6*β*-epoxy-1-oxo-witha-2,24-dienolide (withalongolide A 19-acetyloxy-4,27-di-*p*-chlorobenzoate 79; Scheme 57). To a solution of withalongolide A 4*β*,27-di-*p*-chlorobenzoate **77** (15.0 mg, 0.0196 mmol, 1.0 equiv), Et_3N (0.10 mL), and DMAP (ca. 1.0 mg) in CH_2Cl_2 (0.30 mL) at

rt under nitrogen atmosphere was added acetic anhydride (0.10 mL), and the reaction mixture was stirred for 0.5 h. The reaction mixture was quenched with ethanol and volatile residues were removed under reduced pressure. The crude pale yellow residue obtained was purified by preparative TLC developing three times with 1% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Evaporation of solvents afforded **79** as an off-white solid (15.1 mg, 95%). Withalongolide A 19-acetate-4,27-di-*p*-chlorobenzoate **79**: R_f = 0.50 (1% MeOH/CH_2Cl_2, run twice); IR (neat) 2944, 2869, 1717, 1680, 1593, 1400, 1268, 1092, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (s, 3H), 0.87–0.94 (m, 1H), 0.98–1.20 (m, 4H), 1.02 (d, J = 6.6 Hz, 3H), 1.26–1.43 (m, 2H), 1.62–1.73 (m, 3H), 1.86 (m, 1H), 2.01–2.07 (m, 1H), 2.03 (s, 6H), 2.13 (s, 3H), 2.16–2.21 (m, 1H), 2.55 (dd, J = 17.7, 13.3 Hz, 1H), 3.20 (s, 1H), 4.42 (dt, J = 13.1, 3.3 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.97 (d, J = 5.9 Hz, 1H), 5.13 (s, 2H), 5.23 (d, J = 11.7 Hz, 1H), 6.28 (d, J = 9.9 Hz, 1H), 7.16 (dd, J = 9.9, 5.9 Hz, 1H), 7.37–7.40 (m, 2H), 7.41–7.44 (m, 2H), 7.93–7.97 (m, 2H), 8.02–8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 13.5, 20.9, 21.3, 22.3, 24.4, 27.5, 30.4, 30.9, 31.0, 39.0, 39.6, 42.9, 45.0, 51.0, 52.0, 56.5, 58.8, 59.1, 59.5, 64.5, 72.5, 78.4, 122.1, 127.7, 128.6, 128.8, 129.1, 131.3, 131.6, 133.7, 139.6, 140.2, 140.9, 157.3, 165.3, 165.4, 165.7, 170.7, 198.1; HRMS (ESI) *m/z* calcd for $C_{44}H_{47}Cl_2O_{10}$ $[M + H]^+$ 805.2546, found 805.2542.

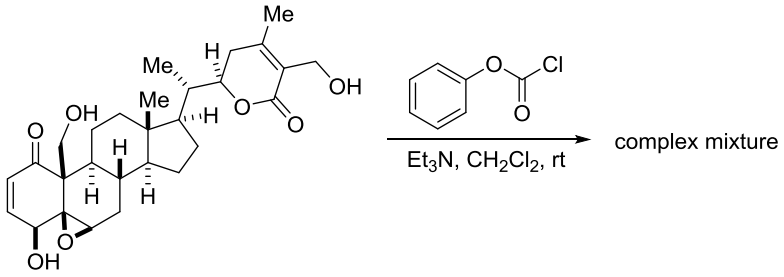


(4*S*,20*S*,22*R*)-4*β*-*N*,*N*-Dimethylcarbamoyloxy-19,27-dihydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 4-dimethylcarbamate 80) and (4*S*,20*S*,22*R*)-19,27-Diacetyloxy-4*β*-*N*,*N*-dimethylcarbamoyloxy-5*β*,6*β*-epoxy-1-oxo-witha-2,24-dienolide (withalongolide A 19,27-diacetyloxy-4-dimethylcarbamate 81; Scheme 58). To a solution of withalongolide A **67** (18.0 mg, 0.0370 mmol, 1.0 equiv), Et_3N (0.10 mL), and a small pellet of DMAP (ca. 1–2 mg) in CH_2Cl_2 (0.40 mL) at 0 °C under nitrogen atmosphere was added dimethylcarbamoyl chloride (0.10 mL). The ice-bath was removed and the reaction mixture was stirred at rt for 20 min. The reaction mixture was concentrated and the crude residue obtained was purified twice by preparative TLC developing two to three times with 3% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 10% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Evaporation of solvents afforded **80** as a colorless oil (15.0

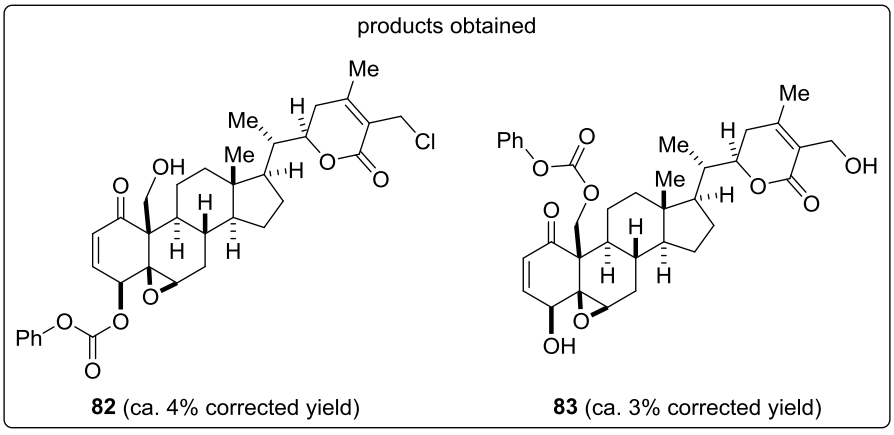
mg, 73%). Withalongolide A 4-dimethylcarbamate **80**: R_f = 0.34 (3% MeOH/CH_2Cl_2); IR (neat) 3511, 2940, 2869, 1698, 1396, 1183, 1048, 909, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (s, 3H), 0.83–0.89 (m, 1H), 0.94–1.00 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.04–1.18 (m, 3H), 1.24–1.40 (m, 2H), 1.57–1.69 (m, 2H), 1.82–1.91 (m, 2H), 1.95–2.02 (m, 4H), 2.02 (s, 3H), 2.15–2.20 (m, 1H), 2.48 (dd, *J* = 17.4, 13.6 Hz, 1H), 2.88–2.96 (m, 2H), 2.89 (s, 3H), 2.91 (s, 3H), 3.24 (s, 1H), 4.10 (t, *J* = 11.0 Hz, 1H), 4.31–4.43 (m, 4H), 4.73 (d, *J* = 5.9 Hz, 1H), 6.21 (d, *J* = 9.9 Hz, 1H), 7.07 (dd, *J* = 9.9, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 13.5, 20.2, 22.1, 24.3, 27.4, 30.0, 30.4, 31.5, 36.3, 36.9, 38.9, 39.7, 43.0, 44.6, 52.0, 52.1, 56.9, 57.6, 59.9, 61.4, 65.6, 72.2, 78.9, 125.8, 133.8, 141.5, 152.9, 155.4, 167.1, 199.2; HRMS (ESI) *m/z* calcd for $C_{31}H_{44}NO_8$ $[M + H]^+$ 558.3067, found 558.3035.

A solution of withalongolide A 4-dimethylcarbamate **80** (7.50 mg, 0.0134 mmol, 1.0 equiv), pyridine (0.30 mL), acetic anhydride (0.30 mL), and a small pellet of DMAP (ca. 1–2 mg) was stirred at rt under nitrogen atmosphere for 1 h. The reaction mixture was concentrated and then quenched with ethanol. The volatile residues were removed under reduced pressure. The pale yellow residue obtained was purified twice by preparative TLC developing two times with 2% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **81** as a colorless waxy solid (6.0 mg, 70%). Withalongolide A 19,27-diacetyloxy-4-dimethylcarbamate **81**: R_f = 0.35 (2% MeOH/CH_2Cl_2, run twice); IR (neat) 2940, 2869, 1738, 1705, 1396, 1229, 1181, 1044, 917, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.76 (s, 3H), 0.86–0.92 (m, 1H), 0.98–1.04 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.06–1.19 (m, 3H), 1.23–1.28 (m, 2H), 1.35–1.42 (m, 1H), 1.60–1.73 (m, 3H), 1.85–1.92 (m, 1H), 1.98–2.04 (m, 3H), 2.05 (s, 3H), 2.07 (s, 6H), 2.14–

2.18 (m, 1H), 2.52 (dd, J = 17.7, 13.3 Hz, 1H), 2.90 (s, 3H), 2.96 (s, 3H), 3.13 (s, 1H), 4.41 (dt, J = 13.2, 3.4 Hz, 1H), 4.44 (d, J = 11.8 Hz, 1H), 4.68 (d, J = 5.9 Hz, 1H), 4.86 (1/2 AB, J = 11.8 Hz, 1H), 4.90 (1/2 AB, J = 11.9 Hz, 1H), 5.11 (d, J = 11.7 Hz, 1H), 6.21 (d, J = 9.9 Hz, 1H), 7.12 (dd, J = 9.9, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 13.5, 20.8, 21.1, 21.3, 22.2, 24.5, 27.5, 30.3, 30.9, 31.1, 36.4, 37.0, 39.0, 39.6, 42.9, 44.9, 50.7, 52.0, 56.5, 58.2, 58.9, 59.7, 64.8, 72.4, 78.3, 122.1, 132.8, 142.6, 155.6, 157.1, 165.5, 170.7, 171.1, 198.4; HRMS (ESI) *m/z* calcd for $C_{35}H_{48}NO_{10}$ $[M + H]^+$ 642.3278, found 642.3259.



67



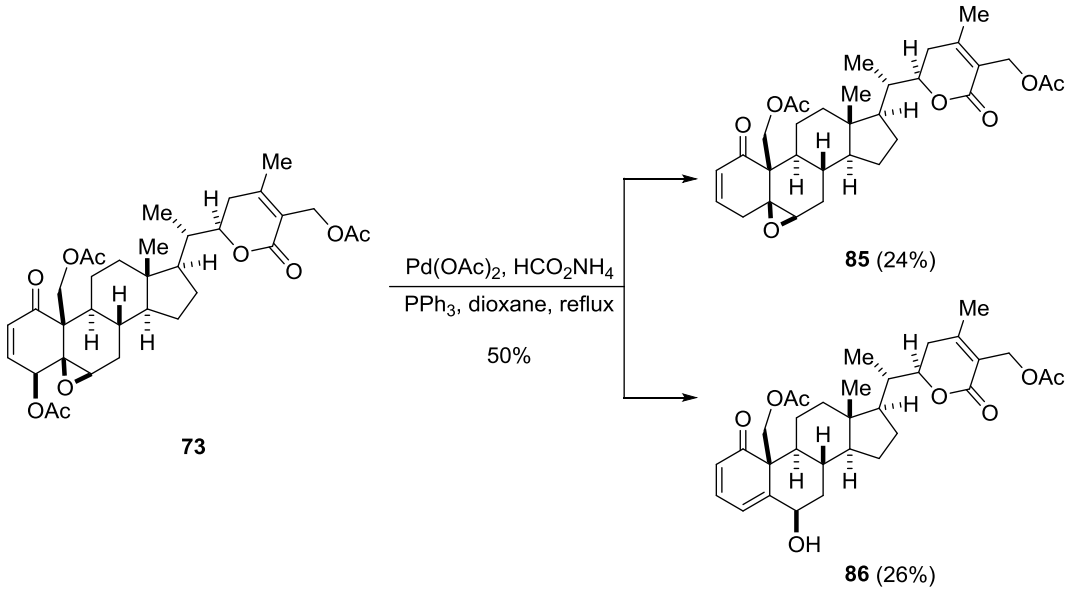
82 (ca. 4% corrected yield) **83** (ca. 3% corrected yield)

(4*S*,20*S*,22*R*)-27-Chloro-19-hydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide-4*β*-phenyl carbonate (withalongolide A 27-chloro-19-hydroxy-4-phenyl carbonate 82) and (4*S*,20*S*,22*R*)-4*β*,27-Dihydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide-19-phenyl carbonate (withalongolide A 4,27-dihydroxy-19-phenyl carbonate 83; Scheme 59). To a solution of withalongolide A **67** (60.0 mg, 0.123 mmol, 1.0 equiv) and Et_3N (0.50 mL) in

CH_2Cl_2 (2.0 mL) at rt under nitrogen atmosphere was added phenylchloroformate (38.6 mg, 0.247 mmol, 2.0 equiv), and the reaction mixture was stirred for 1 h (multitude of spots observed by TLC). Volatile residues were removed under reduced pressure. The crude residue obtained was dissolved in CH_2Cl_2 and was purified by preparative TLC purification developing two times with 2% MeOH/CH_2Cl_2. Two broad bands (band A and band B) comprising of a multitude of overlapping bands were scraped from the plate and eluted separately with 7% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Band A containing multiple bands was subjected twice to preparative TLC purification developing three and four times with 1% MeOH/CH_2Cl_2 and three times with 100% CH_2Cl_2. The band corresponding to compound **82** was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Evaporation of solvents provided an impure sample of **82** as a colorless oil (ca. 3.2 mg, ca. 4% corrected yield; contains ca. 20% of unidentified impurities by ^{1}H NMR). Similarly, band B containing multiple bands was also subjected twice to preparative TLC purification developing two times with 1% MeOH/CH_2Cl_2 and four and nine times with 2% MeOH/CH_2Cl_2. The band corresponding to compound **83** was scraped from the plate and eluted with 6% MeOH/CH_2Cl_2 through a Pasteur pipette containing a cotton plug. Evaporation of solvents provided an impure sample of **83** as a colorless oil (ca. 2.2 mg, ca. 3% corrected yield; contains ca. 25% of unidentified impurities by ^{1}H NMR). Withalongolide A 27-chloro-19-hydroxy-4-phenyl carbonate **82**: IR (neat) 3548, 2944, 1764, 1709, 1681, 1396, 1244, 1209, 1050, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (s, 3H), 0.84–0.90 (m, 1H), 0.95–1.01 (m, 1H), 1.01 (d, J = 6.7 Hz, 3H), 1.05–1.21 (m, 3H), 1.29–1.44 (m, 2H), 1.60–1.70 (m, 2H), 1.84–1.95 (m, 2H), 1.99–2.05 (m, 4H), 2.10 (s, 3H), 2.19–2.24 (m, 1H), 2.54 (dd, J = 17.8, 13.3 Hz, 1H), 2.76 (d, J = 8.2 Hz, 1H), 3.29 (s, 1H), 4.09 (t, J = 10.8 Hz, 1H), 4.32–4.45 (m, 4H), 4.76 (d, J = 6.0 Hz, 1H), 6.34 (d, J = 9.9

Hz, 1H), 7.10 (dd, J = 9.9, 6.0 Hz, 1H), 7.15–7.18 (m, 2H), 7.24–7.28 (m, 1H), 7.37–7.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 13.6, 20.8, 22.0, 24.4, 27.6, 30.3, 30.5, 31.5, 37.4, 39.0, 39.8, 43.1, 44.7, 52.1, 52.3, 57.0, 60.1, 61.1, 65.6, 75.6, 78.5, 121.1, 124.3, 126.6, 129.8, 135.5, 138.9, 151.2, 153.1, 156.4, 164.9, 198.6; HRMS (ESI) *m/z* calcd for $C_{35}H_{42}{}^{35}ClO_8$ $[M + H]^+$ 625.2568, found 625.2474; for $C_{35}H_{42}{}^{37}ClO_8$ $[M + H + 2]^+$ 627.2539, found 627.2462 (chlorine isotopes were observed in mass).

