Sustainable Strategies for the Transition Metal-Catalyzed Direct Functionalization of C–H and C–O Bonds

Dissertation

in partial fulfillment of the requirements for the degree of

doctor rerum naturalium (Dr. rer. nat.)

at the University of Rostock

Faculty for Mathematics and Natural Sciences

submitted by

Jola Pospech

M.Sc. University of Göttingen

Born December 21st 1986

in Pinneberg, Germany.

Leibniz Institute for Catalysis

at the University of Rostock

2014

urn:nbn:de:gbv:28-diss2016-0044-1

Selbstständigkeitserklärung

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer die von mir angegebenen Hilfsmittel und Quellen dazu verwendet habe und die den benutzten Werken inhaltliche und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, den 24.10.2014

…………………………………
Jola Pospech

Die vorliegende Dissertation wurde vom 01.03.2012 bis 24.10.2014 am Leibniz-Institut für Katalyse e.V. an der Universität Rostock unter Anleitung von Prof. Dr. Matthias Beller erstellt.

1. Gutachter: Prof. Dr. Matthias Beller
2. Gutachter: Prof. Dr. Troels Skrydstrup
3. Gutachter: Prof. Dr. Christoph Schneider

Tag der mündlicher Prüfung: 6. Januar 2015

Sustainable Strategies for the Transition Metal-Catalyzed Direct Functionalization of C–H and C–O Bonds

Dissertation

in partial fulfillment of the requirements for the degree of

doctor rerum naturalium (Dr. rer. nat.)

at the University of Rostock

Faculty for Mathematics and Natural Sciences

submitted by

Jola Pospech

Leibniz Institute for Catalysis

at the University of Rostock

2014

Acknowledgements

First of all, I would like to express my gratitude to my supervisor *Prof. Dr. Matthias Beller* for accepting me as a PhD student in his group. I appreciate your kind advice and guidance whenever I needed it. Foremost, I'm grateful to you for giving me free rein to pursue research in my own approach.

Secondly, I'd like to thank *Prof. Dr. Troels Skrydstrup* and *Prof. Dr. Lutz Ackermann* for their kind support and steady interest in my professional development. Thank you!

In direct relevance to this thesis, I'd like to sincerely thank my "proof-reading committee": *Dr. Sabine Fenner*, *Dr. Damien Valette*, *Dr. Helfried Neumann*, *Stefan Oschatz*, *Anja König* and *Irina Profir*. It was shocking that every one of you found different mistakes. I truly don't want to know what's still hiding in here…

In order of appearance in my life in Rostock, I would first like to thank *Irina Profir*. Settling in the middle of nowhere and getting started in the lab was undoubtedly easier with you by my side. *Dr. Ivana Fleischer*, you've been my most precious source of inspiration, scientific guidance and partner in crime during the first two years in Rostock. *Antonia Pioch*, best roommate ever that never shared a flat with me. I loved living two floors above you; I hated it when you had to move out – still thinking of you every single Sunday night. *Stefan Oschatz*, thank you for distracting me during our lunch breaks- we share the same terrible sense of humor. *Anja König*, you are amongst the most kind and caring persons I've ever met. Because of you, I had an incredible and physically active last summer. I'm truly grateful for your support, honesty, advice and faith in me. *Christoph Blunk,* thank you for your company and warmth.

I am greatly indebted to the team of the analytic department of the LIKAT. Although we have a different opinion about lightning speed, I'm grateful for your performance. Special thanks go to *Susanne Schareina*, *Niels Rudat* and *Bianca Wendt* for taking care of my HPLC sample. Talking about lightning speed: *Dr. Anke Spannenberg*, you measure and solve crystal structures within the blink of an eye! *Andreas Koch*, I can't wait to escape from that terrible NMR machine, you have suffered with me. Apropos NMR: *Dr. Dirk Michalik*, thank you for measuring countless samples for me. You have always been exceedingly helpful, interested and enthusiastic. Thank you!

The lady and gentlemen from the *Ausgabe*, *Claudia Zielke*, *Torsten Dwars* and *Torsten Weiss*, you did a great job. I always wondered how you continuously managed to keep equal amounts of right and left handed nitrile gloves in stock. *Mr. Schupp*, *Schiller*, *Hutter* and *Schwemin* thank you for all kinds of technical support. *Mr. Salzwedel,* thank you for being available and supportive in all cases of IT blackouts.

Furthermore, I'd like to thank *Dr. Barbara Heller* for her help and assistance with the *"Rostock's Eleven"* venture which I record as an personally and professionally enriching experience. I also enjoyed our occasional chats at the hallway; the same applies for *Dr. Johannes Treu*. *Mrs. Kirmse*, *Mrs. Koch* and *Ms. Rehbein*, I'm truly sorry for messing with the business trip reimbursement forms every single time – thank you for your patients. *Jan Stetzkowski*, I always enjoyed meeting you at random places in and around Rostock.

Of course, I'd like to extend my gratitude to *Anne Tonn*, *Nicole Aulerich* and *Karin Thiel* for helping with the quest to find a free slot in Matthias' calendar. *Anne*, you have a great personality; Matthias is blessed to have you as a guard.

My Chinese Crowd: *Dr. Qiang Liu*, *Haoquan Li*, *Dr. Yuting Fan*, *Kedong Yuan*, *Lipeng Wu*, *Dr. Min Zhang*, *Dr. Yang Li,* and just recently *Jie Li*, with all of whom I had the pleasure to share the lab during the past 3 years. I hold all of you in high esteem and thank you for your cooperation and kindness. The same applies for our frequent visitors *Zhanjie Fang, Dr. Yuhue Li, Dr. Lin He, Dr. Wanfang Li* and *Dr. Kaiwu Dong*. You created a special atmosphere. Unfortunately, my Chinese is still pretty bad!

Most of all I'd like to thank *Sabine Fenner* for being my best friend and my emergency contact, for offering help in all aspects of life and knowing me by heart.

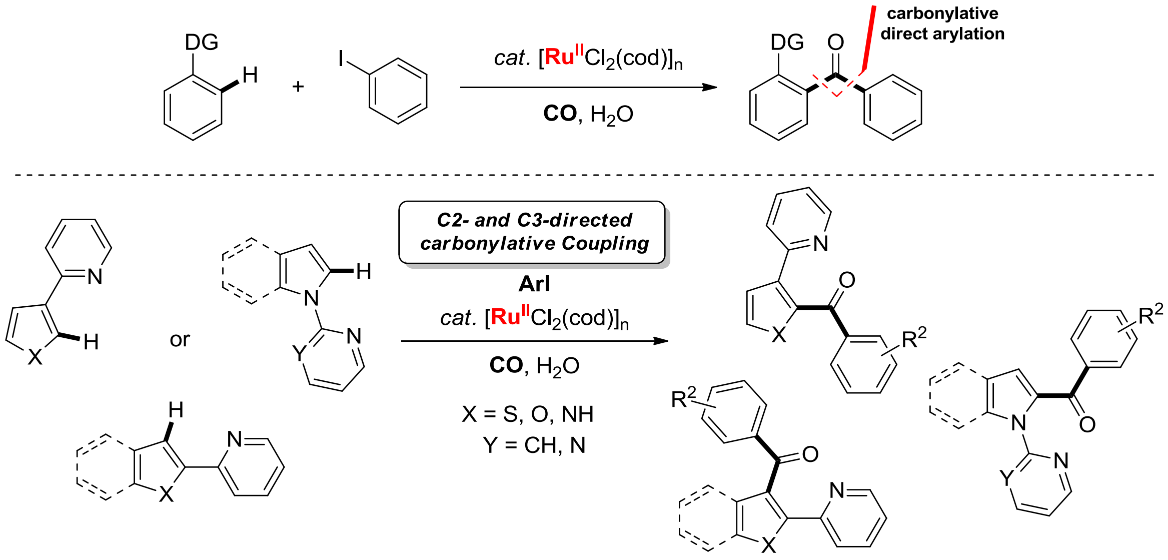
Meine Freunde und Familie: Danke, dass ihr am Tag meiner Verteidigung wie auch an jedem Tag zuvor für mich da wart. Eure Unterstützung bedeutet mir unendlich viel!

Abstract

In the past decades a significant number of pharmaceuticals emerged from conscious design and screening of small molecule drugs, purposely invented and developed by medicinal and pharmaceutical chemists. Medicinal chemistry in its most common guise – directed towards small organic molecules – has become a vivid interplay of synthetic organic chemistry, computational chemistry, chemical biology, enzymology and structural biology, together aiming to discover new therapeutic agents. Organic chemists find themselves in the center of this collaboration, as they are demanded to create and optimize lead structures and supply material for biological assays. Therefore, there is a permanent ambition to create new molecular architectures and methodologies that expand the organic chemist's tool box.

This thesis summarizes the development of new transformations for the transition metal-catalyzed introduction of carbon monoxide and alternative C1-building blocks into molecular scaffolds. The developed methodologies provide novel opportunities for the implementation of functional groups and ideally expand the molecular space of organic building blocks.

The first Chapter targets the development of ruthenium-catalyzed carbonylative direct arylation of (hetero)arenes via C−H bond activation. A facile three component synthesis of complex aryl-heteroaryl ketones was enabled upon exploitation of the multifunctional aptitudes of inexpensive ruthenium(II)-catalyst precursors that allow for a successive twofold C(sp^2)−C(sp^2) bond formation via acetate-assisted C−H bond cleavage on water (Scheme I.1). Starting with simple phenylpyridine derivatives, this chemistry was later extended to the preparation of aryl-heteroarylketones including examples with cleavable directing groups. The synthetic applicability of the developed methodology is showcased in the streamlined synthesis of an unprecedented analog of the top-selling selective estrogen receptor modulator Raloxifene (Evista®) and the gram-scale synthesis of a key intermediate of marinopyrroles and pyoluteorin (Figure I.1).



Scheme I.1. Regioselective ruthenium-catalyzed carbonylative direct arylation.

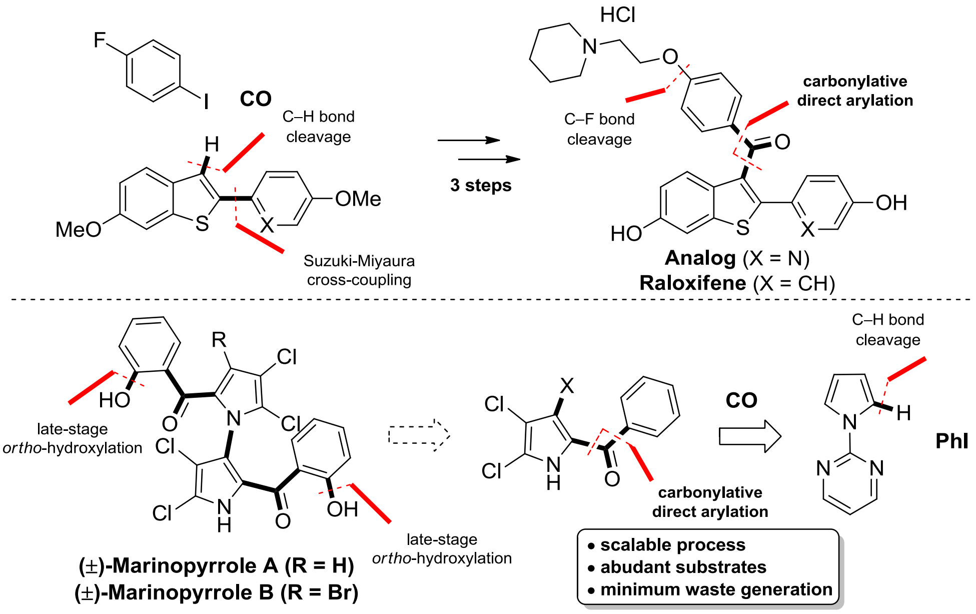
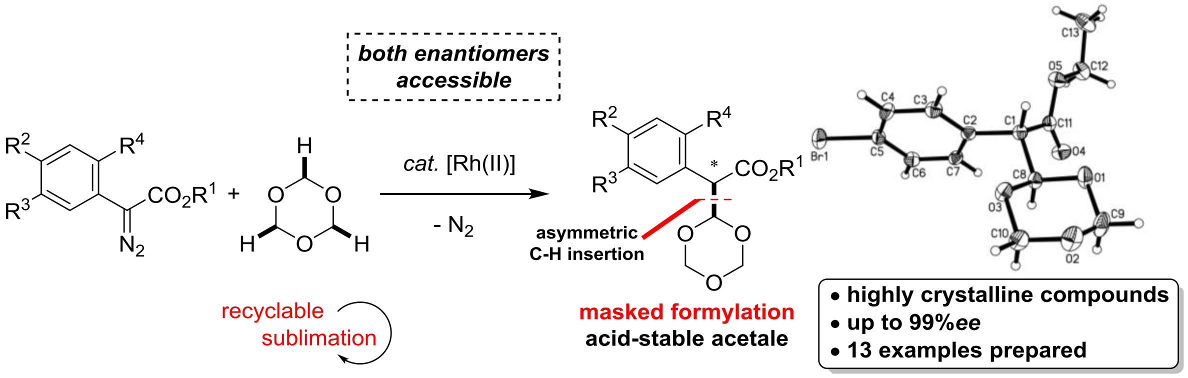


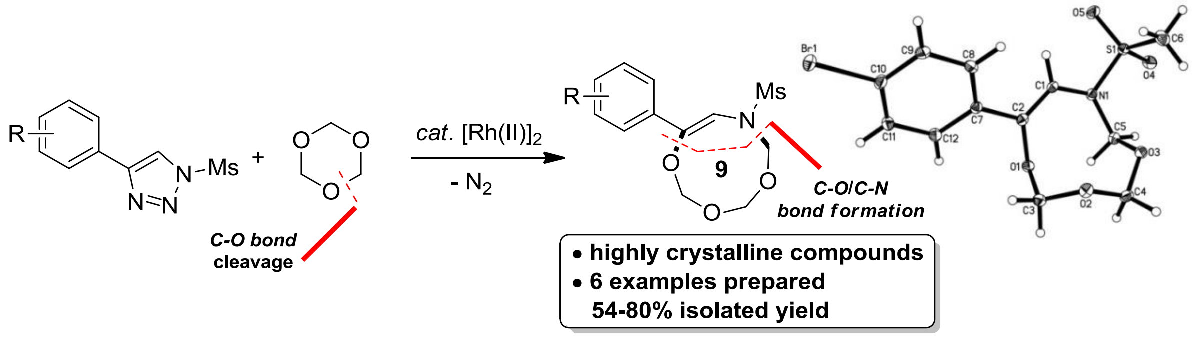
Figure I.1. Synthetic application of the ruthenium-catalyzed direct aroylation protocol. (a) synthesis of a Raloxifene analog. (b) Synthesis of a key intermediate towards the synthesis of marinopyrroles.