Withalongolide A 4,27-dihydroxy-19-phenyl carbonate **83**: IR (neat) 3452, 2939, 1761, 1685, 1396, 1240, 1211, 1023, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74 (s, 3H), 0.86–0.94 (m, 1H), 1.01 (d, J = 6.7 Hz, 3H), 1.04–1.21 (m, 4H), 1.30–1.43 (m, 2H), 1.54–1.74 (m, 6H), 1.95–2.06 (m, 4H), 2.03 (s, 3H), 2.22–2.26 (m, 1H), 2.50 (dd, J = 17.3, 13.7 Hz, 1H), 3.20 (s, 1H), 3.76 (d, J = 6.1 Hz, 1H), 4.33–4.47 (m, 4H), 5.19 (d, J = 10.8 Hz, 1H), 6.27 (d, J = 10.0 Hz, 1H), 7.08 (dd, J = 10.0, 6.1 Hz, 1H), 7.19–7.21 (m, 2H), 7.23–7.26 (m, 1H), 7.36–7.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9, 13.6, 20.2, 22.3, 24.4, 27.5, 30.1, 30.8, 31.1, 39.0, 39.7, 42.8, 44.5, 51.7, 52.1, 56.9, 57.7, 60.6, 61.4, 68.4, 69.7, 78.9, 121.3, 125.9, 126.4, 129.7, 132.6, 144.8, 151.2, 152.9, 153.6, 167.2, 198.1; HRMS (ESI) *m/z* calcd for $C_{35}H_{43}O_9$ $[M + H]^+$ 607.2907, found 607.2864.



(20*S*,22*R*)-19,27-Diacetyloxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (jaborosalactone V 19,27-diacetate 85) and (20*S*,22*R*)-19,27-Diacetyloxy-6*β*-hydroxy-1-oxowitha-2,4,24-trienolide (jaborosalactone B 19,27-diacetate 86; Scheme 61). Following a modification of a reported protocol,[229,248] to a solution of withalongolide A 4,19,27-triacetate **73** (40.0 mg, 0.0652 mmol, 1.0 equiv) in 1,4-dioxane (1.5 mL) at rt under nitrogen atmosphere was added palladium acetate (ca. 1.5 mg, 0.00652 mmol, 0.10 equiv), triphenyl phosphine (3.4 mg, 0.0130 mmol, 0.20 equiv), and ammonium formate (12.3 mg, 0.195 mmol, 3.0 equiv). The reaction mixture was heated at 100 °C for 1 h in a sealed vial. The reaction mixture was concentrated and the residue obtained was purified twice by preparative TLC developing eight to ten times with 1.5% MeOH/CH_2Cl_2. Bands corresponding to products were scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **86** as a pale yellow amorphous solid (9.5 mg, 26%) and **85** after recrystallization from EtOAc as colorless crystals (8.8 mg, 24%). Crystals of **85** were used for X-ray diffraction analysis (Table S27). Jaborosalactone V 19,27-diacetate **85**: R_f = 0.57 (2% MeOH/CH_2Cl_2, run three times); mp 172–174 °C; IR (neat) 2924, 2853, 1734, 1711, 1673, 1377, 1235, 1034, 970 cm^{-1}; ^1H

NMR (500 MHz, $CDCl_3$) δ 0.70 (s, 3H), 0.86–0.92 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 1.02–1.18 (m, 4H), 1.30–1.47 (m, 3H), 1.49–1.71 (m, 4H), 1.90–2.01 (m, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.07–2.10 (m, 1H), 2.13–2.17 (m, 1H), 2.51 (dd, J = 17.8, 13.3 Hz, 1H), 3.05 (s, 1H), 3.18 (dt, J = 18.0, 2.5 Hz, 1H), 4.25 (d, J = 10.2 Hz, 1H), 4.39 (dt, J = 13.2, 3.4 Hz, 1H), 4.74 (d, J = 10.2 Hz, 1H), 4.86 (1/2 AB, J = 11.8 Hz, 1H), 4.89 (1/2 AB, J = 11.8 Hz, 1H), 6.10 (dd, J = 10.1, 2.7 Hz, 1H), 6.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 13.5, 20.8, 21.1, 21.2, 22.7, 24.3, 27.4, 30.3, 30.5, 31.5, 35.3, 38.9, 39.8, 42.7, 44.4, 52.0, 52.1, 56.6, 58.2, 59.9, 62.3, 65.7, 78.3, 122.0, 129.9, 145.2, 157.1, 165.4, 170.5, 171.1, 199.8; HRMS (ESI) *m/z* calcd for $C_{32}H_{43}O_8$ $[M + H]^+$ 555.2958, found 555.2971.

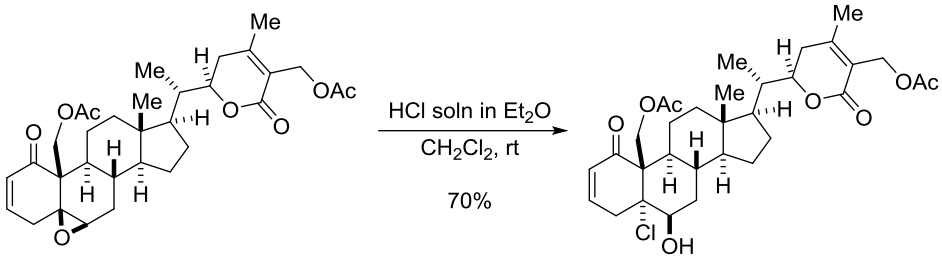
Table S27. Selected Crystallographic and Refinement Parameters for Jaborosalactone V 19,27-Diacetate 85

Compound	Jaborosalactone V 19,27-diacetate **85**
CCDC deposition number	972242
Empirical formula	$C_{36}H_{50}O_{10}$ ($C_{32}H_{42}O_8$ + $CH_3COOCH_2CH_3$)
Formula wt.	642.76
Temperature	100(2) K
Crystal color	Colorless
Crystal system	Monoclinic
Crystal size (mm^3)	0.28 × 0.14 × 0.11
Space group	$P2_1$
a [Å]	11.9047(4)
b [Å]	12.2331(4)
c [Å]	12.3943(4)
α [deg]	90
β [deg]	108.5560(10)
γ [deg]	90
Z	2

Compound	Jaborosalactone V 19,27-diacetate **85**
Volume [$Å^3$]	1711.16(10)
D*calc* [Mg/m^3]	1.247
F (000)	692
Absorption coefficient μ [mm^{-1}]	0.737
Theta range for data collection	3.76 to 69.25°
Range h	–14<=h<=14
Range k	–11<=k<=13
Range l	–14<=l<=14
Reflections collected	15605
Independent reflections	4775
R_{int}	0.0171
Data / Restraints / Parameters	4775 / 1 / 578
Final R indices [I>2σ(I)]	0.0431
wR_2	0.1169
Absolute structure parameter	–0.02(18)
Goodness-of-fit on F^2	1.049
R-factor (%)	4.31
Largest diff. peak and hole ($e \cdot Å^{-3}$)	0.684 and –0.525

Jaborosalactone B 19,27-diacetate **86**: R_f = 0.34 (2% MeOH/CH_2Cl_2, run three times); IR (neat) 3461, 2937, 2873, 1735, 1710, 1660, 1631, 1376, 1236, 1044 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (s, 3H), 0.90–0.95 (m, 1H), 0.96–1.01 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 1.04–1.17 (m, 2H), 1.19–1.28 (m, 1H), 1.34–1.53 (m, 2H), 1.56–1.71 (m, 2H), 1.90–1.94 (m, 1H), 1.90 (s, 3H), 1.97–2.03 (m, 3H), 2.03–2.12 (m, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 2.50 (dd, *J* = 17.7, 13.3 Hz, 1H), 2.87 (br s, 1H), 4.39 (dt, *J* = 13.2, 3.4 Hz, 1H), 4.63 (t, *J* = 2.7 Hz, 1H), 4.75 (d, *J* = 9.7 Hz, 1H), 4.85 (1/2 AB, *J* = 11.8 Hz, 1H), 4.89 (1/2 AB, *J* = 11.8 Hz, 1H), 5.18 (d, *J* = 9.7 Hz, 1H), 6.09 (d, *J* = 9.6 Hz, 1H), 6.28 (d, *J* = 5.9 Hz, 1H), 6.96 (dd, *J* = 9.7, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 13.4, 20.8, 21.0, 21.1, 24.4, 27.5, 30.3, 31.7, 38.9, 39.7, 41.3, 42.9, 50.2, 51.9, 56.5, 58.1, 58.2, 67.8, 74.0,

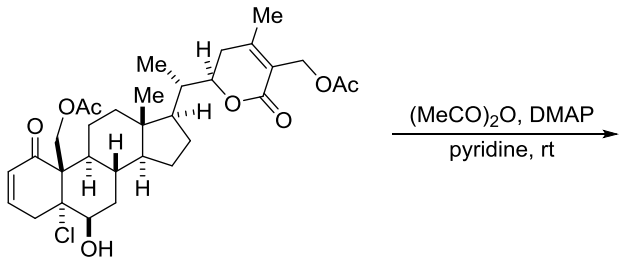
78.3, 120.0, 122.0, 127.0, 140.4, 155.0, 157.1, 165.4, 171.1, 171.4, 202.2; HRMS (ESI) *m/z* calcd for $C_{32}H_{43}O_8$ $[M + H]^+$ 555.2958, found 555.2924.



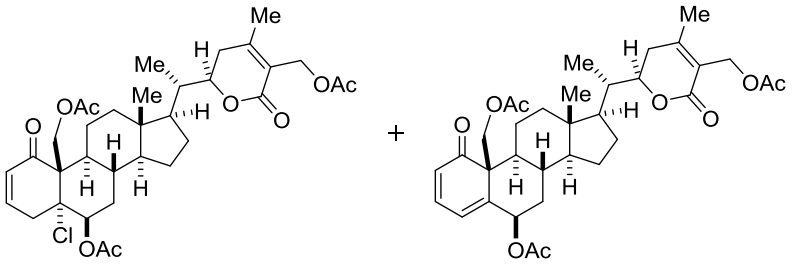
(20*S*,22*R*)-5α-Chloro-19,27-diacetyloxy-6β-hydroxy-1-oxowitha-2,24-dienolide (jaborosalactone E 19,27-diacetate 87; Scheme 61). To a solution of jaborosalactone V 19,27-diacetate **85** (4.0 mg, 0.00721 mmol, 1.0 equiv) in CH_2Cl_2 (0.10 mL) under nitrogen atmosphere was added a 2.0 M HCl solution in diethyl ether (0.50 mL) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated and the pale yellow residue obtained was purified twice by preparative TLC developing one to two times with 2% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **87** as a colorless semisolid (3.0 mg, 70%). Jaborosalactone E 19,27-diacetate **87**: R_f = 0.35 (2% MeOH/CH_2Cl_2, run twice); IR (neat) 3449, 2934, 2873, 1739, 1696, 1381, 1237, 1031, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (s, 3H), 1.02 (d, J = 6.6 Hz, 3H), 1.10–1.19 (m, 3H), 1.22–1.30 (m, 1H), 1.34–1.39 (m, 2H), 1.57–1.81 (m, 4H), 1.94 (br s, 1H), 1.96–1.99 (m, 1H), 1.97 (s, 3H), 2.00–2.06 (m, 4H), 2.06 (s, 3H), 2.08 (s, 3H), 2.28–2.31 (m, 1H), 2.51–2.58 (m, 2H), 3.60 (dt, J = 20.5, 2.6 Hz, 1H), 3.99 (s, 1H), 4.40–4.50 (m, 3H), 4.87 (1/2 AB, J = 11.8 Hz, 1H), 4.90 (1/2 AB, J = 11.8 Hz, 1H), 6.01 (dd, J = 10.2, 1.9 Hz, 1H), 6.62 (ddd, J = 10.2, 4.8, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5, 13.4, 20.8, 21.1, 21.3, 23.4, 24.3, 27.4, 30.3, 30.4, 33.3, 37.9, 39.0, 40.1, 41.6, 43.3,

52.2, 55.3, 55.6, 58.2, 63.6, 73.7, 77.4, 78.4, 122.0, 129.2, 140.5, 157.3, 165.5, 170.6, 171.1, 197.4; HRMS (ESI) *m/z* calcd for $C_{32}H_{44}ClO_8$ $[M + H]^+$ 591.2725, found 591.2737.

In order to confirm the structure of **87**, an acetylation reaction on a small amount of **87** was carried out. The presence of acetyl group was confirmed by ^1H NMR and HRMS analysis of the acetylated compound **87a**. However, the quantity of sample obtained for **87a** was not enough for complete spectroscopic analysis in order to obtain good quality data.



87

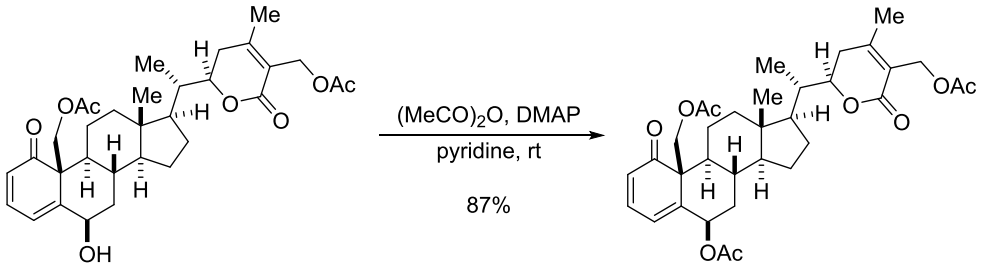


87a **88**

(20*S*,22*R*)-5α-Chloro-6β,19,27-triacetyloxy-1-oxowitha-2,24-dienolide (jaborosalactone E 6,19,27-triacetate 87a). To a solution of jaborosalactone E 19,27-diacetate **87** (ca. 1.1 mg, 0.0019 mmol, 1.0 equiv) and DMAP (ca. 1.0 mg) in pyridine (0.05 mL) was added acetic anhydride (0.01 mL), and the reaction mixture was stirred at rt under nitrogen atmosphere for 2 h (messy reaction by TLC). The reaction mixture was concentrated and the residue obtained was quenched with ethanol. The solution was again concentrated and the residue was purified by preparative TLC developing two times with 2% MeOH/CH_2Cl_2. Bands corresponding to **87a** and **88** (vide infra) were scraped from the

plate and eluted separately with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded a slightly impure sample of **87a** (ca. 0.1 mg) and a slightly impure sample of **88** (ca. 0.2 mg) as colorless oils. Jaborosalactone E 6,19,27-triacetate **87a**: R_f = 0.70 (3% MeOH/CH_2Cl_2, run twice); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (s, 3H), 1.02 (d, J = 6.7 Hz, 3H), 1.10–1.30 (complex, 6H), 1.33–1.40 (m, 2H), 1.58–1.72 (m, 3H), 1.93–1.97 (m, 1H), 1.98 (m, 3H), 1.99–2.04 (m, 2H), 2.05–2.07 (m, 1H), 2.06 (s, 3H), 2.09 (br s, 3H), 2.18 (s, 3H), 2.32–2.35 (m, 1H), 2.51–2.62 (m, 2H), 3.14 (dt, J = 20.4, 2.6 Hz, 1H), 4.40–4.46 (m, 3H), 4.87 (1/2 AB, J = 11.8 Hz, 1H), 4.91 (1/2 AB, J = 11.9 Hz, 1H), 5.12 (m, 1H), 6.03 (dd, J = 10.3, 1.9 Hz, 1H), 6.58 (ddd, J = 10.3, 4.8, 2.3 Hz, 1H); HRMS (ESI) m/z calcd for $C_{34}H_{46}ClO_9$ $[M + H]^+$ 633.2830, found 633.2791.

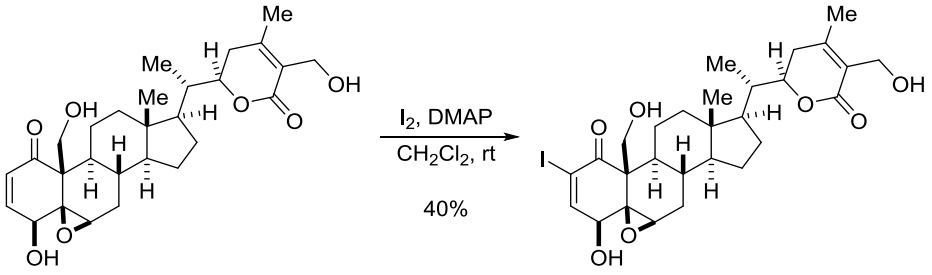
^{1}H and ^{13}C NMR data for **88** obtained from this experiment (acetylation reaction of **87**) matched with the NMR data for **88** obtained from the experiment shown below (acetylation reaction of **86**).



86 **88**

(20*S*,22*R*)-6β,19,27-Triacetyloxy-1-oxowitha-2,4,24-trienolide (jaborosalactone B 6,19,27-triacetate 88; Scheme 61). A solution of jaborosalactone B 19,27-diacetate **86** (4.5 mg, 0.00811 mmol, 1.0 equiv), pyridine (0.050 mL), acetic anhydride (0.050 mL), and a small pellet of DMAP (ca. 1–2 mg) was stirred at rt under nitrogen atmosphere for 1.5 h. The reaction mixture was quenched with ethanol and volatile residues were removed under reduced pressure. The crude pale yellow residue obtained was purified by preparative TLC

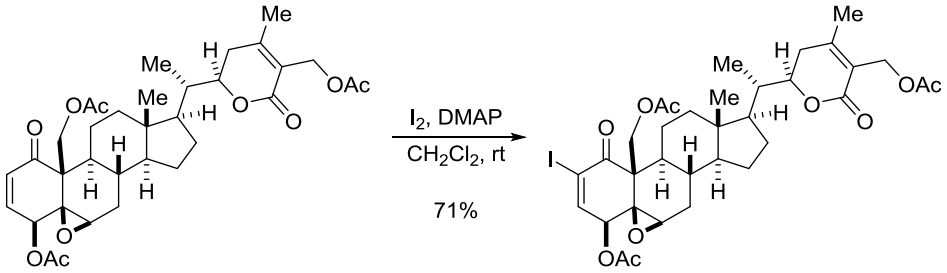
developing two times with 3% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **88** as an off-white solid (4.2 mg, 87%). Jaborosalactone B 6,19,27-triacetate **88**: R_f = 0.19 (2% MeOH/CH_2Cl_2); mp 239–243 °C; IR (neat) 2940, 2869, 1739, 1712, 1664, 1635, 1371, 1247, 1025, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (s, 3H), 0.92–0.97 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 1.00–1.09 (m, 2H), 1.12–1.30 (m, 4H), 1.36–1.50 (m, 2H), 1.55–1.62 (m, 1H), 1.65–1.73 (m, 1H), 1.79–1.83 (m, 1H), 1.86 (s, 3H), 1.89–1.96 (m, 1H), 1.97 (s, 3H), 1.99–2.03 (m, 2H), 2.05 (s, 3H), 2.06 (s, 3H), 2.06–2.10 (m, 1H), 2.50 (dd, J = 17.7, 13.3 Hz, 1H), 4.40 (dt, J = 13.2, 3.4 Hz, 1H), 4.71 (1/2 AB, J = 9.8 Hz, 1H), 4.77 (1/2 AB, J = 9.8 Hz, 1H), 4.86 (1/2 AB, J = 11.8 Hz, 1H), 4.89 (1/2 AB, J = 11.9 Hz, 1H), 5.56 (m, 1H), 6.12 (d, J = 9.6 Hz, 1H), 6.44 (d, J = 6.0 Hz, 1H), 7.00 (dd, J = 9.7, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 13.5, 20.82, 20.83, 21.0, 21.1, 21.4, 24.4, 27.5, 30.3, 32.6, 38.91, 38.96, 39.5, 42.9, 49.7, 51.8, 56.4, 57.4, 58.2, 66.7, 75.0, 78.3, 122.14, 122.19, 127.1, 140.4, 150.0, 157.0, 165.4, 170.3, 170.9, 171.1, 201.5; HRMS (ESI) *m/z* calcd for $C_{34}H_{45}O_9$ $[M + H]^+$ 597.3064, found 597.3058.



67 **89**

(4*S*,20*S*,22*R*)-2-Iodo-4β,19,27-trihydroxy-5β,6β-epoxy-1-oxowitha-2,24-dienolide (2-iodowithalong-olide A 89; Scheme 62). To a suspension of withalongolide A **67** (15.0 mg, 0.0308 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added DMAP (3.8 mg, 0.0308 mmol,

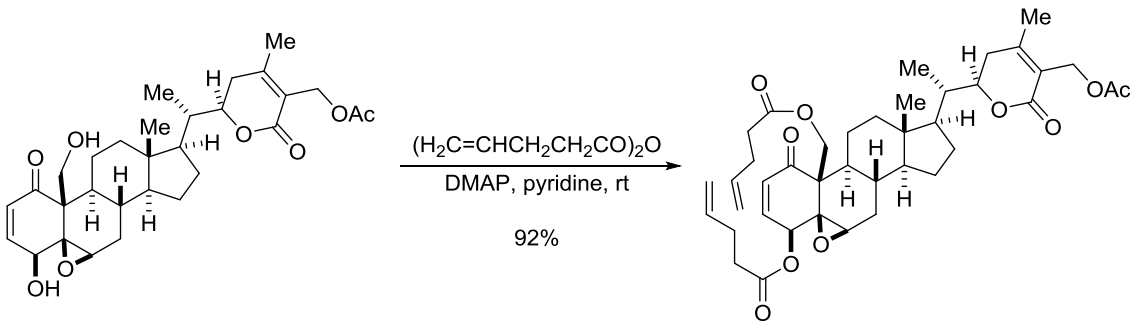
1.0 equiv) and iodine (11.7 mg, 0.0462 mmol, 1.5 equiv), and the reaction mixture was stirred at rt under nitrogen atmosphere for 1 h. The crude reddish-brown reaction mixture was initially purified by preparative TLC developing four times with 3% MeOH/CH_2Cl_2. Broad brownish band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2. The brown-colored elution was treated with few drops of saturated aqueous solution of $Na_2S_2O_3$ until faint yellow. The solvents were evaporated under reduced pressure and the pale yellow residue obtained was purified by preparative TLC developing three times with 3% MeOH/CH_2Cl_2 and two times with 30% EtOAc/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **89** as an off-white semisolid (7.5 mg, 40%). 2-Iodowithalongolide A **89**: R_f = 0.44 (4% MeOH/CH_2Cl_2, run twice); IR (neat) 3337 (br), 2941, 2920, 1686, 1397, 1044, 909, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.87–0.94 (m, 2H), 0.98 (d, J = 6.6 Hz, 3H), 1.01–1.17 (m, 3H), 1.32–1.43 (m, 3H), 1.47–1.55 (m, 1H), 1.60–1.71 (m, 4H), 1.83–1.87 (m, 1H), 1.94–2.01 (m, 3H), 2.03 (s, 3H), 2.20–2.25 (m, 1H), 2.48 (dd, J = 17.4, 13.6 Hz, 1H), 2.87 (br s, 1H), 3.26 (s, 1H), 3.55 (d, J = 6.6 Hz, 1H), 3.79 (d, J = 9.6 Hz, 1H), 4.32–4.42 (m, 4H), 7.75 (d, J = 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 13.5, 20.2, 22.0, 24.3, 27.4, 30.0, 30.4, 31.0, 38.9, 39.5, 42.6, 44.2, 51.9, 55.2, 56.7, 57.6, 61.2, 61.6, 62.1, 70.8, 78.8, 107.5, 125.8, 153.0, 154.4, 167.1, 193.9; HRMS (ESI) *m/z* calcd for $C_{28}H_{41}INO_7$ $[M + NH_4]^+$ 630.1928, found 630.1932.



73 **90**

(4*S*,20*S*,22*R*)-2-Iodo-4*β*,19,27-triacetyloxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (2-iodowithalong-olide A 4,19,27-triacetate 90; Scheme 62). To a solution of withalongolide A 4,19,27-triacetate **73** (20.0 mg, 0.0326 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added DMAP (4.0 mg, 0.0326 mmol, 1.0 equiv) and iodine (12.4 mg, 0.0489 mmol, 1.5 equiv), and the reaction mixture was stirred at rt under nitrogen atmosphere for 1 h. The reaction mixture was quenched with few drops of saturated aqueous solution of $Na_2S_2O_3$ until colorless and CH_2Cl_2 layer was separated. The aqueous phase was extracted with CH_2Cl_2 twice and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude pale yellow residue obtained was purified by preparative TLC developing three times with 2% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **90** as an off-white waxy solid (17.0 mg, 71%). 2-Iodowithalongolide A 4,19,27-triacetate **90**: R_f = 0.21 (1% MeOH/CH_2Cl_2, run twice); IR (neat) 3337 (br), 2943, 2869, 1735, 1704, 1365, 1223, 1022, 911, 728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.73 (s, 3H), 0.86–1.00 (m, 2H), 0.99 (d, J = 6.6 Hz, 3H), 1.06–1.19 (m, 3H), 1.28–1.42 (m, 2H), 1.56–1.78 (m, 4H), 1.83–1.86 (m, 1H), 1.98–2.02 (m, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.16–2.20 (m, 1H), 2.51 (dd, J = 17.7, 13.3 Hz, 1H), 3.14 (s, 1H), 4.36–4.41 (m, 2H), 4.66 (d, J = 6.5 Hz, 1H), 4.85 (1/2 AB, J = 11.8 Hz, 1H), 4.89 (1/2 AB, J = 11.9 Hz, 1H), 5.05 (d, J = 11.5 Hz, 1H), 7.71 (d, J = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 13.5, 20.8, 20.9, 21.1, 21.3, 22.1, 24.3, 27.4, 30.2,

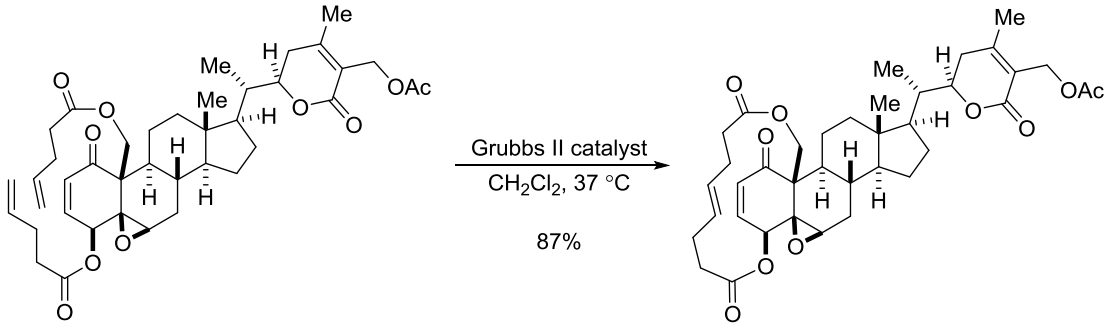
30.6, 30.7, 38.9, 39.4, 42.8, 45.1, 51.8, 51.9, 56.6, 58.1, 58.9, 59.0, 64.0, 72.8, 78.3, 108.2, 122.0, 149.1, 157.1, 165.4, 170.2, 170.5, 171.0, 192.5; HRMS (ESI) *m/z* calcd for $C_{34}H_{44}IO_{10}$ $[M + H]^+$ 739.1979, found 739.1989.



68 **92**

(4*S*,20*S*,22*R*)-27-Acetyloxy-4*β*,19-di-pent-4′-enoyloxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 27-acetyloxy-4,19-di-pent-4′-enoate 92; Scheme 64). A solution of withalongolide A 27-acetate **68** (9.0 mg, 0.0170 mmol, 1.0 equiv), pyridine (0.10 mL), 4-pentenoic anhydride (0.020 mL), and a small pellet of DMAP (ca. 1–2 mg) was stirred at rt under nitrogen atmosphere for 1.5 h. The reaction mixture was quenched with ethanol and volatile residues were removed under reduced pressure. The crude pale yellow residue obtained was purified by preparative TLC developing two times with 2% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **92** as a pale yellow oil (10.8 mg, 92%). Withalongolide A 27-acetyloxy-4,19-di-pent-4′-enoate **92**: R_f = 0.56 (2% MeOH/CH_2Cl_2, run twice) or R_f = 0.21 (1% MeOH/CH_2Cl_2, run three times); IR (neat) 2941, 1736, 1712, 1676, 1639, 1381, 1232, 1161, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (s, 3H), 0.88 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 1.00–1.19 (m, 4H), 1.26 (m, 1H), 1.38 (m, 1H), 1.57–1.72 (m, 2H), 1.79 (tt, J = 11.1, 5.5 Hz, 1H), 1.97–2.03 (m, 4H), 2.05 (s, 3H), 2.06 (s, 3H), 2.15 (ddd, J = 15.1, 4.0,

2.5 Hz, 1H), 2.34–2.54 (m, 10H), 3.13 (s, 1H), 4.36 (d, J = 11.6 Hz, 1H), 4.40 (m, 1H), 4.82 (d, J = 5.9 Hz, 1H), 4.86 (1/2 AB, J = 11.8 Hz, 1H), 4.89 (1/2 AB, J = 11.9 Hz, 1H), 4.97–5.09 (m, 5H), 5.74–5.87 (m, 2H), 6.22 (d, J = 10.0 Hz, 1H), 7.00 (dd, J = 9.9, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 13.5, 20.8, 21.1, 22.5, 24.4, 27.4, 28.8, 28.9, 30.3, 30.9, 31.0, 33.3, 33.8, 38.9, 39.6, 42.8, 44.8, 51.1, 52.0, 56.6, 58.2, 59.2, 59.4, 64.5, 71.1, 78.3, 115.7, 115.9, 122.0, 133.4, 136.4, 136.8, 141.0, 157.1, 165.4, 171.1, 172.5, 172.6, 198.3; HRMS (ESI) *m/z* calcd for $C_{40}H_{53}O_{10}$ $[M + H]^+$ 693.3639, found 693.3630.



92 **93**

(4*S*,20*S*,22*R*)-27-Acetyloxy-4*β*,19-cyclo-(*E*)-oct-4′-enedioyloxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide A 27-acetyloxy-4,19-cyclo-(*E*)-oct-4′-enedioate 93; Scheme 64). Following a modification of a reported protocol,[236] to a solution of withalongolide A 27-acetyloxy-4,19-di-pent-4′-enoate **92** (6.6 mg, 0.00952 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (0.50 mL) at rt under nitrogen atmosphere was added Grubbs 2nd generation catalyst (ca. 0.4 mg, 0.000476 mmol, 0.050 equiv) and the reaction mixture was gently refluxed with stirring at 37 °C for 2 h. The reaction mixture was concentrated and the crude brownish residue obtained was purified by preparative TLC developing four times with 1.5% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **93** as a colorless oil (5.5 mg, 87%). Withalongolide A 27-acetyloxy-

4,19-cyclo-(*E*)-oct-4′-enedioate **93**: R_f = 0.15 (1% MeOH/CH_2Cl_2, run three times); IR (neat) 2933, 1736, 1712, 1676, 1339, 1240, 1157, 1132, 1025, 975 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.69 (s, 3H), 0.91 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 1.07–1.41 (m, 6H), 1.51–1.58 (m, 1H), 1.60–1.72 (m, 2H), 1.88 (qd, J = 11.2, 3.4 Hz, 1H), 1.96–2.04 (m, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.11–2.18 (m, 3H), 2.25 (m, 1H), 2.33–2.43 (m, 3H), 2.46–2.62 (m, 4H), 3.24 (d, J = 2.6 Hz, 1H), 4.20 (d, J = 11.5 Hz, 1H), 4.41 (dt, J = 13.2, 3.3 Hz, 1H), 4.69 (d, J = 11.5 Hz, 1H), 4.86 (1/2 AB, J = 11.8 Hz, 1H), 4.90 (1/2 AB, J = 11.8 Hz, 1H), 5.16 (d, J = 5.7 Hz, 1H), 5.53 (ddd, J = 15.0, 7.6, 3.9 Hz, 1H), 5.85 (ddd, J = 15.1, 9.7, 5.2 Hz, 1H), 6.21 (d, J = 10.0 Hz, 1H), 6.84 (dd, J = 10.0, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6, 13.5, 20.8, 21.1, 23.8, 24.5, 27.4, 27.8, 29.6, 30.2, 31.3, 31.5, 34.4, 36.4, 39.0, 39.6, 42.8, 45.4, 51.5, 52.1, 55.9, 58.2, 59.6, 59.8, 66.8, 69.8, 78.4, 122.0, 129.4, 129.8, 132.8, 141.2, 157.2, 165.5, 171.1, 172.9, 173.2, 200.0; HRMS (ESI) *m/z* calcd for $C_{38}H_{49}O_{10}$ $[M + H]^+$ 665.3326, found 665.3290.