The second Chapter describes the enantioselective masked formylation of phenyldiazo acetates using 1,3,5-trioxane as C1 source (Scheme I.2). This protocol represents a new application of rhodium(II) carbenoid mediated C−H bond cleavage in an enantioselective masked-formylation reaction leading to the synthesis of novel alkyl 2-phenyl-2-(1,3,5-trioxan-2-yl)acetates. These compounds demonstrated a high stability of the trioxanyl moiety, thus enabling further functionalization in its presence. Because of its structural relation to naturally occurring arylpropionates such as atropine and artificial methylphenidates, this substance class holds great promise as valuable building blocks for medicinal chemistry.



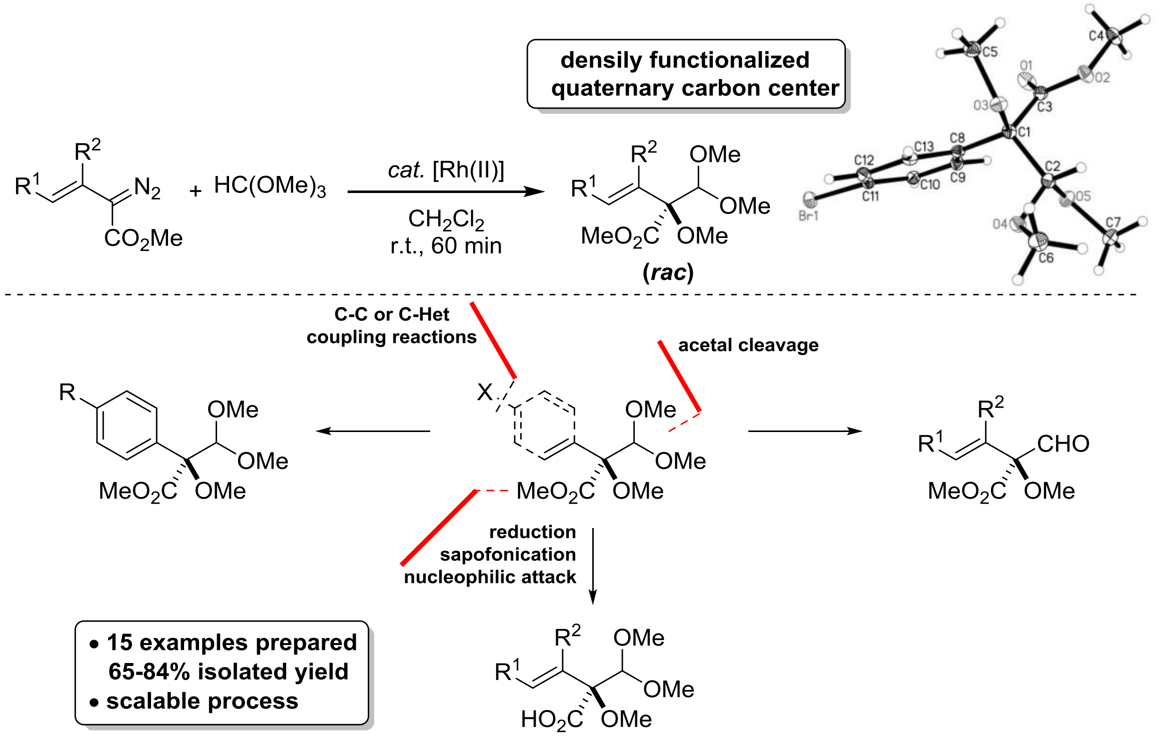
Scheme I.2. Enantioselective masked formylation of rhodium(II) carbenoids using 1,3,5-trioxane.

In a subsequent work, the rhodium(II)-catalyzed decomposition of 1-(methylsulfonyl)-4-aryl-1*H*-1,2,3-triazoles in the presence of 1,3,5-trioxane has been investigated (Scheme I.3). In this reaction, ylide formation of the oxygen-heterocycle with the Rh-carbenoid species outcompetes the C−H bond functionalization pathway. Successful optimization of the reaction condition allowed for the one-pot preparation of unprecedented nine-membered 1,3,5,7-trioxazonine rings.



Scheme I.3. Rhodium(II)-catalyzed decomposition of 1-sulfonyl-1,2,3-triazoles in the presence of 1,3,5-trioxane.

Finally, a conceptually new approach of a concomitant alkoxylation/formylation of diazo compounds through C–O bond activation triggered by rhodium(II) catalysts is described (Scheme I.4). The final Chapter summarizes the development of a new strategy for the one step synthesis of quaternary carbon centers from inexpensive chemical commodities holding an aryl or alkenyl, alkoxy, masked aldehyde and ester functionality.



Scheme I.4. Rhodium(II)-catalyzed alkoxylation-acetalization of donor-acceptor-substituted diazo compounds: one-step synthesis of densely functionalized quaternary carbon centers.

Table of Contents

List of Abbreviations

[M+]	molecular ion peak
Ac	acetyl
Ad	adamantyl
Alk	alkyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*- butyloxycarbonyl
Bu	*n*-butyl
t-Bu	*tert*-butyl
calcd.	calculated
Cat.	catalytic
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCM	Dichloromethane
DFT	density function theory
DG	directing group
2,2-DMB	2,2-dimethylbutane
DMF	*N*,*N*-dimethylacetamide
DMSO	dimethylsulfoxid
DOSP	*N*-(4-dodecylbenzene-sulfonyl) prolinate
d.r.	diastereomeric ratio
Ed.	Editor
ee	enantiomeric excess
EDG	electron-donating group
e.g.	for example
EI	electron ionization
ESI	electrospray ionization
Et	Ethyl
EWG	electron-withdrawing group
equiv.	equivalent
EI-MS	electron ionization mass spectroscopy
OOct	octanoate
eV	electron volt
g	gramm
GC	gas chromatography
h	hours
Hex	*n*-hexyl
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared spectroscopy
isol.	isolated
J	coupling constant
L	ligand
m	*meta*
m	multiplet
[M]	metal
Me	methyl
MeCN	acetonitrile
MeO	methoxy
MeOH	methanol
Mes	mesityl
m.p.	melting point
m/*z*	mass-to-charge ratio
min	minute
mL	milliliter
mmol	millimol
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
o	*ortho*
OAc	acetate
OEt	ethoxy

p	*para*	*t*-AmOH	*tert*-amyl alcohol
Ph	phenyl	TBS	*tert*-butyldimethylsilyl
PhMe	toluene	TFA	trifluoroacetic acid
Piv	pivalate	THF	tetrahydrofuran
ppm	parts per million	TISP	2,4,6-tri-*iso*-propyl-benzenesulfonyl
*i*Pr	isopropyl		
R	rest	TLC	thin layer chromatography
rt	room temperature	TM	transition metal
sat.	saturated	TMS	trimethylsilyl
solv	solved	TPA	triphenylacetate
t	time	X	halide
T	temperature	δ	chemical shift

1 Regioselective ruthenium-catalyzed carbonylative direct arylation of (hetero)arenes

"The development of techniques that can predictably modify C−H bonds selectively would fundamentally change the logic of organic synthesis."

Daniel Morton, Center for Selective C−H Functionalization, Managing Director, Emory University, GA, USA.
(Angew. Chem. Int. Ed. ***2014****, 53, 10256–10259.*)

1.1 Preface

The first chapter outlines the development of ruthenium-catalyzed carbonylative direct arylation of (hetero)arenes through C−H bond cleavage. Introductory, conceptual key factors of transition metal-catalyzed C−C bond formation *via* C−H bond activation are introduced. Special emphasis is put on carbonylative versions of this process. A facile three component synthesis of complex aryl-heteroaryl ketones was enabled by ruthenium(II) catalysis that allows for a successive twofold C(sp^2)−C(sp^2) bond formation *via* acetate-assisted C−H bond cleavage in water.

1.2 Project outline

Aromatic groups are essential and prevailing pharmacophores for medicinal chemistry and drug development. In 2007, more than 75% of all phase III APIs contained at least one arene or heteroarene moiety.[1] The implementation of arenes in drug-like scaffolds proceeds almost entirely *via* arene coupling chemistry. Thus, the functionalization of arenes depicts an aspirational goal in synthetic chemistry. Hence, a main endeavor of our research group is the development of novel carbonylative coupling reactions for the transition metal-catalyzed functionalization of aromatic and heteroaromatic compounds. In the past years, we succeeded to translate the logic of traditional cross-coupling reaction to carbonylative versions of these processes (Figure 1.1).[2]

In the net carbonylative cross-coupling reaction, two new C−C bonds are formed while implementing a valuable carbonyl functionality. The major drawback, as it is in non-carbonylative cross-coupling reactions, is the concomitant generation of stoichiometric waste products. In recent years, the scientific community has made significant progress towards direct C−C coupling strategies *via* transition metal-catalyzed C−H bond activation in which pre-functionalization of one coupling partner is dispensed.

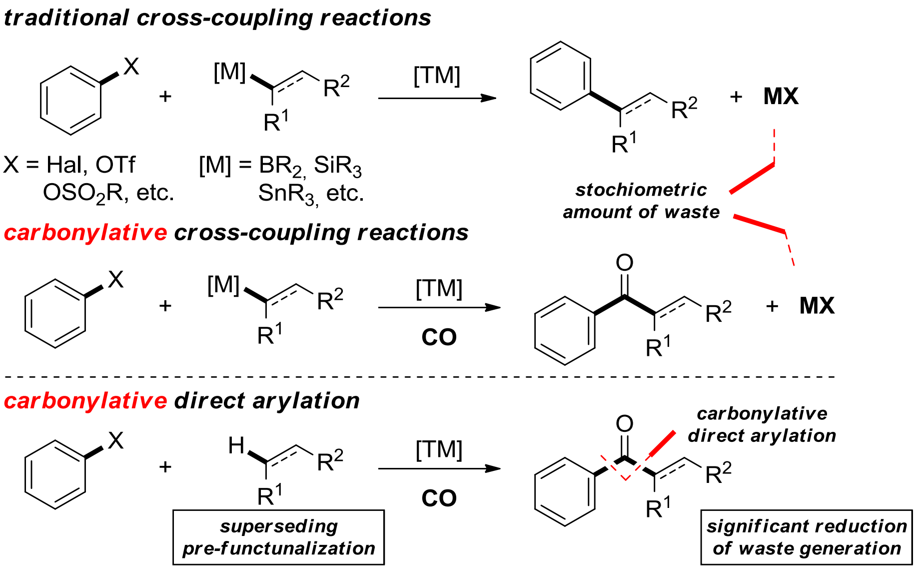


Figure 1.1. General overview (a) traditional cross-coupling, (b) carbonylative cross-coupling and (c) carbonylative direct arylation.

This trend drew our attention towards the conscious conjunction of carbonylative coupling chemistry and C−H bond functionalization (Figure 1.1, below). A facile three component synthesis of complex benzophenone derivatives was enabled upon exploitation of the multifunctional aptitudes of inexpensive ruthenium(II)-catalyst precursors.[3] The synthetic applicability of the developed methodology is showcased in the streamlined synthesis of an analog of the top-selling selective estrogen receptor modulator Raloxifene (Evista®). Furthermore, our endeavors towards the synthesis of marinopyrrole A and B will be discussed.

1.3 Background

1.3.1 Transition metal-catalyzed C−H bond activation

Transition metal catalyzed activation of C−H bonds is a field of major interest in organic chemistry. The C−H bond is the most ubiquitous bond in organic molecules and its regio- and site-selective transformation into more sophisticated value-added architectures is a desired aim. However, the targeted C−H bonds are thermodynamically strong and kinetically inert and intricate to cleave. Homogenous catalysis mediated by transition metal complexes offers a unique opportunity to achieve both high activity and high selectivity in C−H bond cleavage and further functionalization.

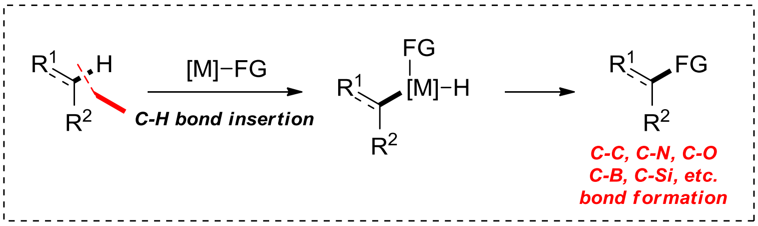
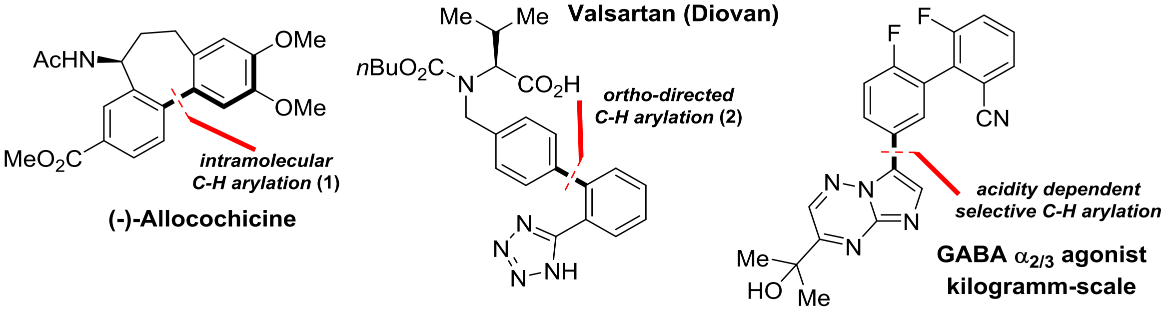


Figure 1.2. Transition metal-catalyzed C−H bond functionalization.

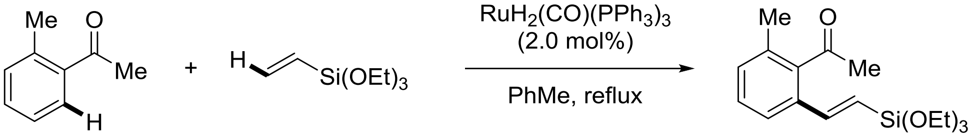
The concept of C−H bond functionalization involves an elementary step wherein a C–H bond is transformed into a C−metal bond *via* a metal insertion process. Important to this definition is that the hydrocarbyl species remains attached to the inner-sphere of the metal in the course of the reaction versus simple deprotonation of C–H acidic compounds that react as external nucleophile *via* an outer-sphere mechanism. The newly formed "activated" C−M bond can then undergo reductive elimination with a functional group bound to the transition metal center (Figure 1.2). This functional group can be a metalloid such as boron- or silicon-based group, or a halogen-atom, however, the crux of the field lies in the ability of subsequent C−C bond formation.[4] In the past years, the concept of direct C−C coupling has been applied in the syntheses of increasingly complex natural products and pharmaceutical targets, meeting the quest for more atom and step economic syntheses.[5]

The key challenge of any C−H bond functionalization is the selective cleavage of a targeted C−H bond preferentially over others present in the molecule.[6] Commonly, regioselectivity is either controlled due to (1) conformationally biased and entropically-favored intramolecular direct arylation, (2) directed intermolecular C−H bond activation in the presence of Lewis-basic directing-groups or (3) site-differentiation by C−H bond acidity (Scheme 1.1).



Scheme 1.1. Representative examples of relevant compounds synthesized by transition metal-catalyzed (1) intramolecular, (2) *ortho*-directed intermolecular and (3) C−H bond acidity-dependent direct arylation.

The cleavage of a σ(C−H) bonds in the coordination sphere of a transition metal complex generally results from two synergetic electronic effects: (1) σ-donation from the bonding $\sigma_{\mathrm{C-H}}$ bond into a vacant orbital of the metal complex (L_nM) and π-backdonation from a filled d_x-L_nM molecular orbital into the antibonding $\sigma^*_{\mathrm{C-H}}$ MO. Thus, the electronic nature of the reactant, allocation of a vacant site on the metal complex and electronic nature of the same contribute to the C−H bond cleavage.[7] The pioneering efforts of Bergman, Ellman and others have deepened the understanding of the factors which govern regioselective C−H bond activation.[7c,8] The work of *Murai* and *Kakiuchi*, in particular, had a profound impact on the development of this field. A significant breakthrough of C–C bond formation based on C–H bond activation was reported in 1993 with the Ru-catalyzed selective hydroarylation of olefins in ortho position to the carbonyl group of aromatic ketones as a directing group (Scheme 1.2).[9]



Scheme 1.2. Chelate-assisted ruthenium-catalyzed direct arylation of olefins.

Directing groups contain a lone pair of electrons that can coordinate to the transition metal catalyst.[10] Most directing groups bear either nitrogen or oxygen containing functional groups in order to achieve regioselective C−H bond activation *via* a five or six-membered intermediate (Figure 1.3. A).

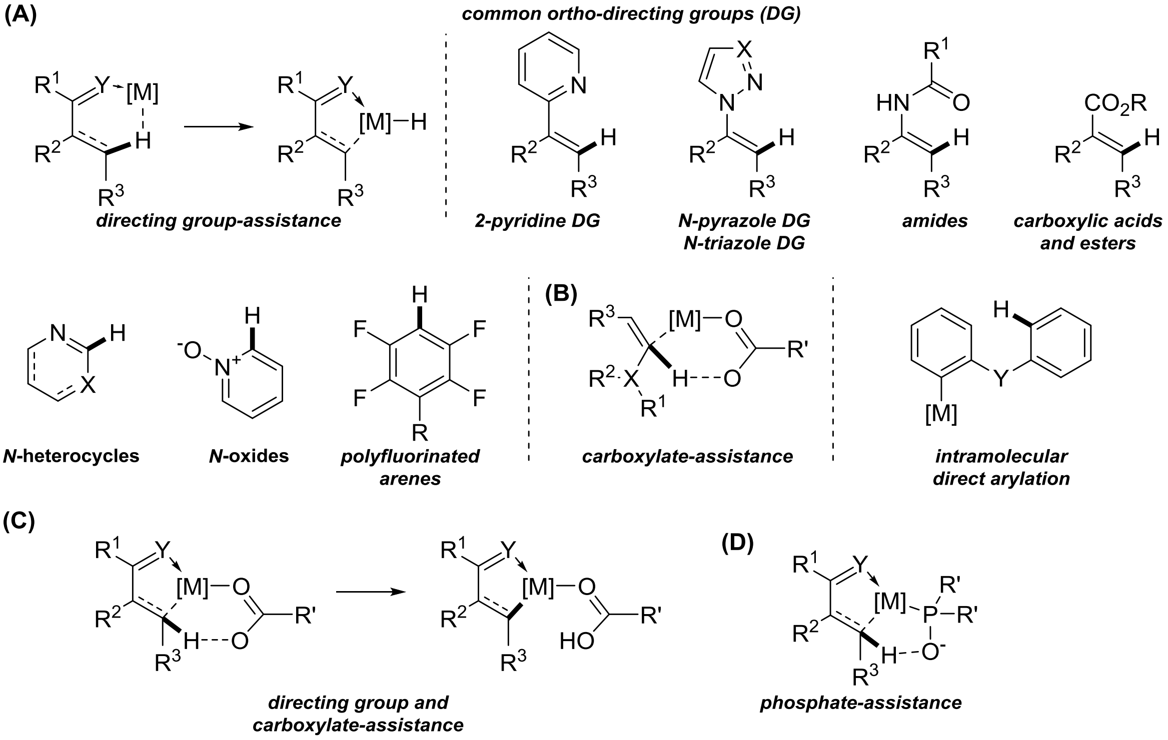


Figure 1.3. Activation mode of directing groups and carboxylate-assisted C–H bond cleavage.

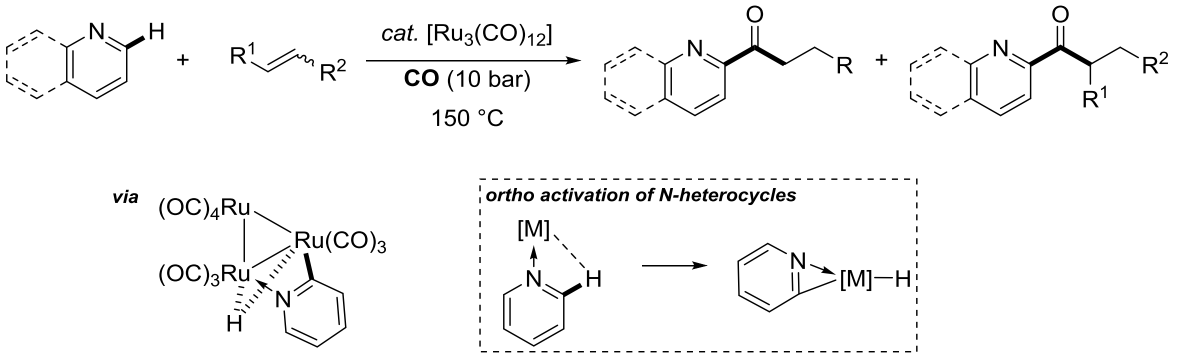
Another major advance was the observation that selectivity can likewise be induced by an external partner such as carboxylate or phosphate bases.[11] Detailed experimental and computational analysis established different models for the assisted C−H bond cleavage: (1) CMD (concerted metalation deprotonation),[12] IES (internal electrophilic substitution)[13] and AMLA (ambiphilic metal ligand activation).[14] The CMD mechanism is by far the most widely encountered mode of activation by carboxylate assistance. The mechanism is postulated to proceed through an innersphere hydrogen abstraction by a coordinated carboxylate ligand *via* a six-membered transition state and simultaneous C−M bond formation, depicted in Figure 1.3.B. This mode of activation has been suggested for a number of Rh- and Pd-catalyzed C−H bond functionalization reactions, involving *N*-heterocycles, polyfluoroarenes or intramolecular aryl-aryl coupling reactions. A combined directed carboxylate-assisted bond cleavage (Figure 1.3.C) has been useful in a number of palladium and ruthenium-catalyzed protocols. Phosphate bases have also been found to facilitate C−H bond breaking event *via* similar five-membered transition states, (Figure 1.3.D).

1.3.2 Carbonylative C−H bond functionalization

> *"In the beginning God created the heaven and the earth. And the carbonyl group. No other functional group can rival its versatility and utility."*
>
> *P . J. Kocienski, "Carbonyl Protecting Groups - Introduction" in Protecting Groups, Thieme, Stuttgart, 2005.*

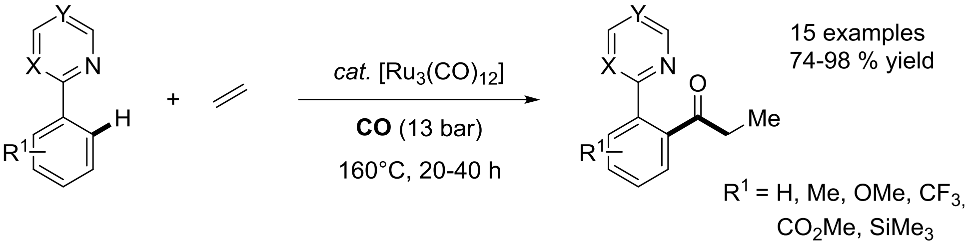
Despite its indisputable value, catalytic carbonylative functionalization of unactivated hydrocarbon bonds has only scarcely been studied.[15] This instance is even more surprising, considering that carbonylative C–C coupling through the C–H bond cleavage are amongst the pioneering examples in the field of transition metal catalyzed C–H bond activation of arenes in general.

The first ruthenium-catalyzed carbonylative C–H activation reaction was discovered in 1992, by *Moore* and co-workers.[16] *Ortho*-acylation of pyridine and other nitrogen-containing aromatic compounds, used in high excess, was performed in the presence of internal and terminal alkenes and CO, using trinuclear $Ru_3(CO)_{12}$ as pre-catalyst (Scheme 1.3). The activation of *N*-heterocycles is commonly believed to proceed through pre-coordination of the transition metal by the nitrogen lone pair and subsequent insertion into the adjacent C−H bond (Scheme 1.3).[17]



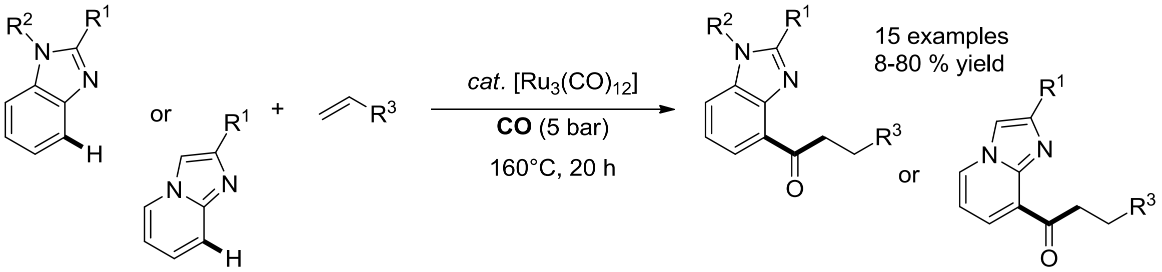
Scheme 1.3. Catalytic and regioselective acylation of *N*-heterocyles with carbon monoxide and olefins.

Murai and co-workers translated the development by *Moore* to the *ortho*-acylation of simple arenes (Scheme 1.4). Herein, they applied the strategy of directing group assisted *ortho*-metalation that has previously been discovered for the chelat-assisted hydroarylation of olefins, vide infra. In the first set of reactions, pyridine and pyrimidine heterocycles were used as directing groups. Mono-*ortho*-substitution of the arene was mandatory to prevent from diacylation.



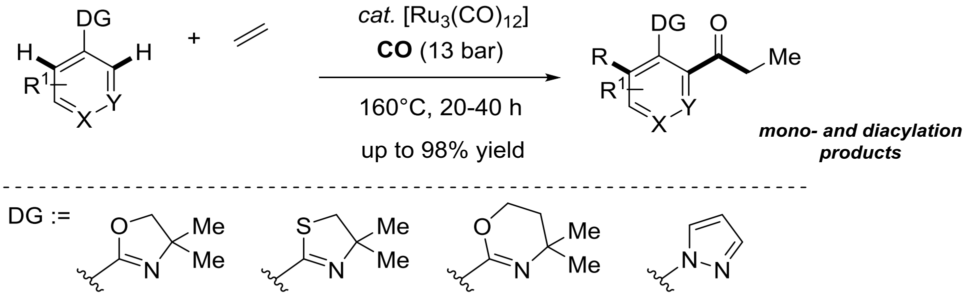
Scheme 1.4. Reaction of 2-pyridyl- and pyrimidylarenes with carbon monoxide and ethylene.

In 1998, the group of *Murai* extended this methodology towards the site-selective carbonylative C–H acylation of aza-heterocycles to aryl-alkylketones.[18] The same catalytic system could be used for the functionalization of 1,2-disubstituted benzimidazole and 2-methylimidazo[1,2-α]pyridine (Scheme 1.5). The significant advantage of these substrates was that they allowed for an extension of the olefin substrate scope. Besides ethylene, 1-hexene, 2-methylstyrene and vinyl cyclohexene were eligible coupling partners and the corresponding ketones were obtained in 25-78% yield.



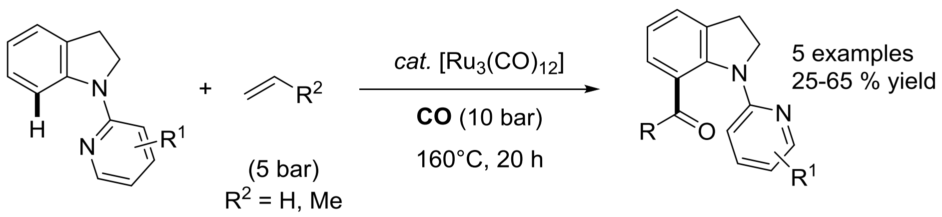
Scheme 1.5. Reaction of aza-heterocycles with carbon monoxide and alkenes.

The protocol could be further extended to the *ortho*-acylation of various arenes and heteroarenes, triggered by various *N*-heterocyclic directing groups, such as oxazines, thiazine and pyrazoles (Scheme 1.6).