Chapter 4

Isolation of a Novel Minor Withanolide, Withalongolide O from *Physalis longifolia*

4.1 Introduction

As discussed in the previous chapter, withanolides are classified as modified ergostane-type C28 steroidal lactones, present mainly in 25 genera of the Solanaceae family, which includes *Acnistus*, *Datura*, *Dunalia*, *Jaborosa*, *Nicandra*, *Physalis*, and *Withania*.[212b,c,249] Approximately 770 withanolides, exhibiting more than 22 different carbon frameworks, have been reported over the past five decades.[212c] Among them, the classically-defined withanolides or the so-called unmodified withanolides, boasting a four-ring steroid nucleus and a nine-carbon side chain featuring a lactone moiety, are the most abundant forms discovered in nature. Within this category alone, nearly 550 compounds were reported thus far in the literature. Furthermore, unmodified withanolides that display the most promising antiproliferative characteristics contain an α,β-unsaturated ketone in ring A, a 5β,6β-epoxide or a 5α-chloro-6β-hydroxy functionality in ring B, and a 17β-oriented δ-lactone ring; e.g. withaferin A **66** (Figure 25).[212c]

Recently, Timmermann and Cohen explored the antiproliferative potential of compounds present in several members of the Solanaceae: *Physalis longifolia* Nutt.,[223a] *Vassobia breviflora* (Sendtn.) Hunz,[220] and *Withania somnifera* (L.) Dunal.[250] Each extract, fraction, and isolated compound from the three genera were evaluated via a series of selected cell lines that probed epithelial tumor response, specifically the HNSCC cell lines (JMAR and MDA-1986) and melanoma cell lines (B16F10 and SKMEL-28), coupled with the toxicity gauging non-malignant fetal lung fibroblast cell line (MRC-5). This work by

Timmermann and Cohen resulted in the isolation, characterization, and cytotoxic evaluation of 35 withanolides.[220,223a,250] Two of the most promising semisynthetic withanolides, withalongolide A 4,19,27-triacetate **73** and withalongolide B 4,19-diacetate **102a** (Figure 25) showed IC_{50} values less than 1 μM against all the cells tested. These two compounds were synthesized from two rare 19-OH withanolides, withalongolide A **67** and B **102** (Figure 25), which originated from the aerial parts of *Physalis longifolia*.[220,223a,250]

To effectively probe the SAR of these analogues and in order to fulfill the requirements of an in vivo biological activity study in a full-term animal tumorigenesis model, a re-isolation of gram quantities of **67** and **102** was warranted. We also needed sufficient quantity of **66** to prepare a semisynthetic withanolide possessing all the essential structural features to maximize the antiproliferative potency. In the course of this work, a minor withanolide was discovered while isolating **66** and details of these endeavors are described here.

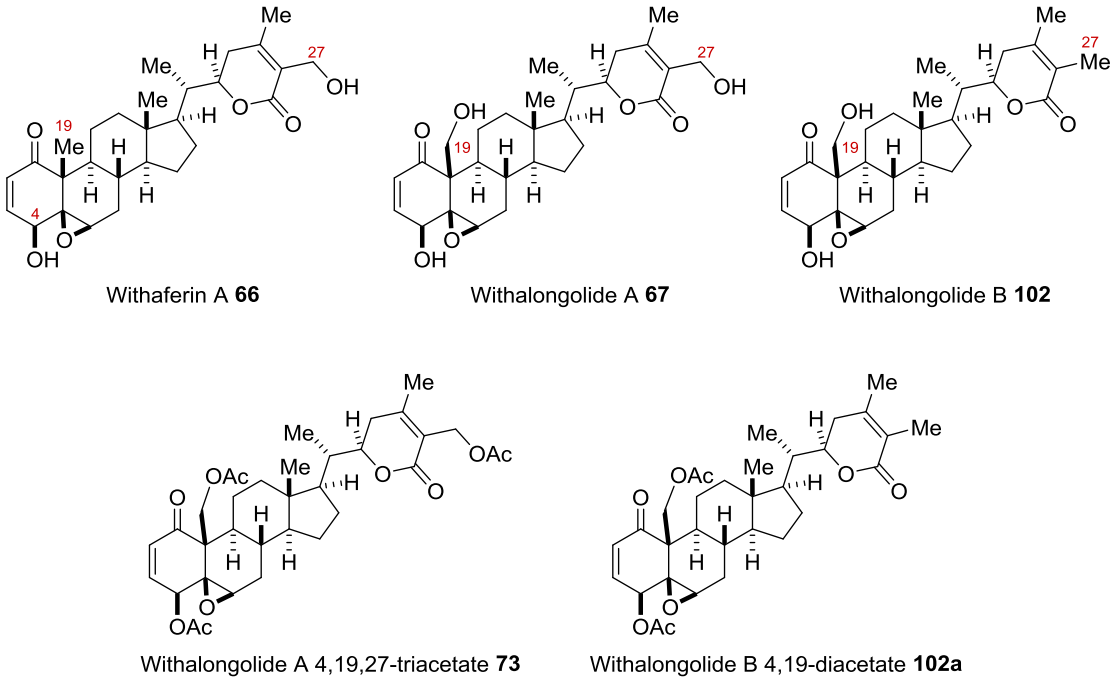


Figure 25. Structures of cytotoxic withanolides.

4.2 Results and Discussions

Isolation of Withaferin A 66 and Withalongolide O 103

Timmermann and co-workers carried out the extraction of 2.97 kg of dried aerial parts of *P. longifolia* with CH_2Cl_2/MeOH (1:1).[251] The extract obtained was suspended in water and subsequently partitioned with hexane, EtOAc, and *n*-BuOH, respectively. Subsequent purifications of the resulting EtOAc-soluble fraction afforded major withanolides, withalongolide A **67** (1.8 g, ca. 0.06% yield), withalongolide B **102** (0.5 g, ca. 0.017% yield), and withaferin A **66** (1.5 g, ca. 0.05% yield), respectively. Two new minor withanolides, withalongolide O **103** (7.0 mg) and withalongolide P **104** (20 mg) were also obtained during this purification process (Figure 26).[251]

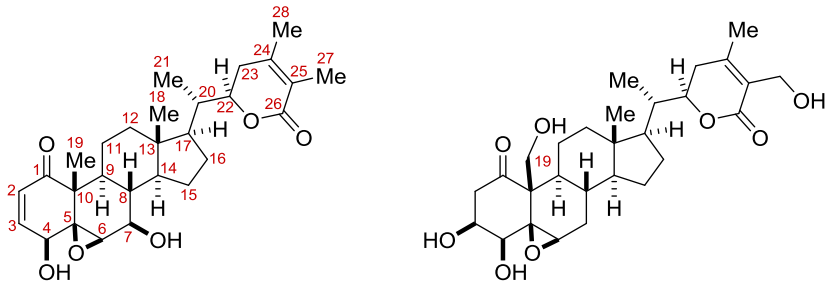


Figure 26. Two novel minor withanolides.

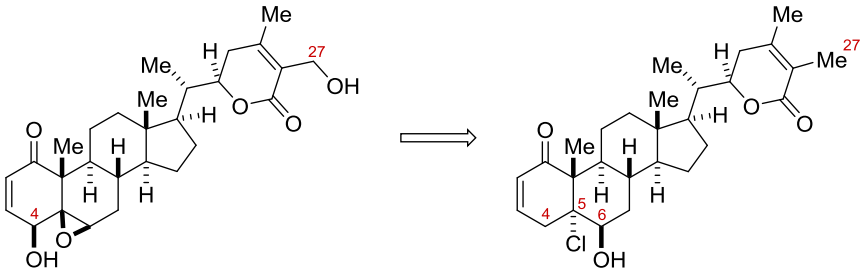
As mentioned above, during the purification of the EtOAc-soluble fraction by Timmermann group, 3.2 g of crude withaferin A **66** was obtained. Prof. Timmermann provided us with 1.52 g of crude **66** to isolate pure **66**. Our goal was to prepare a putative withanolide **105** through semisynthesis from **66** (see Figure 27). Semisynthetic withanolide **105** bears structural resemblance to withanolide C and jaborosalactone E (Figure 27).[231b] The rationale for the synthesis of **105** was:[212c]

(1) An unmodified withanolide skeleton with a 17β-oriented δ-lactone ring shows a more potent cytotoxic activity than withanolides featuring a modified skeleton (see Chapter 3, Figure 21).

(2) The presence of an α,β-unsaturated ketone in ring A is presumed to be an important requirement for possessing the cytotoxic activity.

(3) The presence of a 5β,6β-epoxide or a 5α-chloro-6β-hydroxy functionality in ring B is also presumed to be necessary. In most cases, the presence of the 5α-chloro-6β-hydroxy functionality showed an increased in cytotoxic potency than the 5β,6β-epoxide, when similar pairs of withanolides were compared.

(4) The hydroxyl groups at C-4, 7, 11, 12, 14, 15, 16, 17, 18, 19, 20, 23, 24, and 27 do not contribute to the antiproliferative activity and in some cases, the presence of such hydroxyl groups diminish the potency. Acetylated derivatives of some of these hydroxyl groups such as C-4, 7, 19, and 27 have been reported to enhance the cytotoxic activity significantly.[223a,224,251]



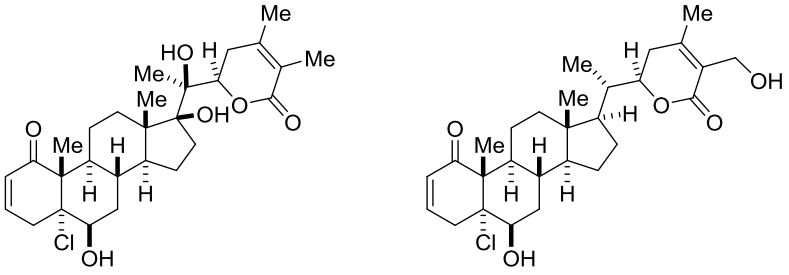


Figure 27. Structure of target semisynthetic withanolide **105** and its related natural withanolides.

The purification of crude withaferin A **66** is summarized in the following flow chart (Figure 28; see the Experimental Section for details). CombiFlash purification of 1.52 g of crude **66** (0–10% MeOH/CH_2Cl_2) afforded impure **66** and mixtures of polar compounds were collected as different fractions. Further purification by charcoal treatment and preparative TLC gave 0.471 g of pure **66**. TLC analysis of fractions **A** and **B** indicated the presence of a limited number of unidentified products, which were amenable to further purification processes. Multiple preparative TLC purifications of fractions **A** and **B** resulted in the isolation of several individual bands, which still contained mixtures of unidentified compounds. Among them, one band containing compound **103** from fraction **B** (see Figure 26) was interesting as ^{1}H NMR displayed characteristic peaks of a withanolide and was obtained in sufficient purity for further spectroscopic analysis. Polar fractions **C**–**E**

contained complex mixtures of unidentified products and were not subjected to further purification.

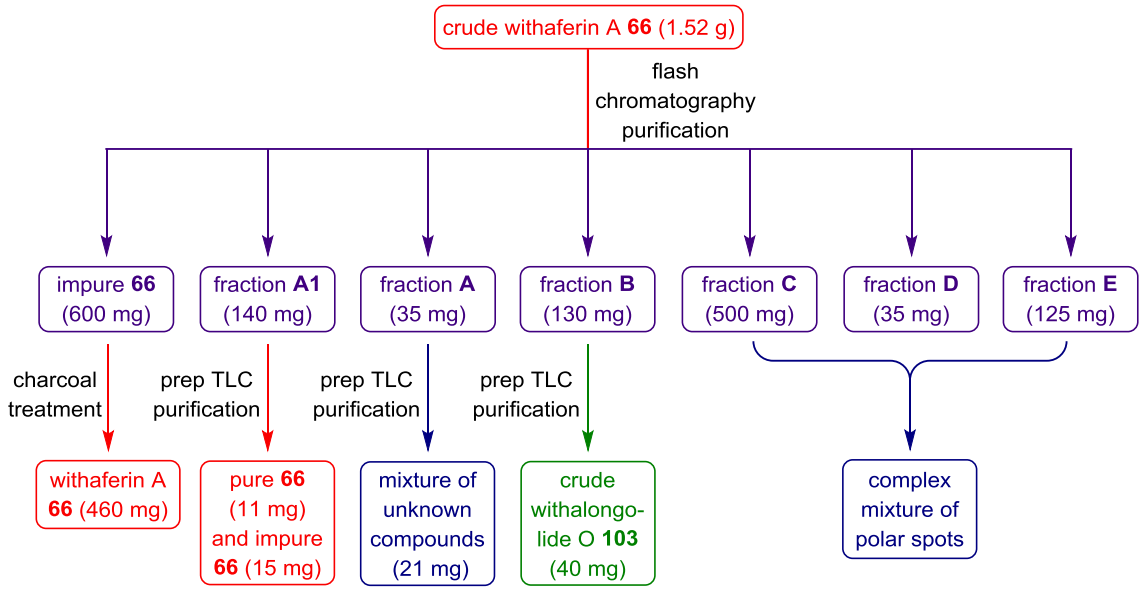


Figure 28. Purification flow chart for crude withaferin A **66**.

The molecular formula of compound **103** was determined to be $C_{28}H_{38}O_6$ by HRMS. The ^{1}H NMR spectrum (in $CDCl_3$) of **103** (Table 21) displayed characteristic signals for five methyl groups at δ_H 0.70 (s, 3H), 0.99 (d, J = 6.6 Hz, 3H), 1.41 (s, 3H), 1.87 (s, 3H), and 1.93 (s, 3H). The ^{13}C NMR (APT) and HSQC spectra of **103** (Table 21) showed 28 carbons differentiated as five CH_3, five CH_2, eleven CH (including two olefins at δ_C 141.7 and 132.8, and four oxygenated carbon at δ_C 78.5, 73.3, 69.6, and 65.6), and seven C (including one ketone carbonyl at δ_C 201.6, one ester carbonyl at δ_C 167.3, two olefins at δ_C 149.2 and 122.2, and one oxygenated carbon at δ_C 68.2). Detailed comparison of the ^{1}H and ^{13}C NMR spectroscopic data of **103** with those of the two previously isolated isomers,[223a] withaferin A **66** and withalongolide B **102**, indicated that **103** contained the same A ring with a Δ^2-1-oxo-4-hydroxy functionality as **66**. The NMR data of **103** also suggested

identical substituent patterns in C and D rings as **66**. The arrangement of substituents on the δ-lactone side chain of **103** was similar to that observed for **102**. This pointed out the obvious difference in the substitution pattern for the B ring. The distinct substituent pattern observed among **103**, **102**, and **66** was the presence of an oxygenated methine (δ_C 73.3, CH) in **103** and an oxygenated methylene in **102** (C-19: δ_C 62.1, CH_2) and **66** (C-27: δ_C 57.7, CH_2),[223a] which implies that **103** was either a 27-deoxy-7-hydroxy derivative of **66** or a 19-deoxy-7-hydroxy derivative of **102**. Moreover, the comparison of the ^{13}C NMR data of **103** and **66** showed relatively high-frequency shifts for C-6 (δ_C 65.6 in **103** and δ_C 62.7 in **66**) and C-8 (δ_C 38.8 in **103** and δ_C 29.9 in **66**) in compound **103**.[223a] Analysis of the COSY and HSQC correlations showed a fragment of $C(O_{epoxide})$–$CH(O_{epoxide})$–CH(OH)–CH–CH for ring B in **103** as compared to $C(O_{epoxide})$–$CH(O_{epoxide})$–CH_2–CH–CH for ring B in **66**, which further corroborated the existence of C-7 hydroxyl group. The HMBC correlations of H-6 (δ_H 3.30) to C-4 (δ_C 69.6), and H-4 (δ_H 3.78) to C-5 (δ_C 68.2) and C-6 (δ_C 65.6) were also observed in **103** (Figure 29). The orientation of the hydroxyl group at C-7 was deduced as β due to the large coupling constant (J = 9.5 Hz) observed between H-7α and H-8β[252] indicating a trans-diaxial relationship and a NOESY correlation observed between H-7 and H-14 (Figure 29).

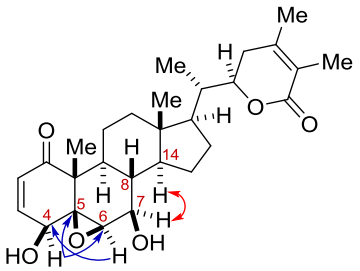


Figure 29. Key HMBC (H→C) and NOESY (H↔H) correlations observed for **103**.

Table 21. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) Data for Withalongolide O 103 and Withalongolide O Diacetate 106[a]

position	withalongolide O **103**		withalongolide O diacetate **106**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	–	201.6	–	200.5
2	6.22, d (9.9)	132.8	6.21, d (9.8)	134.0
3	6.93, dd (9.9, 5.9)	141.7	6.95, dd (9.8, 6.0)	139.8
4	3.78, d (5.9)	69.6	4.62, d (6.0)	71.2
5	–	68.2	–	64.6
6	3.30, d (2.0)	65.6	3.29, d (2.0)	60.6
7	3.57, m	73.3	4.81, dd (9.5, 2.0)	74.7
8	1.43, m	38.8	1.71, m	34.6
9	1.12, m	43.6	1.04, m	43.8
10	–	47.2	–	47.5
11	1.91, m; 1.46, m	27.4	1.58, m; 1.37, m	26.1
12	1.94, m; 1.07, m	39.3	1.89, m; 0.99, m	39.1
13	–	43.5	–	43.5
14	1.09 m	55.7	1.00, m	55.2
15	1.80, qd (16.0, 3.7); 1.47, m	22.3	1.70, m; 1.45, m	21.7
16	1.70, m; 1.37, m	27.9	1.59, m; 1.30, m	27.8
17	1.03, m	51.4	0.96, m	51.3
18	0.70, s	11.8	0.65, s	11.8
19	1.41, s	17.1	1.36, s	15.9
20	1.96, m	39.0	1.90, m	38.9
21	0.99, d (6.6)	13.7	0.93 d (6.6)	13.6
22	4.36, dt (13.3, 3.4)	78.5	4.27, dt (13.3, 3.4)	78.4
23	2.42, t (15.2); 1.90, m	29.8	2.35, t (15.1); 1.81, m	29.8
24	–	149.2	–	149.2
25	–	122.2	–	122.2
26	–	167.3	–	167.2

position	withalongolide O **103**		withalongolide O diacetate **106**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
27	1.87, s	12.7	1.81, s	12.7
28	1.93, s	20.8	1.86, s	20.7
4-OH	2.57, br s	–	–	–
4-OAc	–	–	1.99, s	20.9, 170.0
7-OH	1.62, br s	–	–	–
7-OAc	–	–	2.03, s	21.7, 171.4

[a]Recorded in $CDCl_3$ and δ in ppm. Assignments were made on the basis of HSQC and ^1H–^1H COSY data.

Compound **103** was recrystallized from EtOAc to afford colorless needle-like crystals, which were utilized for a single crystal X-ray diffraction analysis that eventually confirmed the structure of **103** as 27-deoxy-7β-hydroxywithaferin A, and was named as withalongolide O (Figure 30). All of the material obtained was used to acquire spectroscopic, crystallographic, and biological data and to prepare an acetylated derivative **106** (see Scheme 70); doing so unfortunately did not leave enough material for a melting point determination of **103**.

X-Ray diffraction analysis of **103** showed that the dihedral angles of $H_{6\alpha}$–C_6–C_7–$H_{7\alpha}$ and $H_{7\alpha}$–C_7–C_8–$H_{8\beta}$ were 57° and 166° respectively, which explains the observed small coupling constant of $J_{H6\alpha,H7\alpha}$ = 2.0 Hz [equatorial (H-6)–axial (H-7) relationship] and the large coupling constant of $J_{H7\alpha,H8\beta}$ = 9.5 Hz (trans-diaxial relationship between H-7α and H-8β). In our previous X-ray diffraction analyses of **66**, **67**, and **102**,[223a] it was presented that the dihedral angles of $H_{6\alpha}$–C_6–C_7–$H_{7\alpha}$ and $H_{6\alpha}$–C_6–C_7–$H_{7\beta}$ were both close to 57° while those of $H_{7\alpha}$–C_7–C_8–$H_{8\beta}$ and $H_{7\beta}$–C_7–C_8–$H_{8\beta}$ were within the range of 167–174° and 50–59°, respectively. These results are consistent with the small coupling constant of

approximately 2.0 Hz ($J_{H6\alpha,H7\alpha}$ or $J_{H6\alpha,H7\beta}$), the medium coupling constant of 4.0 Hz ($J_{H7\beta,H8\beta}$), and the large coupling constant of 14.5 Hz ($J_{H7\alpha,H8\beta}$) observed for withanolides **66**, **67**, and **102**. It is evident that, in withanolides with an α,β-unsaturated ketone in the A ring and a 5β,6β-epoxy functionality (such as in **66**, **67**, **102**, and **103**), the small coupling constant between H-6 and H-7 (either H-7α or H-7β) could not be used to propose the orientation of the functional group at C-7, but the large coupling constant between H-7α and H-8β can be reliably employed for the determination of the β orientation of the C-7 functional group due to the presence of the axially oriented H-8β in the four ring withanolide moiety.

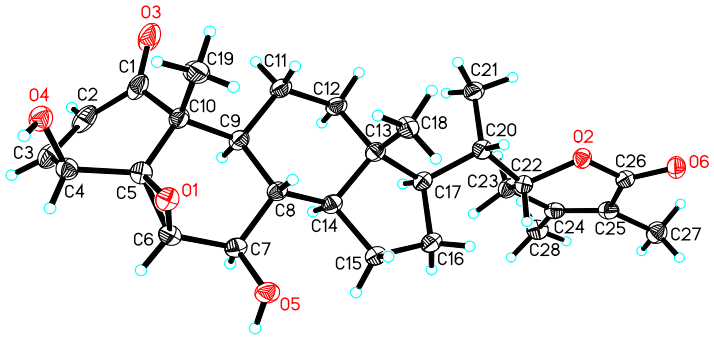
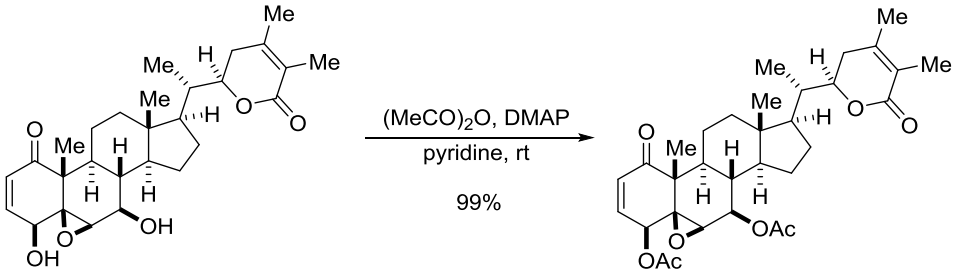


Figure 30. X-Ray ORTEP drawing of withalongolide O **103**.

Acetylation of **103** with acetic anhydride in pyridine yielded the 4,7-diacetate derivative **106** in quantitative yield (Scheme 70). This further confirmed the presence of hydroxyl groups at C-4 and C-7 by a downfield shift of H-4 (from δ_H 3.78 in **103** to δ_H 4.62 in **106**) and H-7 (from δ_H 3.57 in **103** to δ_H 4.81 in **106**), and the disappearance of the signals of the labile protons of 4-OH (δ_H 2.57, br s) and 7-OH (δ_H 1.62, br s) in **103** (see Table 21).

Scheme 70. Acetylation of Withalongolide O 103



Withalongolide O **103** Withalongolide O diacetate **106**

The specific rotation of withalongolide O **103** was determined to be +101.5 (*c* 0.0886, EtOH). The UV–visible spectra in absolute ethanol were also obtained for both withalongolide O **103** and its diacetate **106** (Figure 31). The absorption maximums in **103** and **106** were observed at 206 and 216 nm, respectively, which are characteristic of summation of absorptions of two isolated chromophores (α,β-unsaturated ketone in ring A and α,β-unsaturated-δ-lactone side chain).[252a,253]

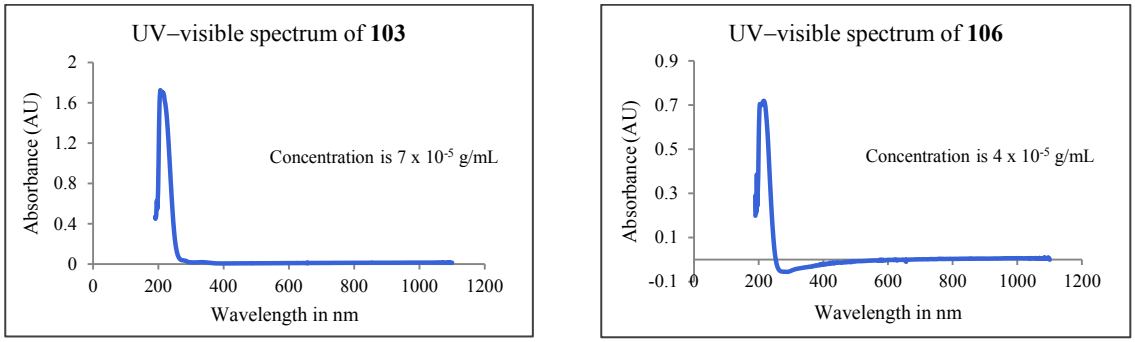
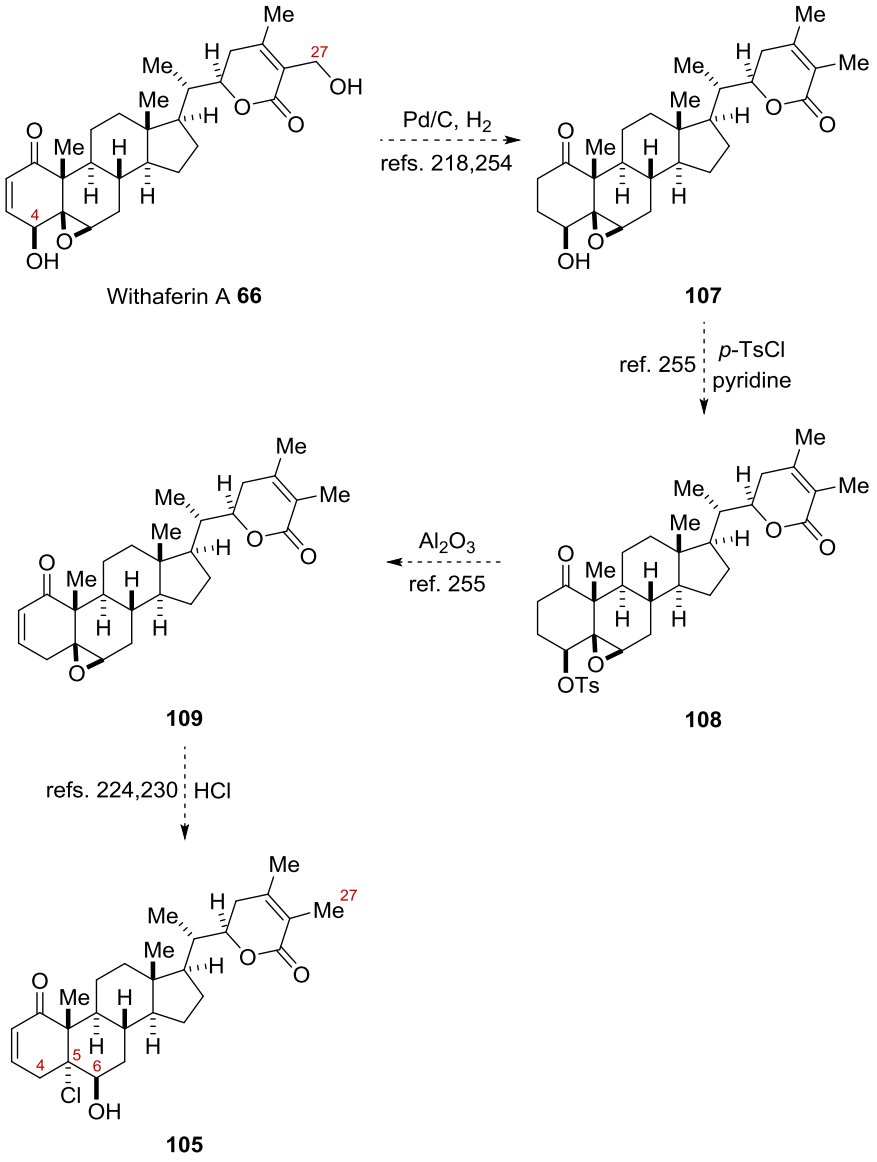


Figure 31. UV–visible spectra of **103** and **106**.

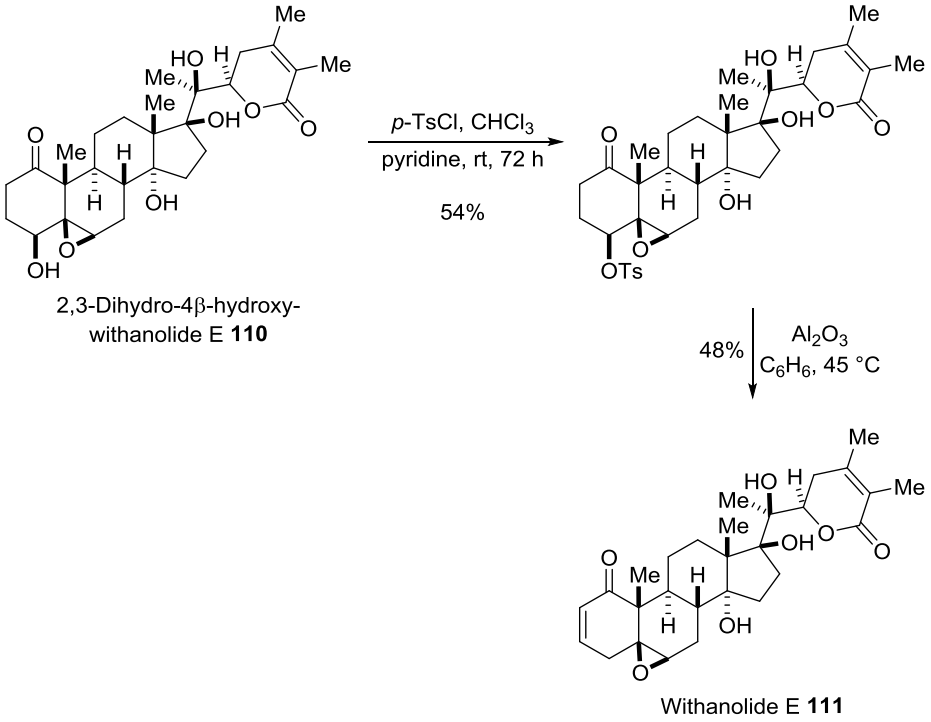
Synthetic Approach towards Withanolide 105

Having made the serendipitous discovery of the new withanolide **103** during the purification of **66**, we focused our attention back on our original goal of synthesizing withanolide **105** from **66** (see Figure 27). Withanolide **105** could be synthesized from **66** in four steps as proposed in Scheme 71. The stepwise hydrogenation of **66** is known to give deoxydihydrowithaferin A **107**.[218,254] Tosylation of a C-4 hydroxyl group of compound **107** would give tosylate **108**, which upon treatment with alumina (Al_2O_3) would afford enone **109**. This tosylation-deoxygenation protocol to afford the α,β-unstaurated ketone in ring A has been used for the conversion of 2,3-dihydro derivative of 4β-hydroxywithanolide E **110** to withanolide E **111** (Scheme 72).[255] Lastly, there are literature precedents for the opening of the 5β,6β-epoxide ring in withanolides lacking 4β-hydroxyl group with HCl solution in ether to provide 5α-chloro-6β-hydroxy derivative such as **105** (see Figure 27 and Scheme 71).[224,230]