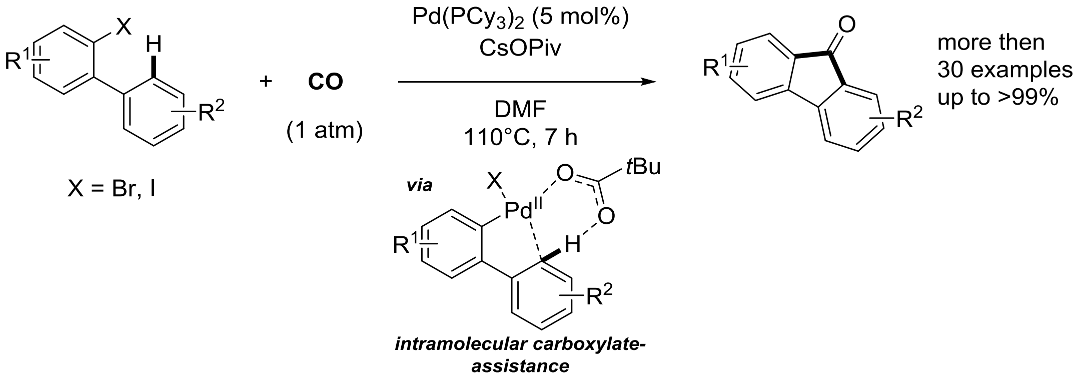
Scheme 1.6. *N*-heterocyclic directing groups in the *ortho*-acylation of (hetero)arenes.

A related activation mode, however, in this case *via* a 6-membered ruthenacycle has been pursued in the C-7 selective acoylation of *N*-pyridylindolines (Scheme 1.7).[19] The corresponding coupling products were obtained in reasonable yields up to 65%.



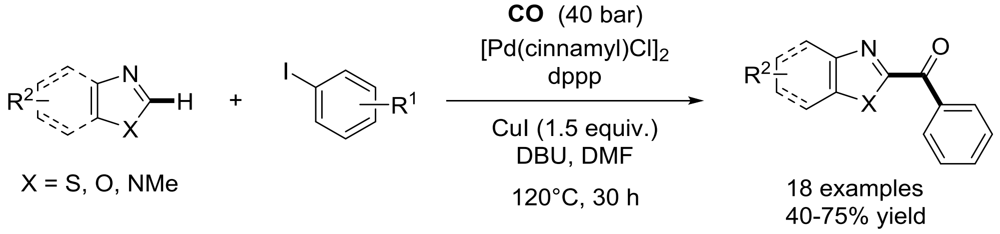
Scheme 1.7. Reaction of *N*-pyridylindolines in the presence of carbon monoxide and ethylene or propen.

Thus, in conclusion, the group of *Murai* and *Kakiuchi* made an extensive effort and thoroughly explored the chemical space of ruthenium-catalyzed direct acoylation of aza-arenes and benzene derivatives. However, the harsh reaction conditions render these protocols less applicable on larger scale, or as alternative to existing protocols. Surprisingly, no further extensions or variations have been investigated to explore the limiting factors of this process. The remainder of ruthenium-catalyzed C−H carbonylation protocols concern intramolecular lactonization or lactamization reactions.[15b]



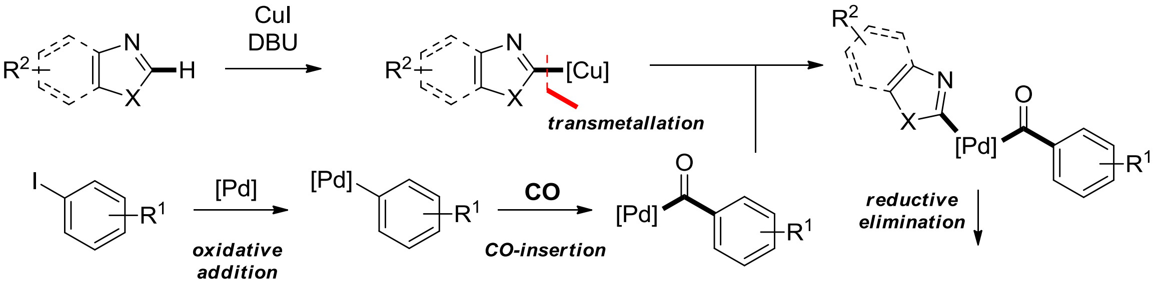
Scheme 1.8. Intramolecular Pd-catalyzed cyclocarbonylation.

Outside the ruthenium regime, in 2000 and 2001, *Larock* published the first intramolecular palladium-catalyzed carbonylative direct arylation for the synthesis of flurophen-9-ones from *ortho*-biaryls (Scheme 1.8).[20] The synthesis proceeded under relatively mild reaction conditions under atmospheric carbon monoxide pressure. A catalytic system comprising Pd(PCy)$_3$ and pivalic acid suggests a carboxylate-assisted C−H bond cleavage. This reaction conditions proved general for a great range of substrates. Besides biphenyls, several heterocyclic starting materials underwent carbonylative ring closure, e.g. fused isoquinoline, indole, pyrrole, thiophene, benzothiophene, and benzofuran products could be obtained.



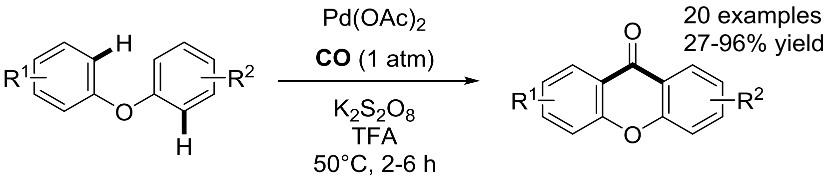
Scheme 1.9. Palladium-catalyzed copper-mediated carbonylative direct arylation of heteroarenes.

The first example of an intermolecular direct carbonylative coupling of aromatic compounds by means of C–H bond activation was described by the group of *Beller* in 2010.[21] C–H acidic heteroarenes such as oxazoles, thiazoles, and imidazoles were found to be suitable nucleophiles in a carbonylative coupling reaction with aryl iodides (Scheme 1.9). This reaction applies a palladium catalyst and a twofold excess in bidentate dppp ligand and superstochiometric CuI. The cleavage of the C−H bond is suggested to proceed *via* deprotonation at the two position of the heterocycle to form a heteroaryl-copper species. This species then undergoes transmetallation with a Pd-aroyl intermediate that is formed upon oxidative addition and CO-insertion (Scheme 1.10). Noteworthy, a high CO pressure of 40 bar was needed to obviate undesired aryl-heteroaryl coupling.



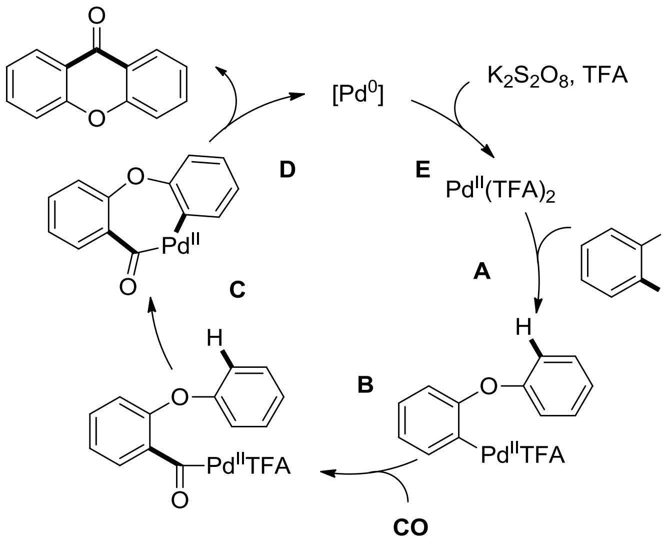
Scheme 1.10. Proposed mechanism.

From the literature it is known, that C−H acidic heterocycles can be deprotonated by a strong base to form adducts with appropriate Cu(I) salts. These species, have been applied, for instance, in copper-mediated carboxylation reactions with gaseous CO_2.[22] Thus, this reaction does not fully meet the introductory described definition of a direct C−H bond functionalization.



Scheme 1.11. Palladium-catalyzed oxidative double C−H functionalization/carbonylation for the synthesis of xanthones.

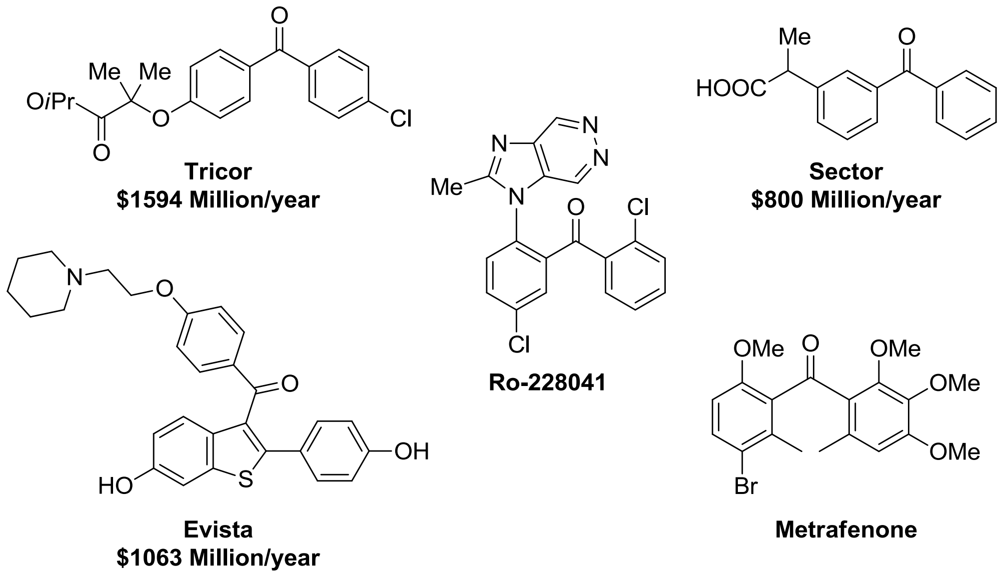
In 2012, the group of *Lei* disclosed a protocol on palladium-catalyzed oxidative double C–H bond functionalization/carbonylation of diaryl ethers (Scheme 1.11).[23] $Pd(TFA)_2$ formed *in situ* from $Pd(OAc)_2$ in trifluoroacetic acid is a competent catalyst precursor to undergo electrophilic palladation of the diarylether starting material, step **A** in Scheme 1.12. The subsequent CO insertion (**B**) is followed by activation of a second C–H bond (**C**) and reductive elimination of the carbonylation product (**D**). Eventually, the Pd^0 species is re-oxidized by $K_2S_2O_8$ as sacrificial oxidant to turn-over the catalytic cycle (**E**). Mechanistic studies suggest that the second C–H bond activation represents the rate-determining step. The yield was significantly affected by the electronic nature on the arenes, resulting in a broad variation in yield from 27-96%. Electron-rich arenes were generally better received in this transformation.



Scheme 1.12. Proposed mechanism for the double C−H carbonylation.

1.3.3 Benzophenones

Benzophenones constitute widely used building blocks in organic chemistry and are attractive targets in pharmaceutical and finechemical industry, exhibiting a plethora of biological activities. Prominent examples are Tricor, applied for cholesterol regulation in patients at risk of cardiovascular disease, the anti-inflammatory drug Sector and selective estrogen receptor modulation Raloxifen (Evista®) (Scheme 1.13). These drugs are listed among the top 200 drugs by sales in 2012 and thus are of sever economical interest for the pharma industry.[24]



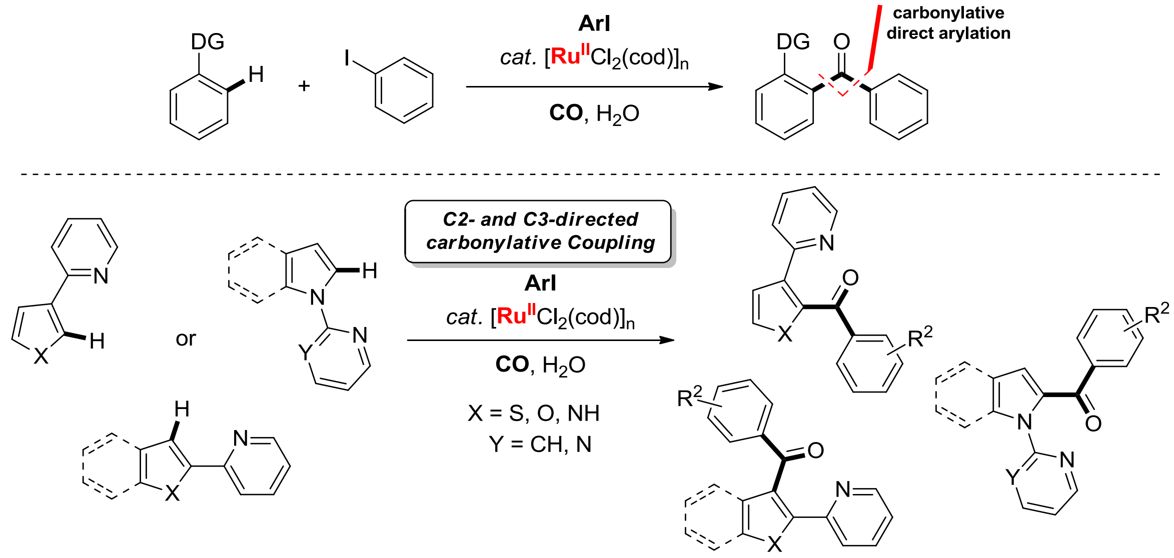
Scheme 1.13. Selected examples of bioactive benzophenone derivatives.

Benzophenone derivatives provide a broad-spectrum ultraviolet coverage, including UVB and short-wave UVA rays.[25] Oxybenzophenones, (2-Hydroxy-4-methoxyphenyl)-phenylmethanone, is the most widely applied UVA filter used in sunscreen. Besides medicinal and cosmetic applications, benzophenones are used as photoprotective agents in UV-curing applications such as inks, imaging, and clear coatings in the printing industry.[26]

In recent years, classic synthetic routes such as copper-catalyzed oxidation of diphenylmethane or Friedel-Crafts acylation face competition by transition-metal catalyzed carbonylative coupling reactions of arenes.[27] Carbon monoxide represents an inexpensive and atom economic C1 building block, which allows the introduction of a carbonyl group into the desired target molecule by various carbonylation reactions. Representative examples include the carbonylative Suzuki-Miyaura,[28] Negishi,[29] Stille,[30] and Hiyama[31] reactions. However, these processes require pre-functionalized reaction partners and lead to concomitant generation of stoichiometric waste which ought to be circumvented in times of limited resources and growing environmental awareness.

1.4 Result and discussion

The direct arylation of (hetero)arenes by means of C−H bond activation represents an enormously growing field in organometallic chemistry and has a tremendous impact on synthetic organic chemistry. Our preceding success in the development of carbonylative versions of a plethora of traditional cross-coupling reactions[2a,2c] drew our attention towards the conscious conjunction of carbonylative coupling chemistry and C−H bond functionalization.



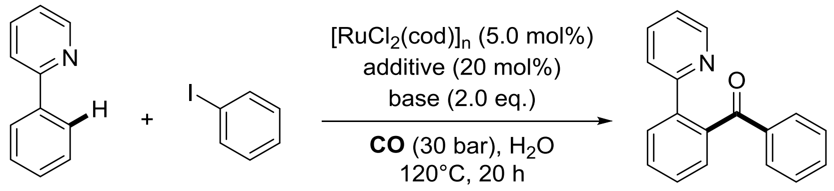
Scheme 1.14. Regioselective ruthenium-catalyzed carbonylative direct arylation of five-membered and condensed heterocycles.

It was our primary goal to develop a methodology for the selective carbonylative direct-arylation of simple arenes *via* successive twofold C(sp^2)−C(sp^2) bond formation for the rapid build-up of complex aryl-heteroaryl ketone (Scheme 1.14). Seminal experiments revealed that ruthenium is the metal of choice to strive for this endeavour.

1.4.1 Screening of reaction conditions

Initial experiments were carried out using 2-phenylpyridine (**1.1a**) as model substrate, phenyl iodide (**1.2a**) and 5 mol% of [Ru(cod)Cl_2] polymer under carbon monoxide pressure (30 bar) at 120 °C. The product formation was determined by calibrated GC after 20 hours reaction time, using hexadecane as an internal standard. Various bases, solvents and additives were tested under these conditions (Table 1.1). Most organic solvents gave no or little conversion of the starting material (Table 1, entries 1-6). However, when changing the reaction media to water, selective conversion to the desired carbonylated product was observed in 56% yield (entry 7). Variation of the base and carbonate additive further improved the yield of **1.3a** up to 65% (entry 16). The reaction proofed to be rather sensitive to reduced carbon monoxide pressure. Thus, further optimization of the ruthenium-catalyst precursor was performed at 30 bar carbon monoxide pressure.

Table 1.1. Ruthenium-catalyzed carbonylative C–H bond activation of 2-phenylpyridine: Optimization of reaction conditions.[a]



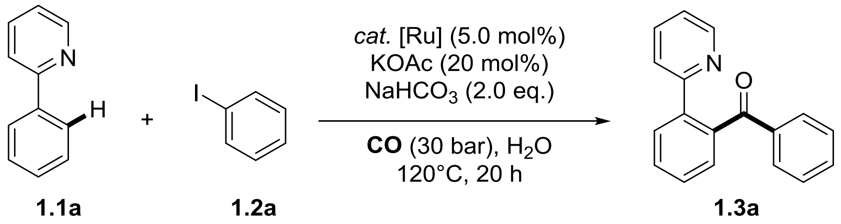
1.1a **1.2a** **1.3a**

entry	solvent	base	additive	yield (%)[b]
1	DMSO	K_2CO_3	KOAc	0
2	DMF	K_2CO_3	KOAc	4
3	NMP	K_2CO_3	KOAc	13
4	PhMe	K_2CO_3	KOAc	5
5	MeCN	K_2CO_3	KOAc	12
6	*t*-AmOH	K_2CO_3	KOAc	8
7	H_2O	K_2CO_3	KOAc	56, 44[c], 54[d]
8	H_2O	K_2CO_3	NaOAc	54
9	H_2O	K_2CO_3	CsOPiv	36
10	H_2O	K_2CO_3	$MesCO_2H$	28
11	H_2O	K_2CO_3	Cl_3CO_2H	54
12	H_2O	Cs_2CO_3	KOAc	54
13	H_2O	K_3PO_4	KOAc	44
14	H_2O	KOH	KOAc	44
15	H_2O	NaO*t*Bu	KOAc	<1
16	**H_2O**	**$NaHCO_3$**	**KOAc**	**65**

Reaction conditions: [a] Reactions were performed with iodobenzene (**1.2a**, 1.0 mmol), 2-phenylpyridine (**1.1a**, 0.5 mmol), [RuCl(cod)$]_n$ (5.0 mol%), additive (20 mol%) and base (1.0 mmol) under 30 bar of carbon monoxide, at 120 °C for 20h; unless otherwise noted; [b] GC yields with hexadecane as internal standard, average of two runs; [c] Reaction was performed under 20 bar of CO; [d] Reaction was performed under 40 bar of CO.

Next, we decided to investigate the effect of different ruthenium complexes on the carbonylative C–H bond functionalization. In the related direct coupling reaction, weakly coordinating anions had a positive effect on transition metal catalyzed activation of C–H bonds. In some instances, generating a more cationic metal species may encourage σ-donation from the bonding σ(C–H) molecular orbital to stabilize the vacant orbital on L_nM. However, in the present model reaction the addition of silver acetate or silver hexafluoroantimonate led to complete inhibition of the catalytic activity of the reaction system (Table 1.2, entry 2 and 3). Furthermore, lower conversions and yields were observed when other ruthenium precursors were used (Table 1.2, entry 4-9). A low product yield was also observed when the related ruthenium dimer dichloro(*p*-cymene)ruthenium(II) was used (Table 1.2, entry 6). This initially surprising result could be rationalized and will be discussed later on. Employing other ruthenium catalysts with different oxidation states (0, II and III) gave marginal product formation (Table 1.2, entries 7-9).

Table 1.2. Ruthenium-catalyzed carbonylative C–H bond activation of 2-phenylpyridine 1.1a: Catalyst screening.[a]



entry	*cat.* [Ru]	additive	yield (%)[b]
1	$[RuCl_2(cod)]_n$	none	**65**
2	$[RuCl_2(cod)]_n$	$Ag(OAc)_2$ (10 mol%)	<1
3	$[RuCl_2(cod)]_n$	$AgSbF_6$ (10 mol%)	<1
4	RuOAc(cod)	none	24
5	$[RuCl_2(p\text{-cymene})]_2$	none	16
6	$CpRuCl(PPh_3)_2$	none	0
7	$Ru(Cl)_3Cl_2$	none	<1
8	$Ru(acac)_3$	none	<1
9		none	<1

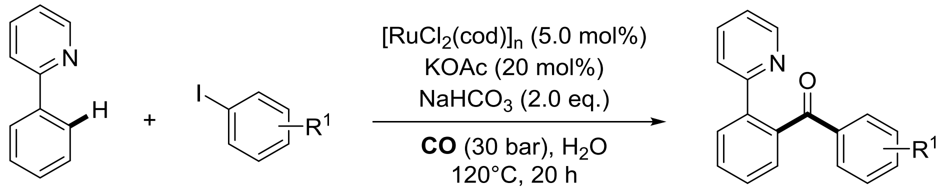
Reaction conditions: Reactions were performed with iodobenzene (**1.2a**, 1.0 mmol), 2-phenylpyridine (**1.1a**, 0.5 mmol), $[RuCl(cod)]_n$ (5.0 mol%), KOAc (20 mol%) and $NaHCO_3$ (1.0 mmol) under 30 bar of carbon monoxide, at 120 °C for 20h; unless otherwise noted; [b] GC yields with hexadecane as internal standard, average of two runs.

1.4.2 Scope and limitations

Having a practical protocol in hand for the ruthenium-catalyzed preparation of benzophenone derivatives with a three-component carbonylative direct arylation strategy, we studied the scope of iodoarenes (Table 1.3). Many aryl iodides afforded the corresponding products in good yields. Electron-donating (**1.3a-g**) as well as electron-withdrawing (**1.3j-l**) functionalities were tolerated. The electronic nature of the electrophile did not have a crucial impact on the product formation. It is important to note that in the case of 4-iodotoluene the optimum yield was obtained with potassium carbonate as a base. Other yields were not significantly affected by the choice of carbonate base. Aryl iodides substituted with alkyl groups in *para*-, *meta*-, or *ortho*-positions were invariably applicable under our reaction conditions (Table 1.3, **1.3b-1.3i**).The best result was obtained with 2-iodotoluene as a coupling partner. The corresponding ketone **1.3b** was obtained in 74% isolated yield (Table 1.3).

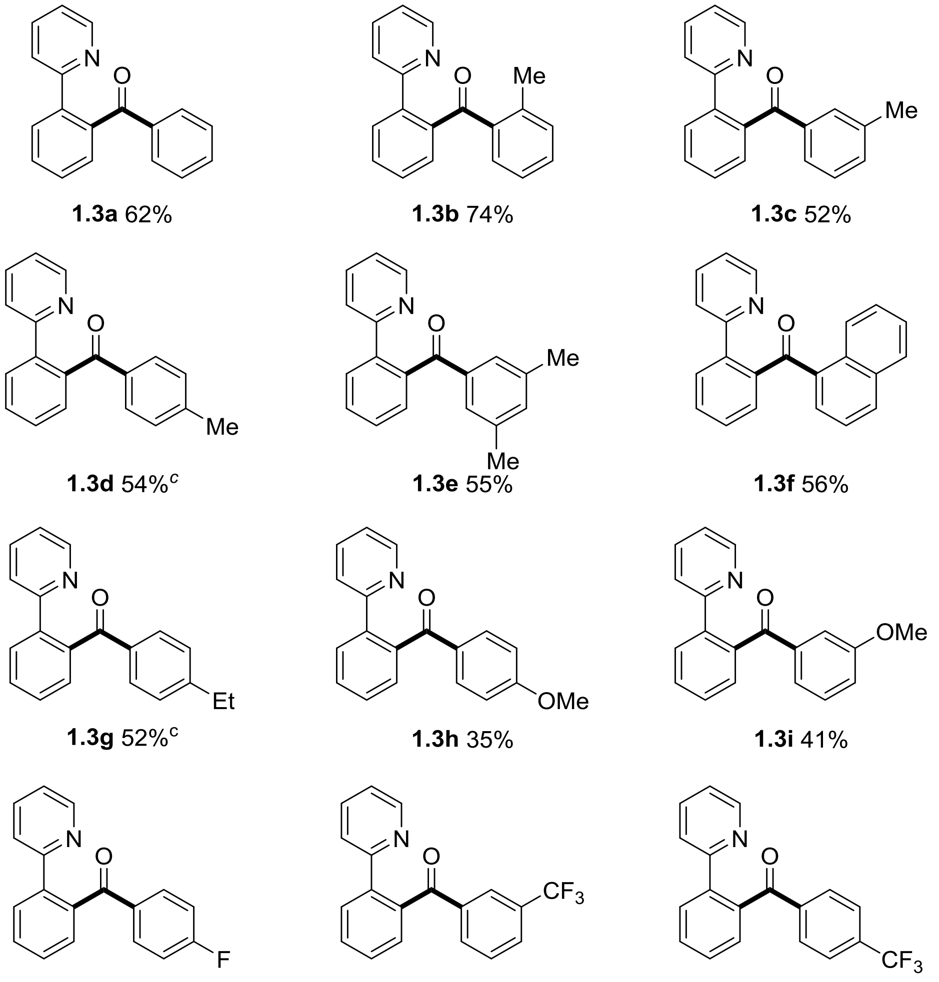
However, more sterically encumbered 2,6-dimethyl-iodobenzene or electrophiles bearing coordinating substituents such as hydroxyl or methoxy groups in the *ortho*-position were less eligible coupling partners.

Table 1.3. Ruthenium-catalyzed carbonylative direct arylation of phenylpyridine (1.1a).[a]



1.1a **1.2** **1.3**

products[a] yields (%)[b]



1.3a 62% **1.3b** 74% **1.3c** 52%

1.3d 54%[c] **1.3e** 55% **1.3f** 56%

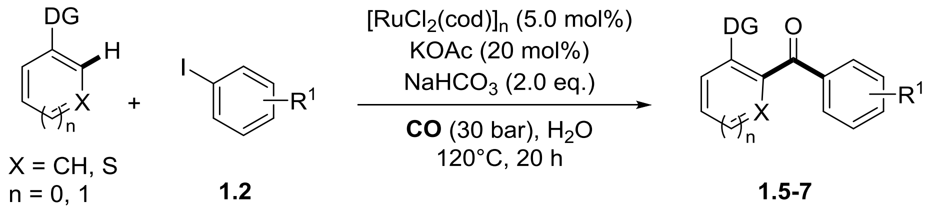
1.3g 52%[c] **1.3h** 35% **1.3i** 41%

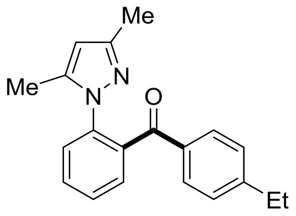
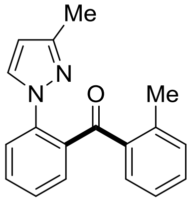
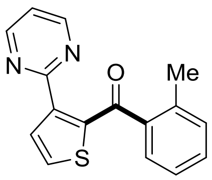
1.3j 40% **1.3k** 54% **1.3l** 46%

Reaction Conditions: [a] Phenylpyridine **1.1a** (0.5 mmol), iodoarene **1.2** (1.0 mmol), [RuCl$_2$(cod)]$_n$ (5.0 mol%), KOAc (20 mol%), NaHCO$_3$ (1.0 mmol), H$_2$O (1.0 mL), CO (30 bar), 120 °C, 20 h. [b] isolated yields are shown. [c] Reaction performed with K$_2$CO$_3$ as base.

After having observed the general activity with several aryl iodides, we turned our attention to study the effect of different directing groups (Table 1.4). To our delight, phenyl derivatives bearing pyrazole as a directing group were also suitable. Hence, 3,5-dimethyl-1-phenyl-1*H*-pyrazole **1.4a** was successfully converted with 4-ethyliodobenzene as well as with 2-iodotoluene. When 2-iodotoluene was reacted with the monomethylsubstituted pyrazole under carbon monoxide pressure the corresponding diarylketone **1.6a** was formed. Besides pyridine, 2-(hetero)aryl pyrimide could be employed in the carbonylative coupling reaction. In this instance, the methodology was extended to the direct arylation of heteroarenes for the first time. 2-(Thiophen-3-yl)pyrimidine was activated exclusively in the 2-position. The corresponding heteroaryl-aryl ketone, (3-(pyrimidin-2-yl)thiophen-2-yl)(o-tolyl)methanone (**1.7c**), was isolated in satisfying 68% yield (Table 1.4).