Scheme 71. Proposed Synthetic Route for 105 from 66

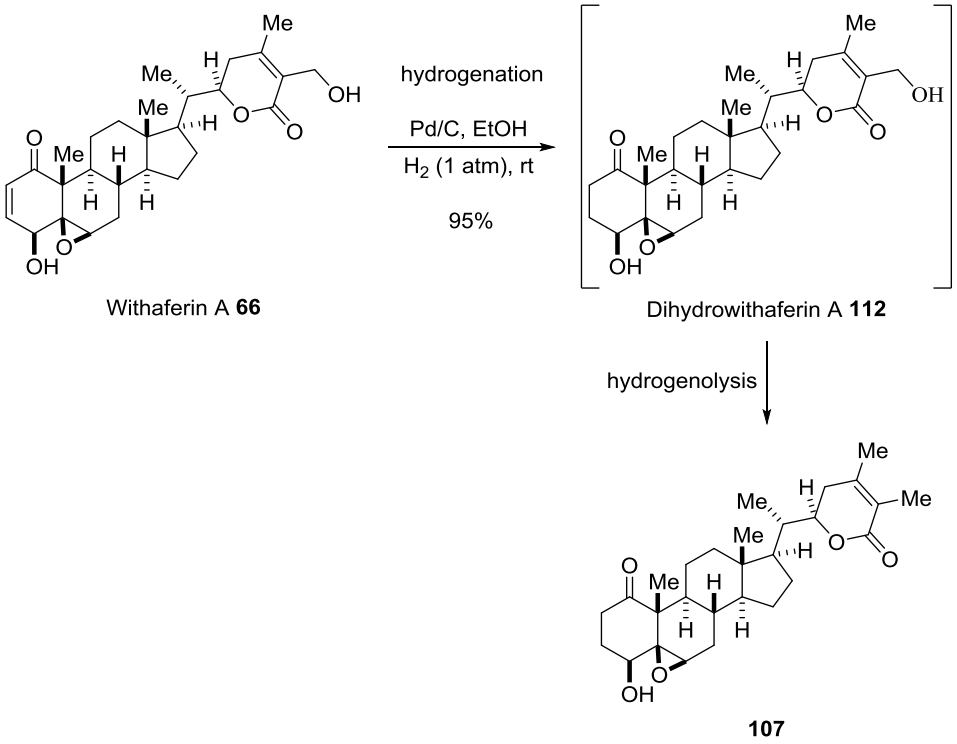


Scheme 72. Conversion of 2,3-Dihydro-4β-hydroxywithanolide E into Withanolide E



On the basis of above-mentioned precedents, the synthesis of **105** began with the initial hydrogenation step in the synthetic sequence (Scheme 73). Treatment of **66** with palladium on carbon (Pd/C) in the presence of H_2 gave **107** in excellent yield via a dihydrowithaferin A intermediate **112**. During the optimization of the hydrogenation reaction of **66**, we found that short reaction times predominantly gave the hydrogenated product, dihydrowithaferin A **112**, as a major product. However, running the same reaction for slightly longer period afforded complete conversion of **112** to **107** through hydrogenolysis.

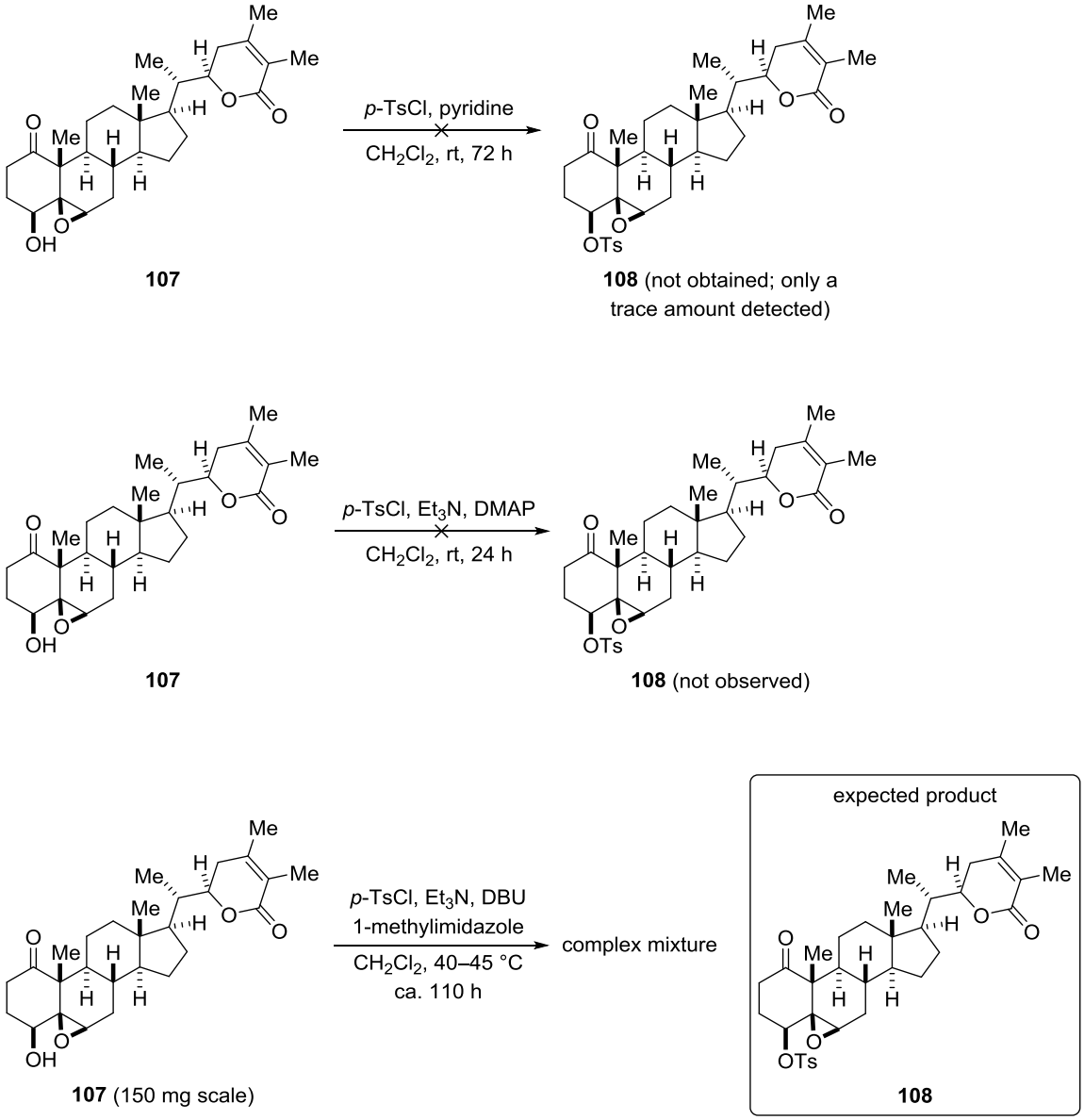
Scheme 73. One-Pot Hydrogenation and Hydrogenolysis Reaction of 66 to 107



With **107** in hand, several attempts were made to synthesize the corresponding tosylate **108** (Scheme 74). Initially, a small scale tosylation reaction of **66** was carried out with excess *p*-TsCl and pyridine following a reported protocol.[255] To our surprise, only a trace amount of tosylate product **108** was detected from the mass analysis of a crude reaction mixture even after 72 h of stirring at room temperature. No product was observed when stronger bases such as Et_3N and DMAP were used. Another small scale reaction (on a 10 mg scale) employing excess amounts of *p*-TsCl, Et_3N, 1-methylimidazole,[256] and DBU at 40 °C led to some product formation as seemed evident by mass and ^1H NMR analysis of a mixture. Unfortunately, running the tosylation reaction under similar conditions on a 150 mg scale resulted in a complex mixture (Scheme 74). Attempts to isolate the desired product **108** from this complex mixture through multiple purification processes were

unsuccessful. During these trial experiments, all of the starting material **107** was exhausted, thus no further pursuits were made to complete the synthesis of **105**.

Scheme 74. Unsuccessful Attempts toward the Synthesis of Tosylate 108 from 107



Cytotoxic Evaluation (carried out in the laboratory of Dr. Mark Cohen)

Withanolides **66**, **67**, **102**, **103**, and **106** were tested against the HNSCC (JMAR and MDA-1986), melanoma (B16F10 and SKMEL-28), and normal fetal lung fibroblast (MRC-5) cells for their antiproliferative activities. As shown in Table 22, withanolides **66**, **67**, **102**, **103**, and **106** exhibited cytotoxic effects against the cells tested with IC_{50} values in the range of 0.15–12.5 μM. As consistent with previous observations,[212c,223a] **103** and **106** containing essential functionalities (the α,β-unsaturated ketone in ring A, the 5β,6β-epoxide in ring B, and the δ-lactone side chain) were active. The acetylated analogue **106** showed increased cytotoxic activities against all cell lines tested compared to the parent compound **103**. It is interesting to note that all three isomers, **66** (with a 27-hydroxyl group), **102** (with a 19-hydroxyl group), and **103** (with a 7β-hydroxyl group), only differing in the position of their hydroxyl groups demonstrated potent cytotoxic activities. This observation not only revealed the significance of the above-mentioned functionalities, but also supported the hypothesis that the presence of a hydroxyl group at either C-27, C-19, or C-7 is not critically responsible for the observed antiproliferative activity.[212c]

Table 22. Cytotoxicity IC_{50} of Withanolides (μM) against Five Cell Lines[a]

compound	B16F10	SKMEL-28	JMAR	MDA-1986	MRC-5
withalongolide O **103**	1.82 ± 0.21	0.33 ± 0.06	3.2 ± 0.62	1.5 ± 0.08	1.3 ± 0.11
withalongolide O diacetate **106**	0.69 ± 0.14	0.18 ± 0.03	0.83 ± 0.14	0.54 ± 0.07	0.53 ± 0.12
withaferin A **66**	0.27 ± 0.04	3.5 ± 0.15	1.5 ± 0.23	0.86 ± 0.25	0.32 ± 0.06
withalongolide A **67**	11.6 ± 0.19	5.6 ± 0.60	5.1 ± 0.23	3.10 ± 0.46	12.1 ± 0.42
withalongolide B **102**	0.26 ± 0.07	3.3 ± 0.48	0.25 ± 0.14	1.7 ± 0.08	0.38 ± 0.03
cisplatin (positive control)	1.4 ± 0.35	1.7 ± 0.32	1.5 ± 0.41	1.9 ± 0.58	9.1 ± 0.25

[a]For cell lines used, see the text.

4.3 Conclusions

A novel withanolide, withalongolide O **103**, bearing a rare C-7 hydroxyl group was discovered during the isolation of withaferin A **66**. The structure elucidation of **103** was carried out through extensive spectroscopic data interpretations and chemical methods (acetylation), and its structure was finally confirmed by single-crystal X-ray analysis. Efforts were made to synthesize withanolide **105** from **66** through semisynthesis; however, all attempts towards the tosylation reaction of C-4 hydroxyl of **107** were unsuccessful, eventually leading to its depletion.

4.4 Experimental Section

General Information. All reactions were performed under nitrogen atmosphere either in capped vials or oven-dried glassware. All chemicals were used as received from commercial source without further purification. Commercial anhydrous pyridine was used. TLC was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Preparative TLC was carried out using glass-backed TLC plates (silica gel GF with UV 254 nm, 1000 microns). Visualization was accomplished with UV light. Solid phase extraction (SPE) phase separator tabless (6 mL) was used for filtration/elution during preparative TLC purification. Flash chromatography was carried out on a CombiFlash Rf purification system using a 24 g normal-phase RediSep silica flash column. IR spectra were acquired as thin films on a FTIR instrument. All NMR spectra (^{1}H, ^{13}C, APT, COSY, HSQC, HMBC, and NOESY) were recorded on a 500 MHz with a dual carbon/proton cryoprobe instrument. All NMR samples were recorded in $CDCl_3$ that was passed through basic alumina. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent (δ 7.26 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR). Coupling constants are given in Hertz (Hz). HRMS data were collected with a LCT Premier time-of-flight mass spectrometer and an electrospray ion source. Optical rotation was measured on a Rudolph RS Autopol IV automatic polarimeter. UV–visible spectrum was obtained on Agilent 8453 UV–Visible Spectrophotometer. Data was processed using Agilent UV–Visible Chemstation and Microsoft Excel. Single-crystal X-ray analyses were performed using Cu Kα radiation (λ = 1.54178 Å) with either Bruker APEX2 or Platinum 135 CCD detector. X-rays were provided by a Bruker MicroStar microfocus rotating anode equipped with Helios multilayer optics.

Cytotoxicity Assay. The cytotoxicity assays were performed as previously described.[220] In general, ten concentrations ranging from 50 nM to 20 μM were tested for each withanolide. Statistical analysis was carried out by one-way ANOVA on ranks test using GraphPad Prism 5 software. IC_{50} values were obtained from cell viability plots fitted with a sigmoidal dose-response function with variable slope using GraphPad Prism 5 software.

Experimental Procedures

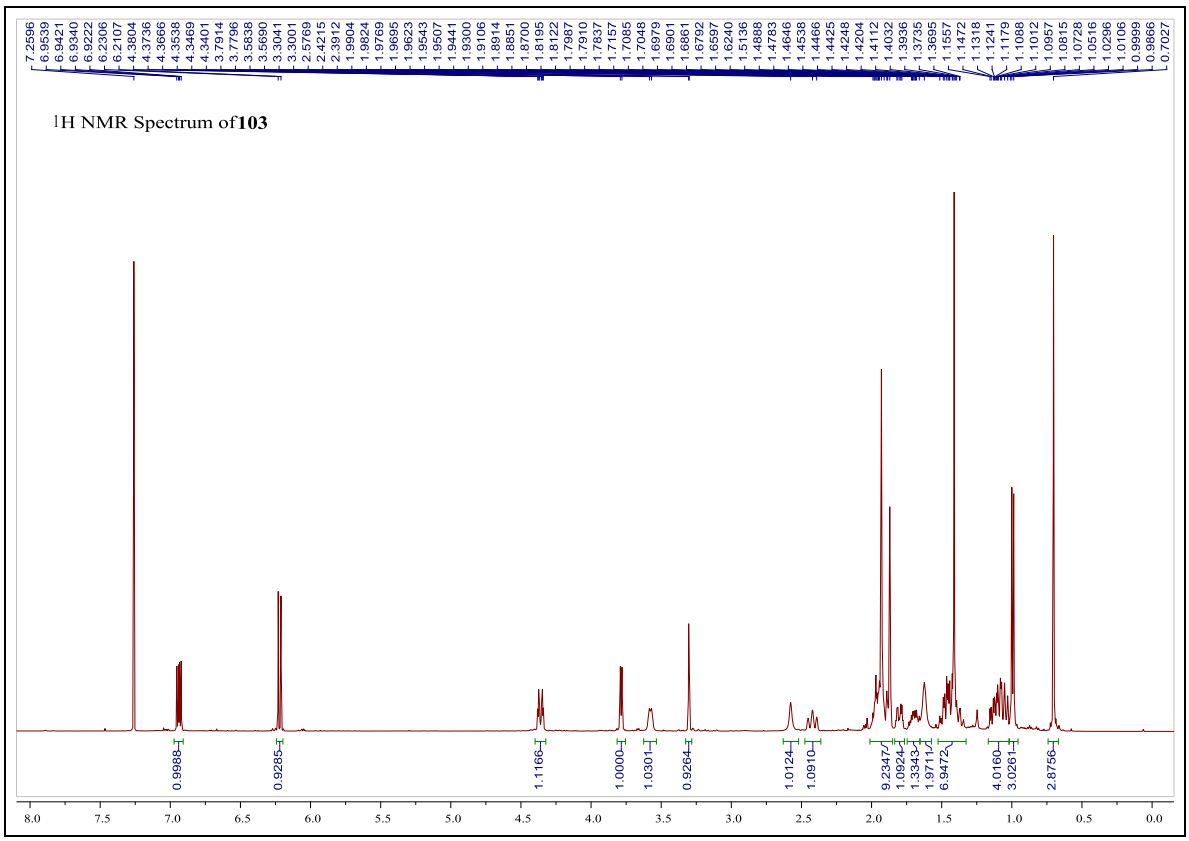
Isolation of Withaferin A 66 and Withalongolide O 103 (Figure 28). Purification of 1.52 g of crude **66** using a 24 g flash column on a CombiFlash Rf system (0–10% MeOH/CH_2Cl_2) afforded 600 mg of impure **66** (eluted out at 2% MeOH in CH_2Cl_2), followed by 140 mg of fraction **A1** containing a mixture of impure **66** and other unidentified products (eluted out at 2–3% MeOH in CH_2Cl_2). Then, 35 mg of fraction **A** containing a mixture of other unidentified compounds eluted out at 3% MeOH in CH_2Cl_2, followed by 130 mg of fraction **B** containing a complex mixture of unidentified compounds (eluted out at 3–5% MeOH in CH_2Cl_2), and 500 mg of fraction **C** containing a complex mixture of polar unidentified products (eluted out at 5–10% MeOH in CH_2Cl_2). Finally, elution with 100% MeOH provided 35 mg of fraction **D** and 125 mg of fraction **E**.