Table 1.4. Variation of directing groups.[a]



products[a]	yields (%)[b]
 **1.5a**	42%
 **1.5b**	40%
 **1.5c**	68%

Reaction Conditions: [a] **1.4** (0.5 mmol), iodoarene **1.2** (1.0 mmol), [RuCl$_2$(cod)]$_n$ (5.0 mol%), KOAc (20 mol%), NaHCO$_3$ (1.0 mmol), H$_2$O (1.0 mL), CO (30 bar), 120 °C, 20 h. [b] isolated yields are shown.

It is noteworthy to mention that the reaction proved to be rather sensitive towards substituents attached to the phenyl core of the nucleophile. On the other hand, this sensitivity displays a positive effect on the regioselectivity of the reaction. Although phenylpyridines and related arylpyrazoles possess two chemically equal *ortho*-C−H bonds only one C−C bond is selectively formed. This effect is presumably owed to the retarded reactivity of a subsequent bond formation on the now substituted phenylpyridine derivative.

1.4.3 Regioselective ruthenium-catalyzed carbonylative direct arylation of 5-membered and condensed heterocycles

Heterocycles are ubiquitous structural motifs in natural products and pharmaceuticals (Figure 1.4). The reduced symmetry and aromaticity renders the C−H bonds of heterocycles chemically more distinguishable which in turn facilitates to selectively address certain sites in the heterocycle. For instance as introductory discussed early examples for the carbonylative direct functionalization utilized pyridine as substrate. The C−H bond cleavage in the 2-position of the pyridine is facilitate due to advantageous resonance effects stemming from the adjacent heteroatom. The C-2 C−H bond represents also the most activated position for transition-metal C−H bond insertion in five-membered heterocycles because of its high nucleophilicity and C−H bond acidity.[32]

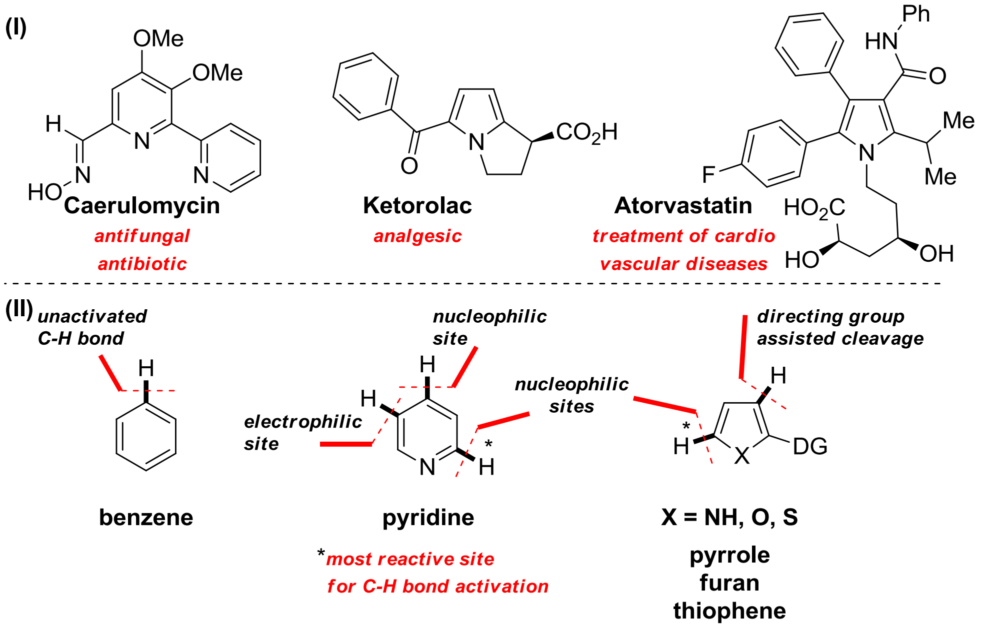
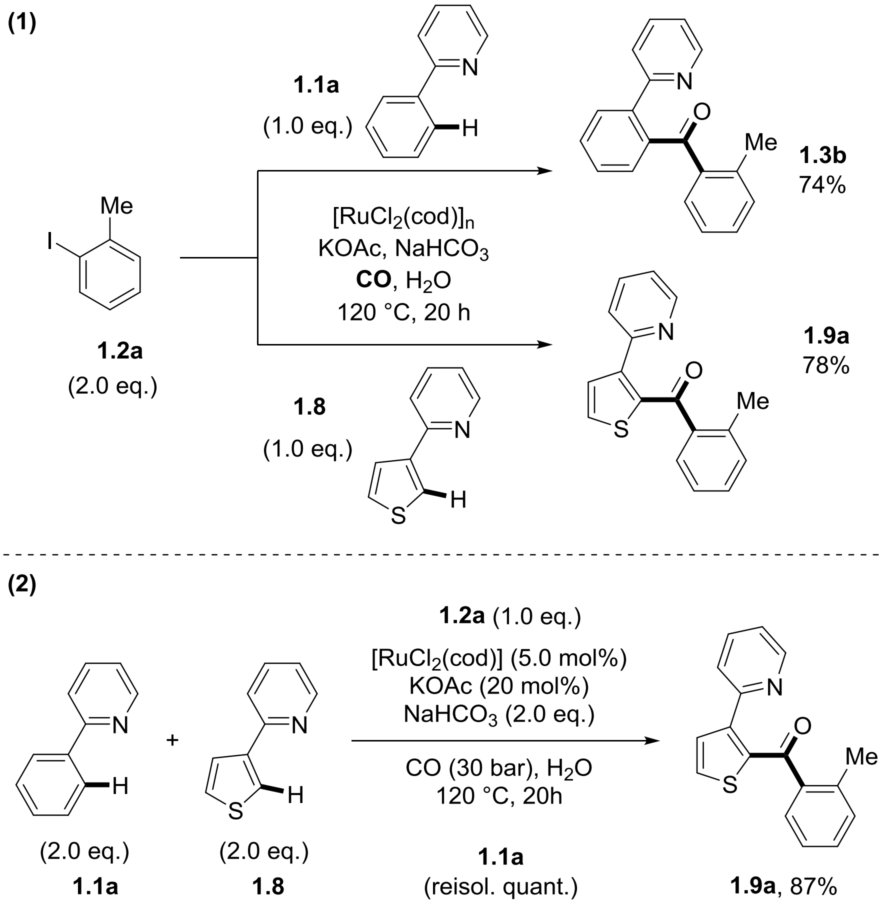


Figure 1.4. Important heterocycle containing pharmaceuticals and reactive site differentiating in heteroarenes.

Unfortunately, the direct carbonylation reaction proved rather sensitive to modifications on the phenyl core. Gratifyingly, we found that pyridine-containing bisheteroaryls, such as 3-(2’-pyridyl)thiophene (**1.8**), were equally eligible for the directed aroylation (Scheme 1.15). Incited by our finding we strived to extent the substrate scope of the direct carbonylative *ortho*-aroylation.

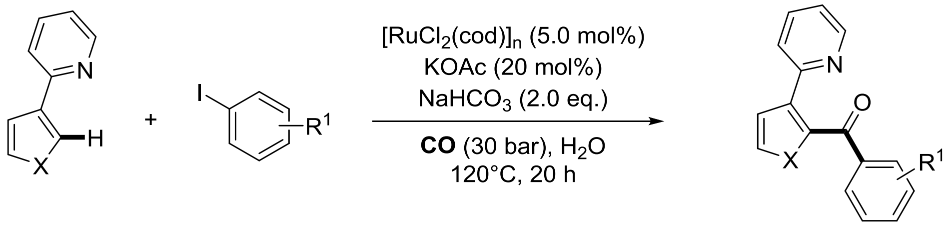
A competition experiment between 2-phenylpyridine (**1.1a**) and 3-(2’-pyridyl)thiophene (**1.8**) was conducted. Using a large excess of the competing nucleophiles revealed a remarkable selectivity in favor of exclusive conversion of the thiophenyl nucleophile **1.8** to (3-(pyridin-2-yl)thiophen-2-yl)(o-tolyl)methanone (**1.9**) in 87% isolated yield, while **1.1a** was re-isolated in quantitative yield (Scheme 1.15). Further optimization showed that an excess of the nucleophile was beneficial for the aroylation of heteroarenes and significantly accelerated the overall process; *vice versa* resulting in higher yields of the desired coupling product.



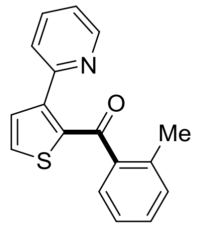
Scheme 1.15. Comparison of the reactivity of 2-phenylpyridine (1.1a) and 3-(2'-pyridyl)thiophene (1.8).

With this slightly modified reaction conditions, the ruthenium-catalyzed carbonylative direct arylation of 3-(2'-pyridyl)heteroarenes, including thiophenyl, furanyl, and pyrrol-based heterocycles, was conveniently accomplished. The pendent pyridine moiety selectively biased the carbonylative coupling which allowed for a highly regioselective functionalization at the 2-position of five-membered heterocycles (Table 1.5). The corresponding heteroaryl–aryl ketones were isolated in moderate to good yields (10–91 %, Table 1.5). The best result was obtained when **1.8** was reacted with 2- iodotoluene, resulting in 91% isolated yield of the desired [3-(pyridin-2-yl)thiophen-2-yl](o-tolyl)methanone (**1.9a**). In general, *ortho*-substituted iodoarenes gave superior results compared to other substitution patterns.

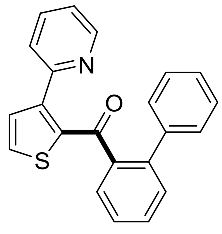
Table 1.5. Scope for C2-directed carbonylative direct arylation of 5-membered heterocycles.[a,b]



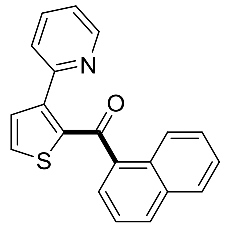
products[a] yields (%)[b]



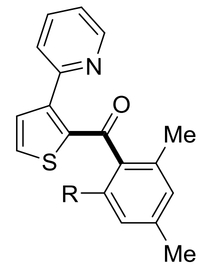
1.9a, 91%



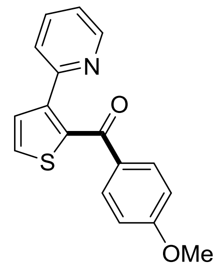
1.9b, 72%



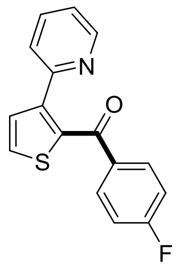
1.9c, 59%



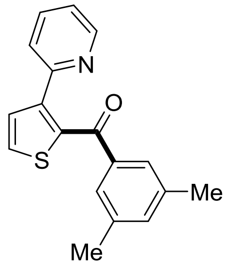
1.9d (R = H), 41%
1.9e (R = Me), <10%



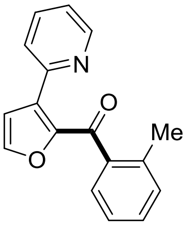
1.9f, 56%



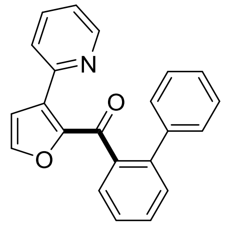
1.9g, 55%



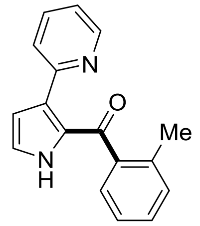
1.9h, 47%



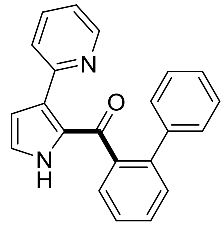
1.10a, 54%



1.10b 65%



1.11a, 47%

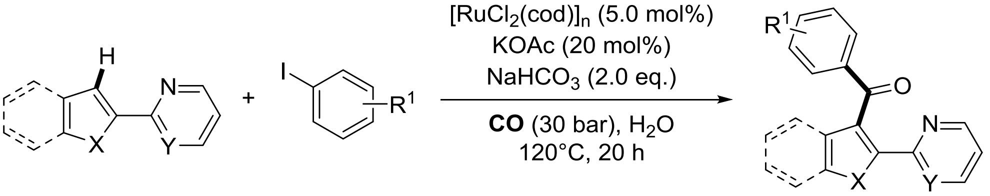


1.11b, 63%

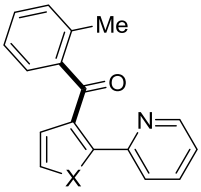
Reaction Conditions: [a] 3-(2'-pyridyl)heteroarene (1.0 mmol), iodoarene **1.2** (0.5 mmol), $[RuCl_2(cod)]n$ (5.0 mol%), KOAc (20 mol%), $NaHCO_3$ (1.0 mmol), H_2O (1.0 mL), CO (30 bar), 120 °C, 20 h. [b] isolated yields are shown.

The activation of the C3-position of five-membered heterocycles is a more challenging goal because of its reduced C−H bond acidity which attenuates its bias to be engaged into C−H activation. However, this inherent bias can be evaded by the use of an *ortho*-directing group. The scope of the C3-directed carbonylative direct arylation is shown in Table 1.6.

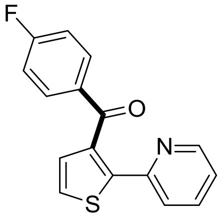
Table 1.6. Scope for C3-directed carbonylative direct arylation of 5-membered and condensed heterocycles.[a,b]



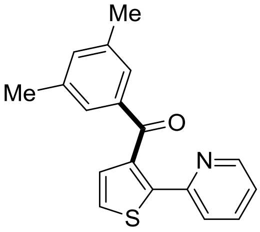
products[a] yields (%)[b]



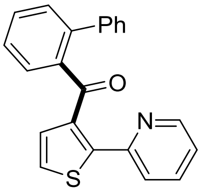
1.12a, X = S, 57%
1.13a, X = O, 20%



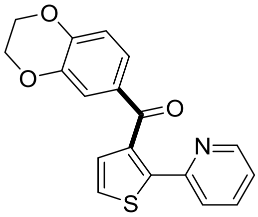
1.12b, 47%[c]



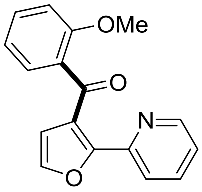
1.12c, 68%



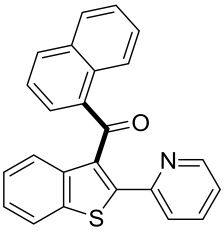
1.12d, 57%



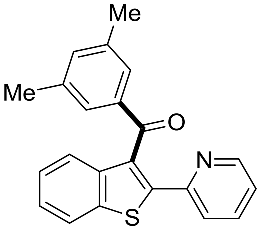
1.12e, 51%



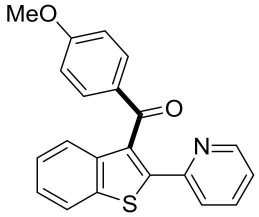
1.13b, -%



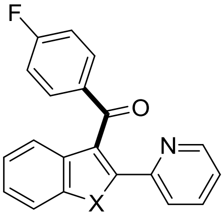
1.14a, 66%



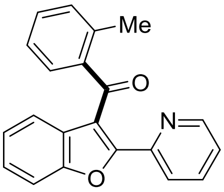
1.14b, 64%



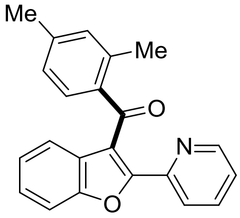
1.14c, 49%



1.14d, X = S, 53%
1.15a, X = O, 40%



1.15b, 71%



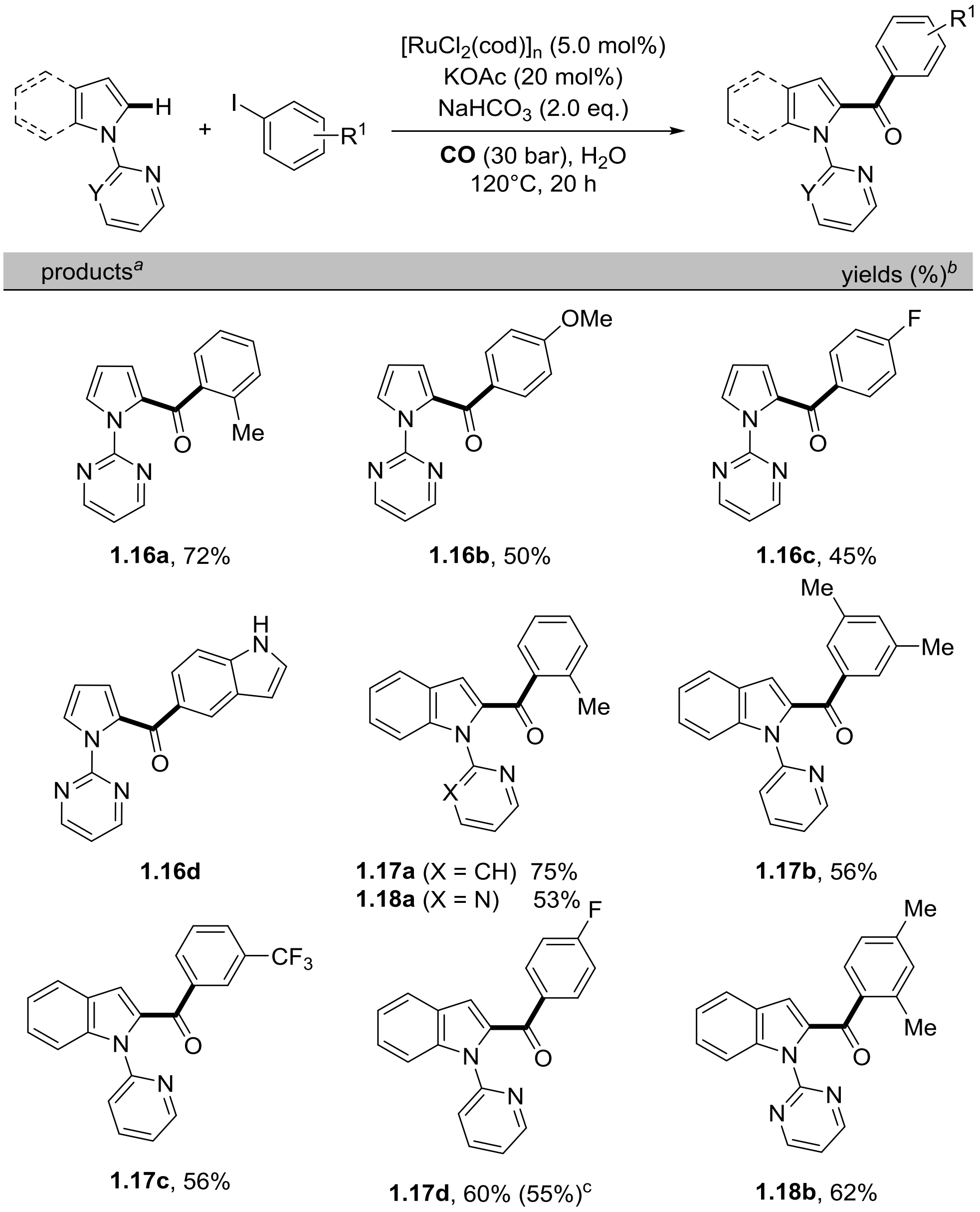
1.15c, 66%

Reaction Conditions: [a] 2-(2'-pyridyl)heteroarene (1.0 mmol), iodoarene **1.2** (0.5 mmol), $[RuCl_2(cod)]n$ (5.0 mol%), KOAc (20 mol%), $NaHCO_3$ (1.0 mmol), H_2O (1.0 mL), CO (30 bar), 120 °C, 20 h. [b] isolated yields are shown.

Five-membered and condensed *S*- and *O*-containing heterocycles were successfully converted to the corresponding aryl heteroaryl methanones **1.12-1.15** in good yields (20–71%, Table 1.6). The isolated yields for 2-(2-heteroaryl)pyridines are comparable to those that have been obtained for the C2-

directed carbonylative coupling. However, the aforementioned beneficial "*ortho*-effect" was not observed with this substitution pattern of the nucleophile. Yields up to 68% were obtained (Table 1.6. **1.12c**), whereas 2-furanyl-2'-pyridine proved to be less efficient. Gratifyingly, when condensed heteroarenes, such as 2-(benzo[*b*]thiophen-2-yl)pyridine and 2-(benzo[*b*]furan-2-yl)pyridine were employed, improved yields were achieved with diverse electrophiles (**1.14a-d** and **1.15a-c**).

Table 1.7. Scope for the C2-selective carbonylative direct arylation of *N*-arylated heterocycles.



products[a] yields (%)[b]

1.16a, 72%

1.16b, 50%

1.16c, 45%

1.16d

1.17a (X = CH) 75%
1.18a (X = N) 53%

1.17b, 56%

1.17c, 56%

1.17d, 60% (55%)[c]

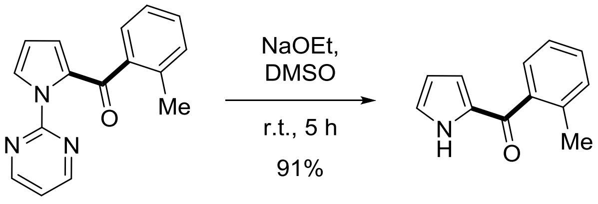
1.18b, 62%

Reaction Conditions: [a] 3-(2'-pyridyl)heteroarene (1.0 mmol), iodoarene (0.5 mmol), $[RuCl_2(cod)]n$ (5.0 mol%), KOAc (20 mol%), $NaHCO_3$ (1.0 mmol), H_2O (1.0 mL), CO (30 bar), 120 °C, 20 h. [b] isolated yields are shown. [c] K_2CO_3 as base.

The synthetic applicability of *ortho*-directed C−H bond functionalization strategies is often restricted due to the presence of the directing group. This constraint can be elegantly circumvented by the installation of a cleavable directing group. To demonstrate the versatility of the direct carbonylation protocol, *N*-heteroarylated indole-based compounds, **1.17a** and **1.17b**, as well as 2-(1*H*-

pyrrol-1-yl)pyrimidine (**1.16**) have been prepared according to literature procedures.[33] These substrates demonstrated decent reactivity and predictable site-selectivity of the carbonylative coupling reaction under our optimized reaction conditions (Table 1.7) and the resulting heteroaryl aryl ketones **1.16a-1.16d** were isolated in moderate to good yields (45–75 %). The C2-aroylation of indole proceeded in moderate yields of 55 to 75% (**1.17a-d** and **1.18a** and **b**). Again, 2-substituted iodoarenes were superior coupling partners compared to *meta*- and *para*-substituted electrophiles. However, strongly chelating di-heteroarenes, such as 2-(1*H*-pyrazol-1-yl)pyridine and 2-(1*H*-imidazol-1-yl)pyridine proofed incompatible as substrate in this reaction.

The cleavage of the pyrimidine-based directing element was easily accomplished when starting with [1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl](o-tolyl)methanone (**1.16a**) and NaOEt in DMSO at 100°°C for 5°h, yielding (1*H*-pyrrol-2-yl)(o-tolyl)methanone (**1.19**) in 91% isolated yield (Scheme 1.16).



1.16a **1.19**

Scheme 1.16. Cleavage of the pyrimidine protecting/directing group.

1.4.4 Application of the developed methodology

Di(hetero)aryl ketones constitute a common structural motif in natural products and pharmaceuticals, and can be found in the selective estrogen receptor modulator Raloxifene (Evista®),[34] in indole-based natural products uvarindole C, calothrixin A and B, as well as marinopyrrole A and B (Figure 1.5).[35] To showcase the applicability of the developed reaction we drew our attention to the synthesis of a Raloxifene analog and the synthesis of a key intermediate in the biosynthesis of marinopyrroles.

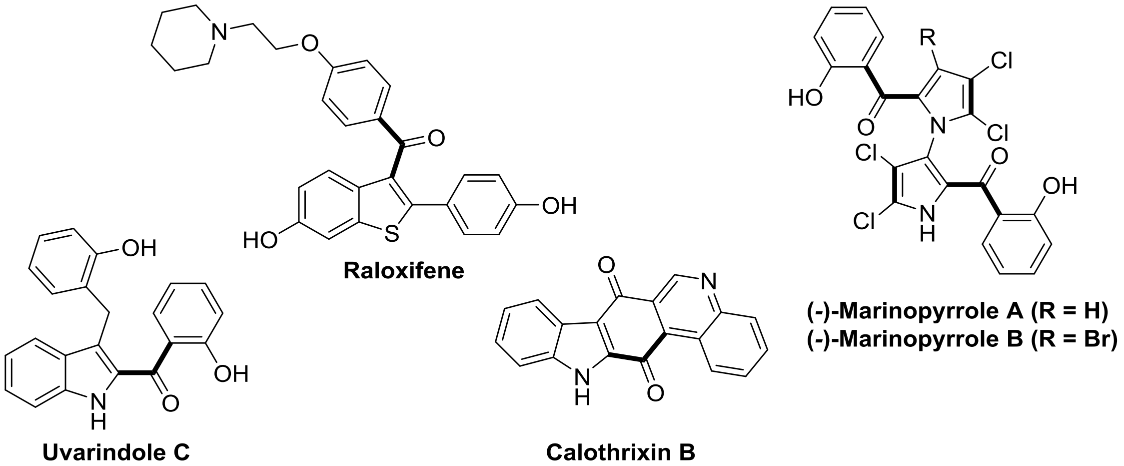


Figure 1.5. Selected natural products bearing a heteroaryl–aryl methanone moiety.

Marinopyrroles are densely-halogenated bipyrrole natural products, produced by a marine-derived streptomycetes isolated from ocean sediments.[36] These axially chiral biaryl compounds exhibit a unique 1,3'-bipyrrole motif and possess potent antibiotic activity against methicillin-resistant staphylococcus aureus.[37] Several total syntheses of racemic marinopyrrole A and B have been pursued and were published by a number of research teams.[35b-d,38] In 2012, *Moore* and co-workers contributed to the elucidation of the enzymology pathway for the atropo-selective synthesis of these bipyrrole natural products.[35a] According to their results a pair of $FADH_2$- dependent halogenases is involved in marinopyrrole biosynthesis. It catalyzes an atropo-selective *N*,*C*-biaryl homocoupling reaction of (4,5-dichloro-1*H*-pyrrol-2-yl)(2-hydroxyphenyl)methanone **1.20**. Thus, the synthesis of this intermediate was elected as target structure (Figure 1.6).

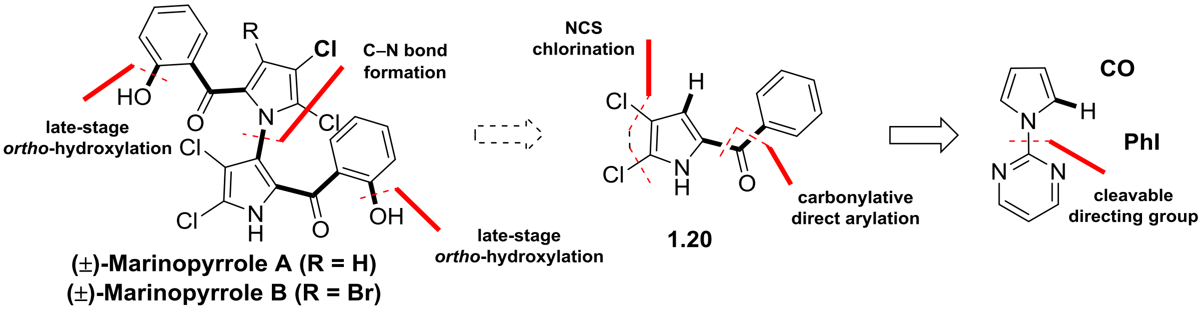
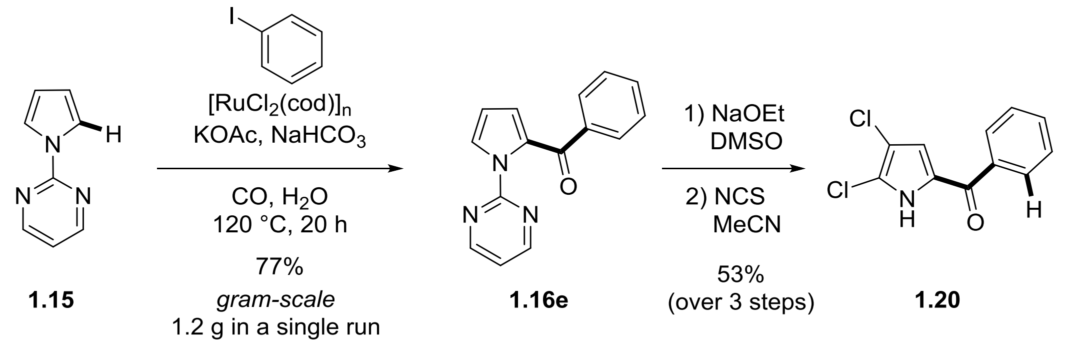


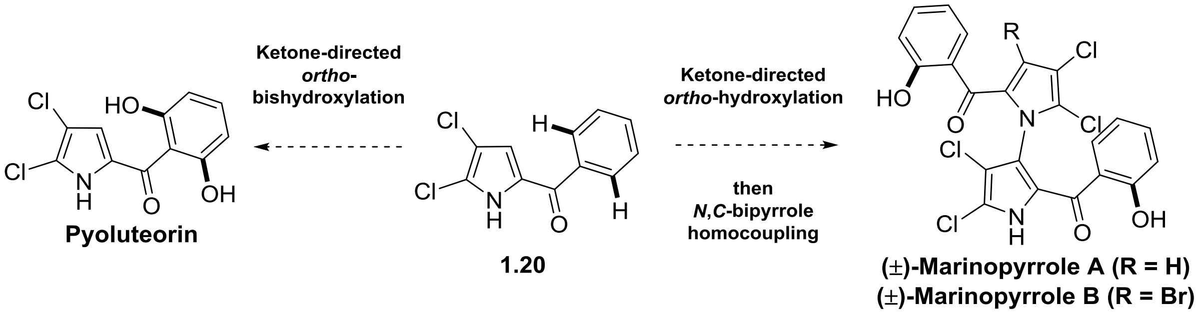
Figure 1.6. Rerosynthetetic analysis of marinopyrroles A and B and key intermediate (4,5-dichloro-1*H*-pyrrol-2-yl)-phenylmethanone 1.20.