Treatment of 600 mg of impure **66** (greenish oily residue) with activated charcoal in hot CH_2Cl_2 followed by precipitation with ether afforded 460 mg of pure **66** as a creamish-brown solid. Fraction **A1** containing some impure **66** was purified twice by preparative TLC plate developing three times with 3% MeOH/CH_2Cl_2, three times with 20% EtOAc/CH_2Cl_2, and one time with 2% MeOH/CH_2Cl_2. The band corresponding to the **66** was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator

tabless. Evaporation of solvents gave an additional 11 mg of pure **66** (overall yield of **66** = 471 mg).

Prep TLC purification of fraction **A** was unsuccessful and led to 21 mg of a mixture of unidentified compounds. Fraction **B** was purified by preparative TLC developing three times with 3% MeOH/CH_2Cl_2, one time with 20% EtOAc/CH_2Cl_2, and two times with 10% EtOAc/CH_2Cl_2. A mixture of overlapping low R_f bands was scraped from the plate and eluted with 10% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents gave 40 mg of a crude mixture containing **103**. This crude mixture was re-purified by preparative TLC plate developing three times with 20% EtOAc in CH_2Cl_2 and one time with 2% MeOH in CH_2Cl_2. A high R_f band containing **103** and low R_f bands consisting of a mixture of unidentified products were scraped from the plate separately and eluted with 5% MeOH in CH_2Cl_2. Evaporation of solvents for the high R_f band gave 7.0 mg of sufficiently pure **103** as an off-white solid, which was recrystallized from EtOAC to afford a partially crystallized material as off-white crystals. Crystals of **103** were used for X-ray diffraction analysis (see Table S28). The mixture of unidentified products present in a low R_f bands were not purified further. Fractions **C**, **D**, and **E** containing complex mixtures of polar spots were not subjected to additional purification processes.

(4*S*,20*S*,22*R*)-4*β*,7*β*-Dihydroxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide O, 103). R_f = 0.26 (4% MeOH/CH_2Cl_2, run twice); $[\propto]_D^{25}$ = +101.5 (*c* 0.0886, EtOH); UV λ_{max} (EtOH) nm = 206; IR (neat) 3419 (br), 2937, 1685, 1397, 1128, 1034, 916, 732 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{39}O_6$ $[M + H]^+$ 471.2741, found 471.2749. For ^1H and ^{13}C NMR data, see Table 21. For 1D and 2D NMR spectra, see below.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6.9340
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6.2306
6.2107
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4.3469
4.3401
3.7914
3.7796
3.5838
3.5690
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1.9904
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1.9106
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1.4204
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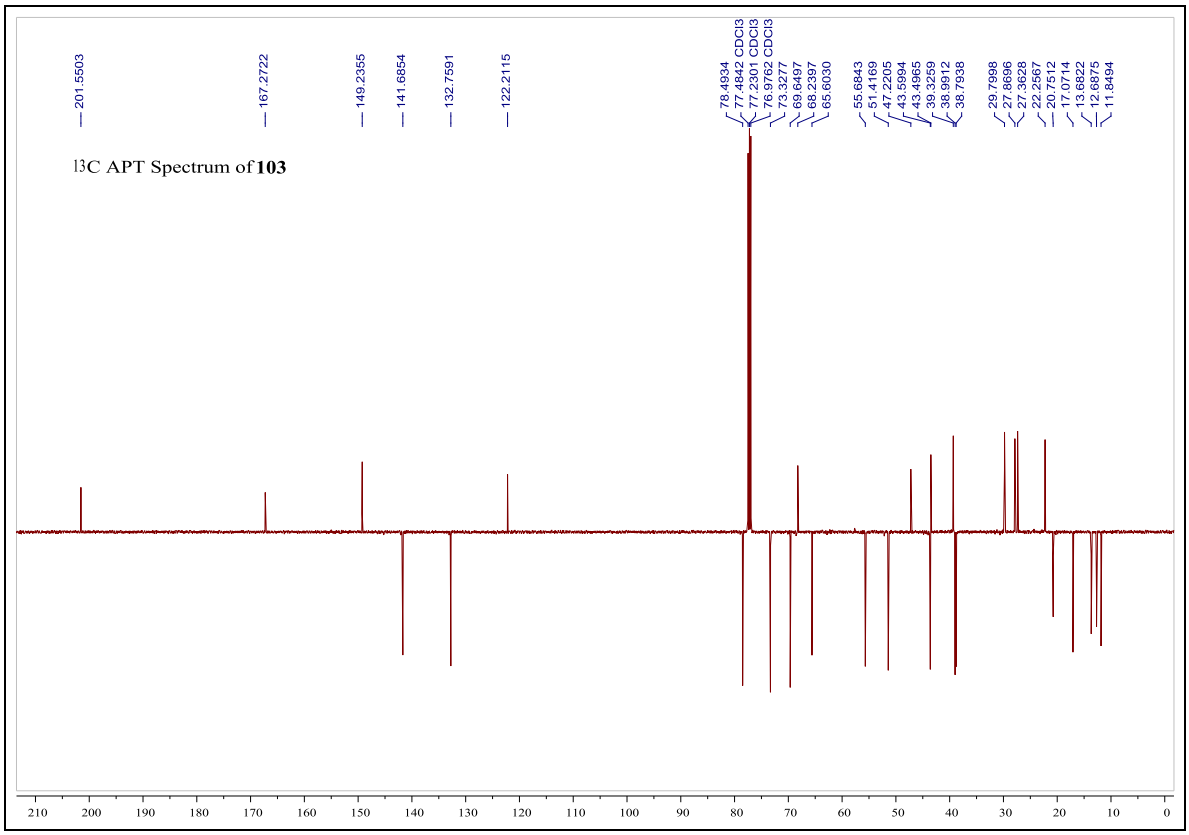
1.1472
1.1318
1.1241
1.1179
1.1088
1.1012
1.0957
1.0815
1.0728
1.0516
1.0296
1.0106
0.9999
0.9866
0.7027
1H NMR Spectrum of 103
0.9988
0.9285
1.1166
1.0000
1.0301
0.9264
1.0124
1.0910
9.2347
1.0924
1.3343
1.9711
6.9472
4.0160
3.0261
2.8756
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


201.5503
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149.2355
141.6854
132.7591
122.2115
78.4934
77.4842 CDCl3
77.2301 CDCl3
76.9762 CDCl3
73.3277
69.6497
68.2397
65.6030
55.6843
51.4169
47.2205
43.5994
43.4965
39.3259
38.9912
38.7938
29.7998
27.8696
27.3628
22.2567
20.7512
17.0714
13.6822
12.6875
11.8494
13C APT Spectrum of 103
210
200
190
180
170
160
150
140
130
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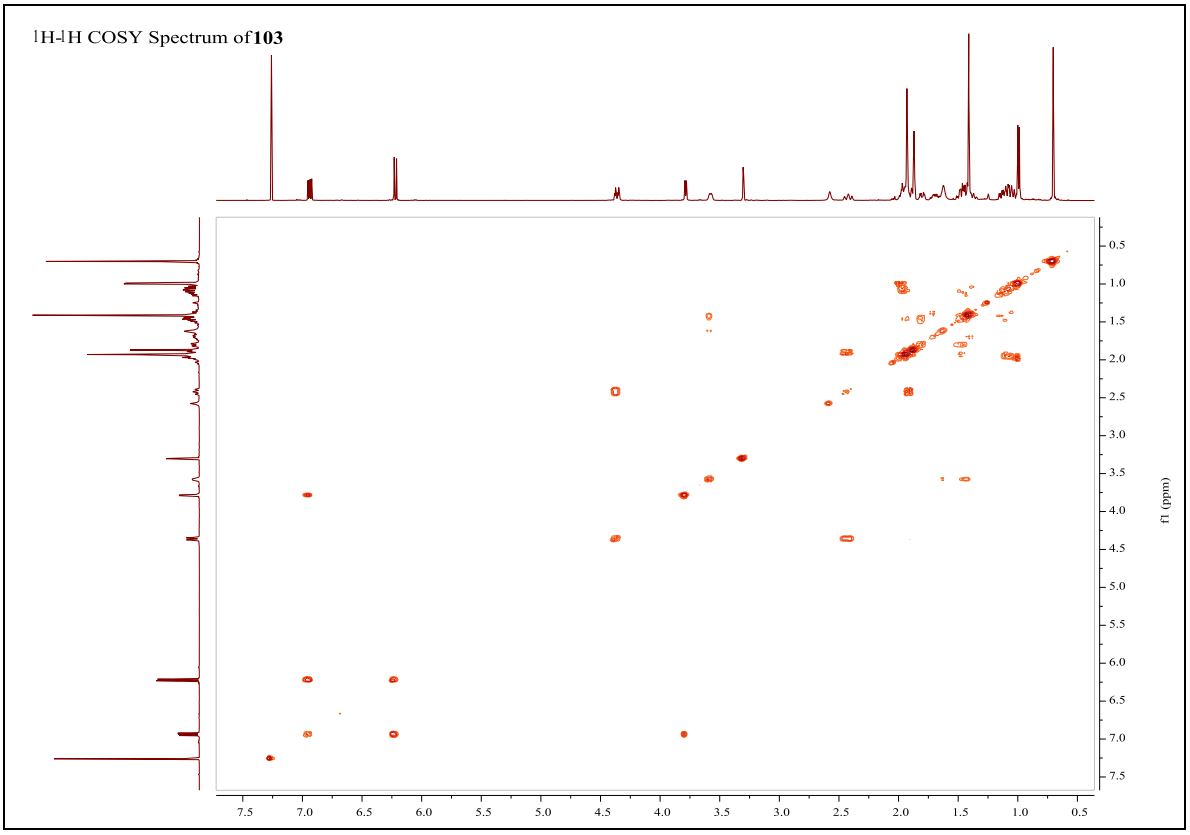
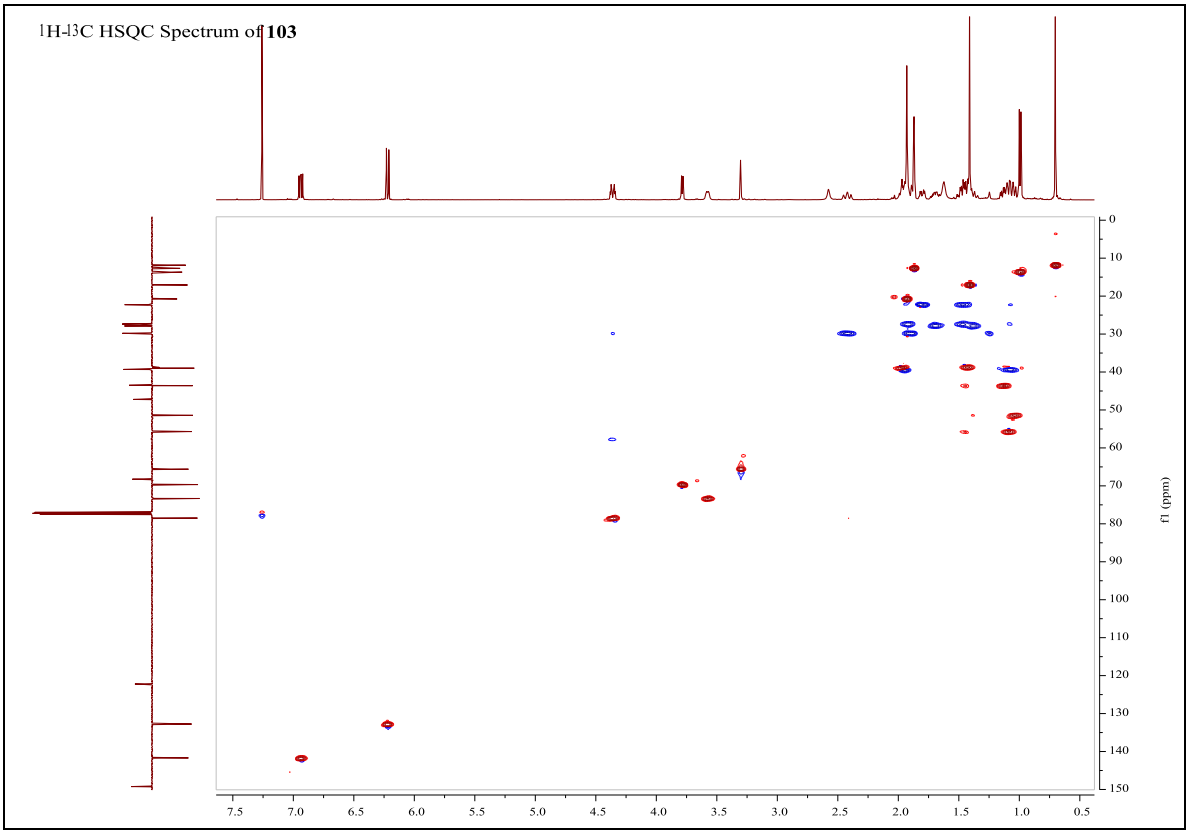
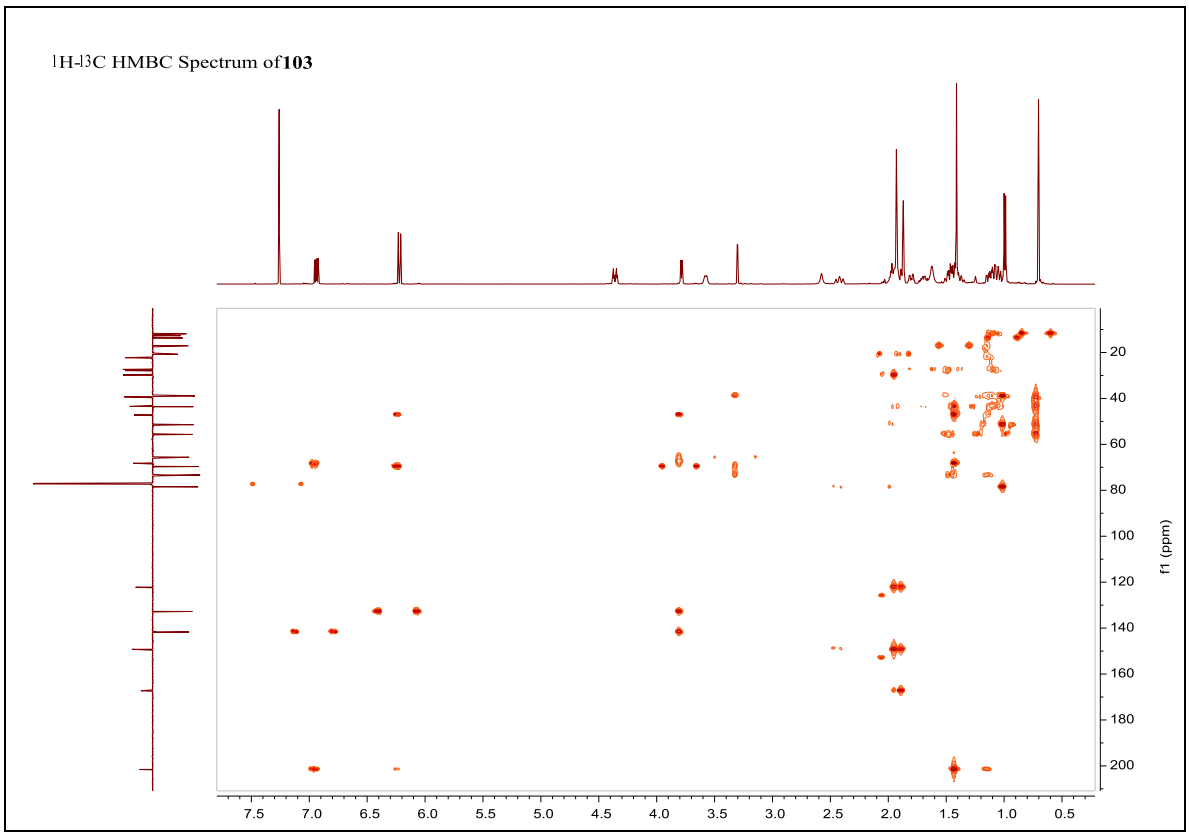
90
80
70
60
50
40
30
20
10
0


^{1}H-^{1}H COSY Spectrum of **103**
f1 (ppm)


^{1}H-^{13}C HSQC Spectrum of **103**
f1 (ppm)

^{1}H-^{13}C HMBC Spectrum of **103**



^{1}H-^{1}H NOESY Spectrum of **103**

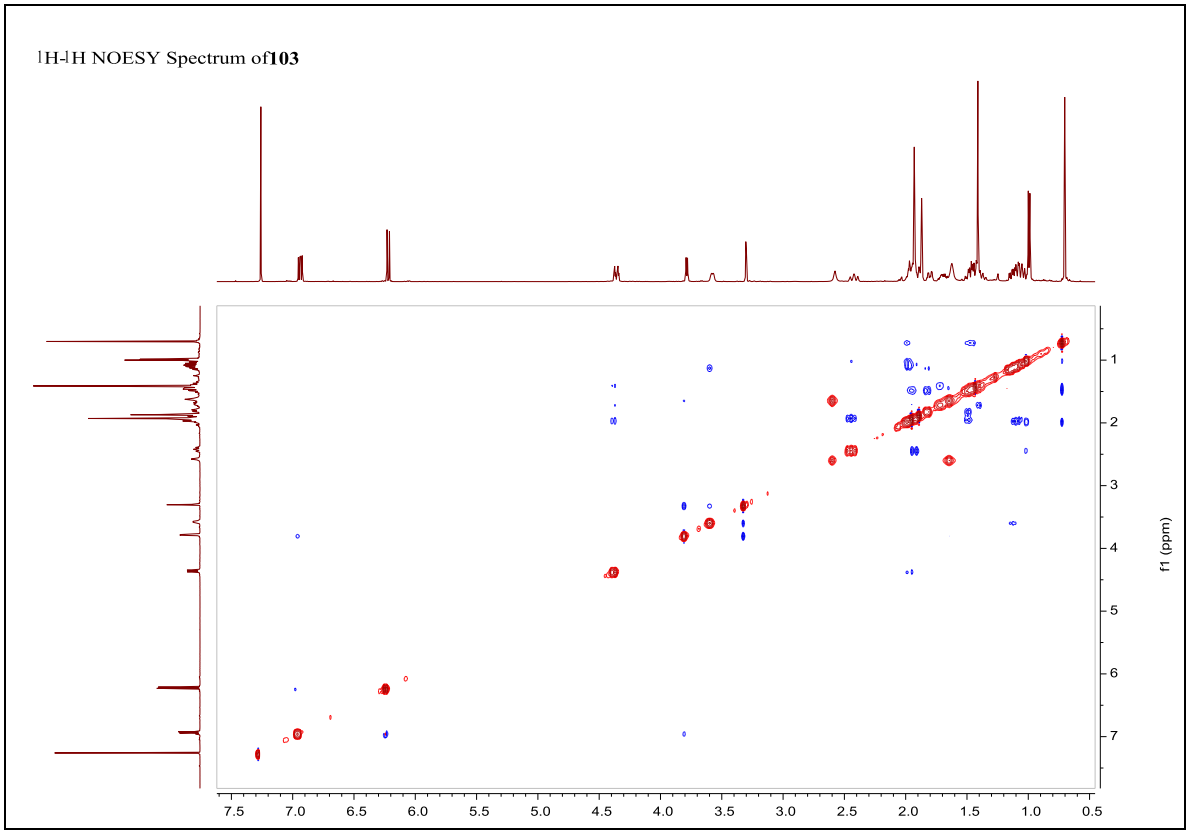


Table S28. Selected Crystallographic and Refinement Parameters for Withalongolide O 103

Compound	Withalongolide O **103**
CCDC deposition number	974653
Empirical formula	$C_{32}H_{46}O_8$ ($C_{28}H_{38}O_6$ + $CH_3COOCH_2CH_3$)
Formula wt.	558.69
Temperature	100(2) K
Crystal color	Colorless
Crystal system	Monoclinic
Crystal habit	Triangular plate
Crystal size (mm^3)	0.34 × 0.26 × 0.09
Space group	$P2_1$
a [Å]	10.8300(19)
b [Å]	12.273(2)
c [Å]	11.693(2)
α [deg]	90
β [deg]	112.283(3)
γ [deg]	90
Z	2
Volume [$Å^3$]	1438.0(4)
D*calc* [Mg/m^3]	1.290
F (000)	604
Absorption coefficient μ [mm^{-1}]	0.743
Theta range for data collection	4.09 to 67.39°
Range h	–12<=h<=12
Range k	–14<=k<=14
Range l	–13<=l<=12
Reflections collected	15638
Independent reflections	4754
R_{int}	0.0235
Data / Restraints / Parameters	4754 / 1 / 533
Final R indices [I>2σ(I)]	0.0257
wR_2	0.0678

Compound	Withalongolide O **103**
Absolute structure parameter	0.02(10)
Goodness-of-fit on F^2	1.031
R-factor (%)	2.57
Largest diff. peak and hole ($e \cdot Å^{-3}$)	0.190 and –0.154

The HPLC purity of crude **66** and different fractions were deceptive as the HPLC chromatogram showed a number of overlapping and merged peaks. Thus, the actual content of **66** in the crude material was misleading in terms of percent purity.

fractions	HPLC purity of **66**
crude **66**	85%
fraction **A**	42%
fraction **B**	29%
fraction **C**	28%
fractions **D** and **E**	0%

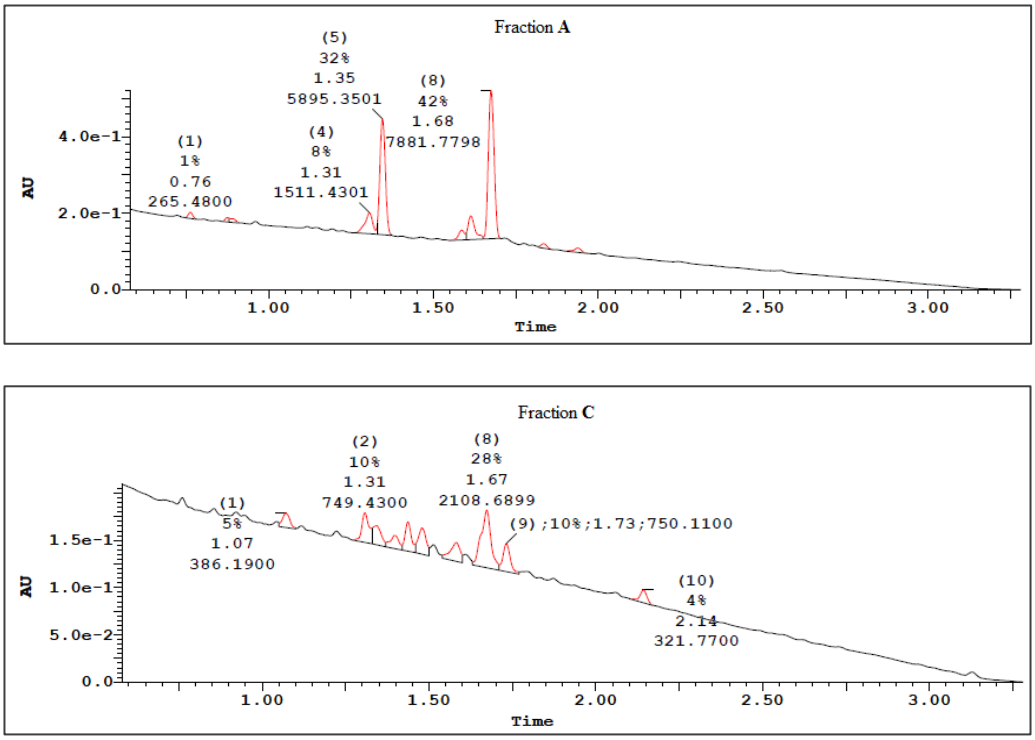
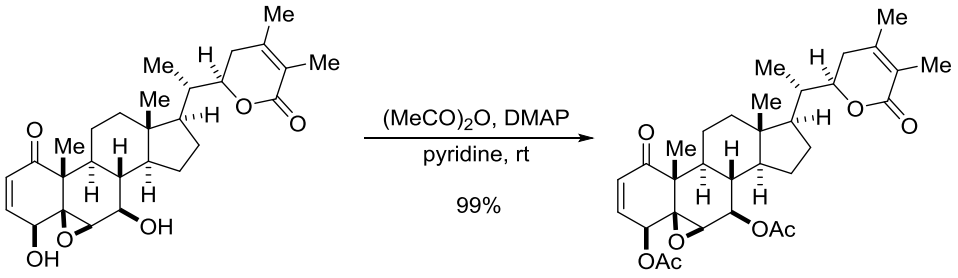
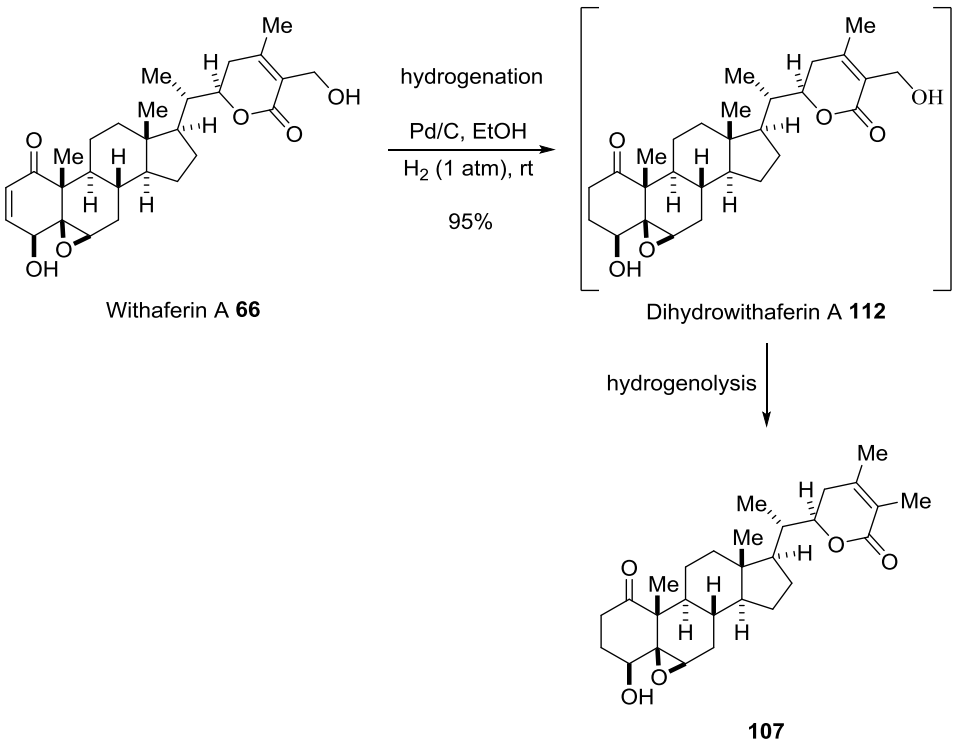


Figure S5. Representative HPLC chromatograms for fractions **A** and **C** containing **66** (peak (8) in chromatograms).



Withalongolide O **103** Withalongolide O diacetate **106**

(4*S*,20*S*,22*R*)-4*β*,7*β*-Diacetyloxy-5*β*,6*β*-epoxy-1-oxowitha-2,24-dienolide (withalongolide O diacetate 106; Scheme 70). A solution of withalongolide O **103** (4.2 mg, 0.0089 mmol, 1.0 equiv) and a small pellet of DMAP (ca. 1–2 mg) in pyridine (0.10 mL) and acetic anhydride (0.10 mL) in a nitrogen-flushed vial was stirred at rt for 1.5 h. The reaction mixture was concentrated and then quenched with ethanol. The volatile residues were removed under reduced pressure. The pale yellow residue obtained was purified by preparative TLC developing two times with 2% MeOH/CH_2Cl_2. The band corresponding to the product was scraped from the plate and eluted with 5% MeOH/CH_2Cl_2 through a phase separator tabless. Evaporation of solvents afforded **106** as a colorless waxy solid (4.9 mg, 99%). Withalongolide O diacetate **106**: R_f = 0.84 (4% MeOH/CH_2Cl_2, run twice); UV λ_{max} (EtOH) nm = 216; IR (neat) 2927, 1736, 1702, 1372, 1230, 1125, 1023, 914, 731 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{43}O_8$ $[M + H]^+$ 555.2952, found 555.2944. For ^1H and ^{13}C NMR data, see Table 21.



(4*S*,20*S*,22*R*)-2,3-Dihydro-5β,6β-epoxy-4β-hydroxy-1-oxowitha-24-enolide (deoxydihydrowithaferin A 107; Scheme 73).[218] A flask containing a stirring suspension of withaferin A **66** (200 mg, 0.426 mmol, 1.0 equiv) and Pd/C (10% Pd basis; 20.0 mg) in ethanol was sealed with a septum and evacuated briefly under vacuum. The reaction flask was refilled with a hydrogen (H_2) gas using a H_2 balloon (atmospheric pressure) and the reaction mixture was allowed to stir at rt for 3.5 h (TLC analysis showed the presence of mostly dihydrowithaferin A **112** at 75 min and both **112** and **107** at 3.5 h). Since the reaction was progressing slowly, additional Pd/C (10.0 mg) was added and the old H_2 balloon was replaced with a new one. The reaction mixture was further strirred at rt for 1.5 h (TLC analysis showed complete conversion to **107**). The reaction mixture was concentrated and the suspension of resulting residue in CH_2Cl_2 was loaded on a silica gel in a 5 g sample cartridge. Purification using a 4 g flash column on a CombiFlash Rf system (0–1% MeOH/CH_2Cl_2) afforded **107** (eluted between 0.7–1% MeOH/CH_2Cl_2) as a colorless crystals in 95% yield (185 mg, 0.405 mmol). R_f = 0.62 (4% MeOH/CH_2Cl_2, run

twice); IR (neat) 3403, 1706, 1686, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.63 (s, 3H), 0.88–0.93 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 1.02–1.15 (complex, 4H), 1.22–1.40 (complex, 5H), 1.27 (s, 3H), 1.57–1.70 (m, 2H), 1.84 (s, 3H), 1.86–1.88 (m, 1H), 1.90 (s, 3H), 1.90–2.03 (m, 3H), 2.04–2.12 (m, 1H), 2.17 (m, 1H), 2.39 (t, J = 15.3 Hz, 1H), 2.46–2.63 (m, 2H), 2.75 (br s, 1H), 3.10 (s, 1H), 3.47 (t, J = 3.4 Hz, 1H), 4.32 (dt, J = 13.2, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 12.6, 13.5, 15.5, 20.7, 21.5, 24.4, 26.4, 27.4, 29.5, 29.7, 31.5, 31.8, 38.9, 39.2, 42.8, 43.2, 50.6, 52.1, 56.4, 58.9, 66.8, 72.9, 78.4, 122.1, 149.2, 167.2, 211.6; HRMS (ESI) *m/z* calcd for $C_{28}H_{41}O_5$ $[M + H]^+$ 457.2954, found 457.2973.

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