(4,5-dichloro-1*H*-pyrrol-2-yl)-phenylmethanone (**1.20**) was prepared in a gram-scale from 2-(1H-pyrrol-1-yl)pyrimidine and iodobenzene and carbon monoxide following the previously described protocol for the ruthenium-catalyzed carbonylative direct arylation. 1.2 g of **1.16e** were obtain as a colorless solid from a singly run. The directing group was quantitatively cleaved using sodium ethoxide in DMSO at elevated temperature. Subsequent dichlorination of the 4,5-position of the pyrrole core yielded the desired product **1.20** in 53% over-all yield from **1.15** (Scheme 1.17).



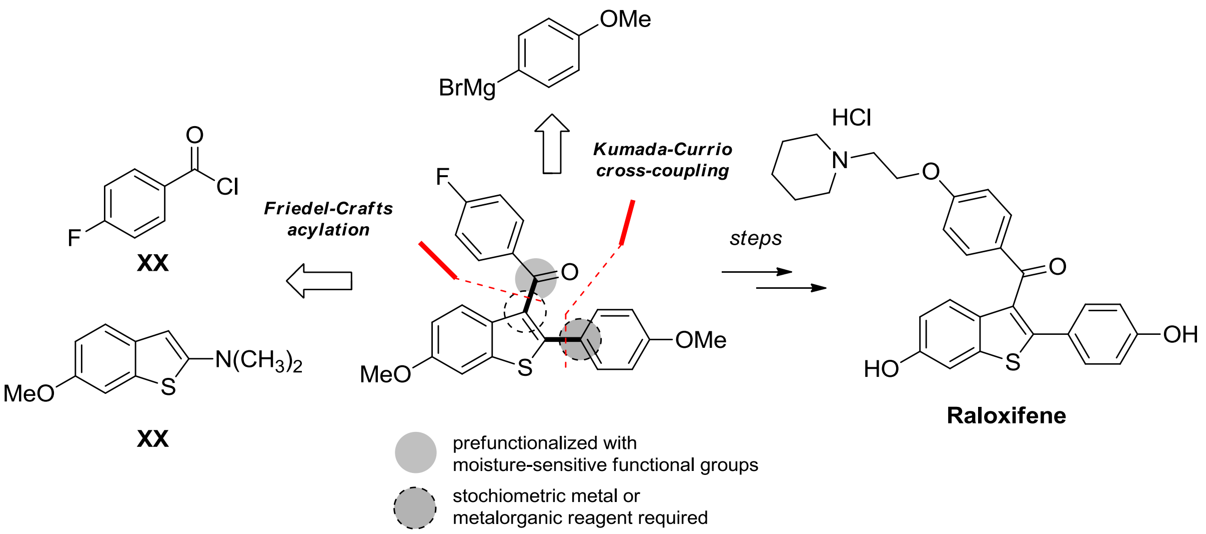
Scheme 1.17. Synthesis of marinopyrrole intermediate 1.20.

Although the presence of an *ortho*-hydroxy group is not tolerated in the carbonylative coupling reaction, (4,5-dichloro-1*H*-pyrrol-2-yl)-phenylmethanone (**1.20**) is an ideal candidate for ketone directed *ortho*-hydroxylation that has been described in manifold variants both by palladium and ruthenium-catalyst.



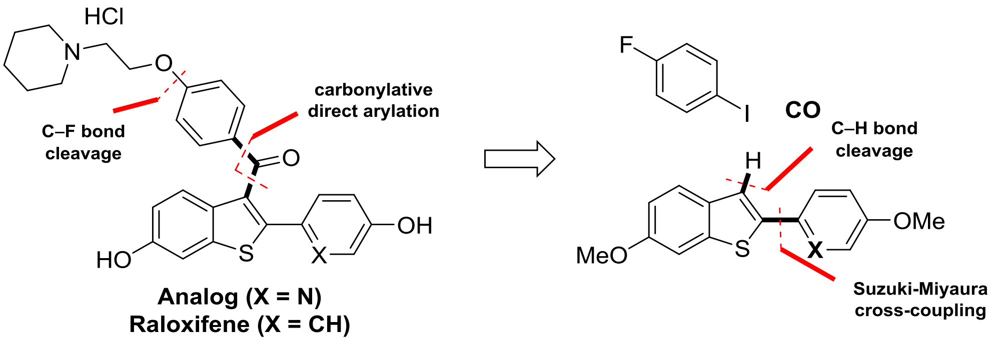
Scheme 1.18. Ketone-directed hydroxylation grants access to pyoluteorin and marinopyrroles A and B.

Raloxifene, distributed under the trade name Evista® (EllyLilly), is a synthetic, non-steroidal, selective estrogen-receptor modulator used for the treatment and prophylaxis of osteoporotic fractures in postmenopausal women. It was also evaluated to have a positive effect for the prevention of invasive breast cancer. Raloxifen is listed among the top one hundred drugs by sales, ranked highest at #77 in 2010 and at #92, post-patent expiration, in 2013. Distinct routes for the syntheses of Raloxifene derivatives frequently involve Friedel-Crafts-type acylation of the benzo[*b*]thiophene followed by Kumada–Corriu coupling for the C–C bond formation at the 2-position. These procedures require the use of stoichiometric metal salts, extensive substrate prefunctionalization and necessitate handling of air and moisture-sensitive compounds.



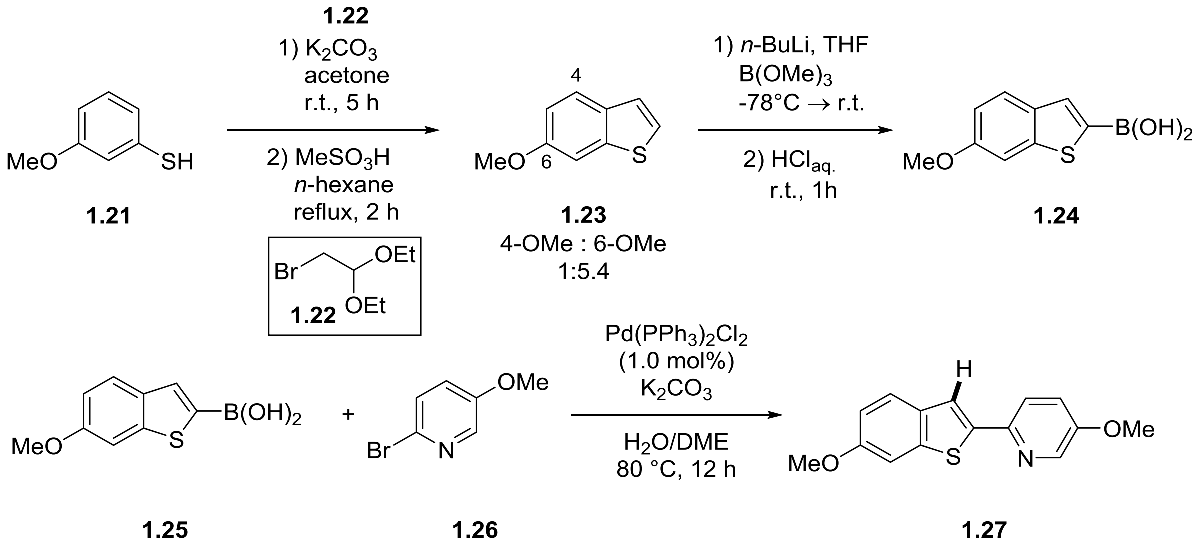
Scheme 1.19. Traditional synthesis of Raloxifen hydrochloride through sequential Friedel-Crafts reaction and Kumada-Currio cross coupling.

The carbonylative direct arylation ought to offer a considerable advantage in the synthesis of Raloxifene derivatives in terms of step- and atom-economy. Moreover, complementing traditional routes, the demonstrated approach offers the good opportunity for facile implementation of an isotopically labeled ketone functionality upon usage of labeled carbon monoxid which can be beneficial for the elucidation of the metabolic pathway of a pharmaceutical.



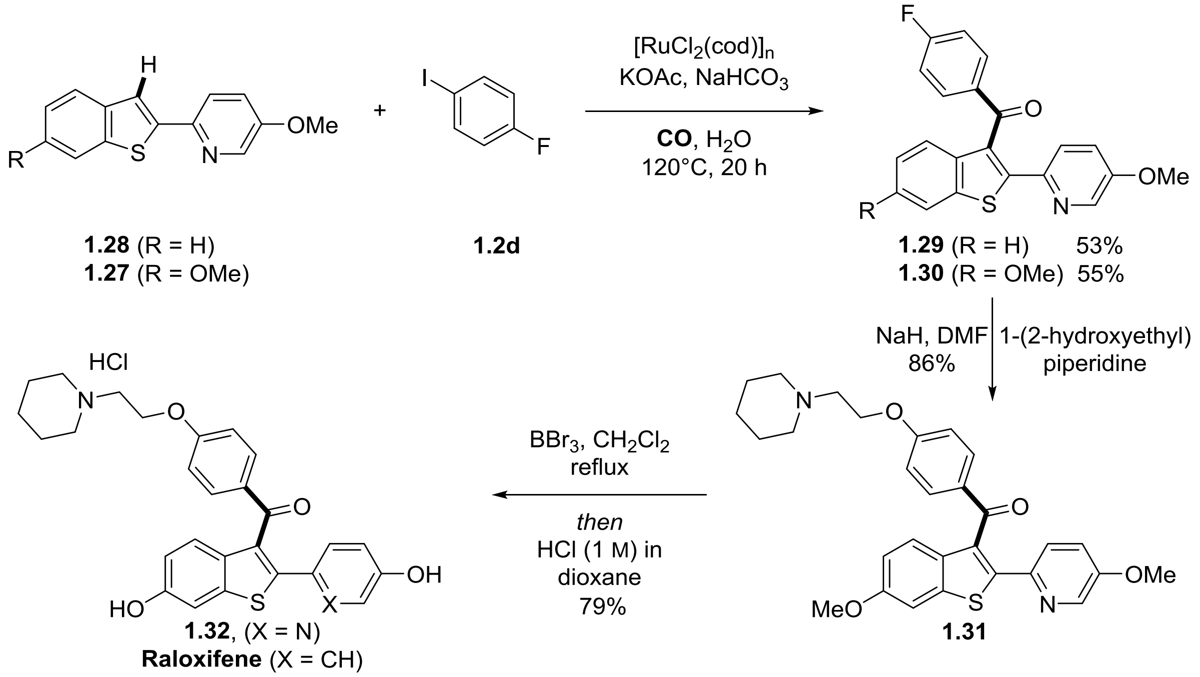
Scheme 1.20. Retrosynthetic analysis for the symthesis of Raloxifen through carbonylative direct arylation.

The directing-group was directly embedded in the core-structure of the pharmacophore. The precursor 4’-methoxy-2-(6-methoxybenzo[*b*]thiophen-2-yl)pyridine (**1.27**) was readily prepared by Suzuki–Miyaura coupling of 6-methoxybenzo[*b*]thiophen-2-ylboronic acid and 2-bromo-5-methoxypyridine (**1.26**). Noteworthy, unprotected 4’-hydroxy-2-(6-methoxybenzo[*b*]thiophen-2-yl)pyridine did not serve as adequate starting material. Under the applied reaction conditions, 3-hydroxypyridine tautomerizes to a zwitterionic form in which the pyridinium nitrogen atom is ineligible for coordination to the metal center.[39]



Scheme 1.21. Preparation of precursor 4’-methoxy-2-(6-methoxybenzo[*b*]thiophen-2-yl)pyridine (1.27).

Starting from the bismethoxylated substrate **1.27** and 4-fluoro iodobenzene (**1.2d**), the desired diarylketone **1.30** was obtained in 55% isolated yield. When 4’methoxy-2-(6*H*-benzo[*b*]thiophen-2-ylpyridine (**1.28**) was used as core structure, the C−H bond carbonylation proceeded likewise in 53% yield.[30] The structure of the corresponding product **1.29** was confirmed by X-ray analysis (Figure 1.7). Analogous to previous Raloxifene syntheses, the next step of the synthesis was the installation of the piperidine ethylether by SNAr reaction onto the aryl C−F bond. Eventually, deprotection of the two methoxy groups led to the target compound **1.32** in 42% isolated yield from **1.27**.



Scheme 1.22. Synthesis of pyridine-containing Raloxifene analog 1.32.

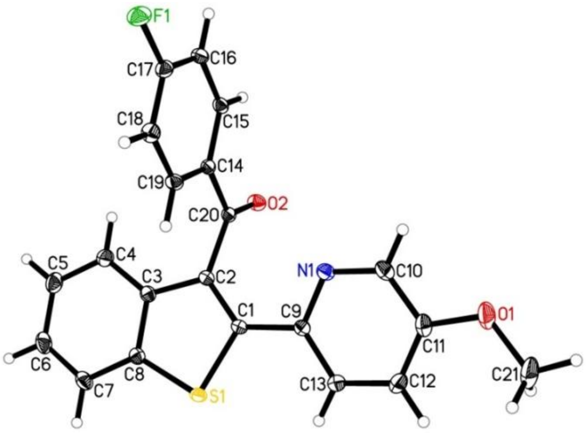
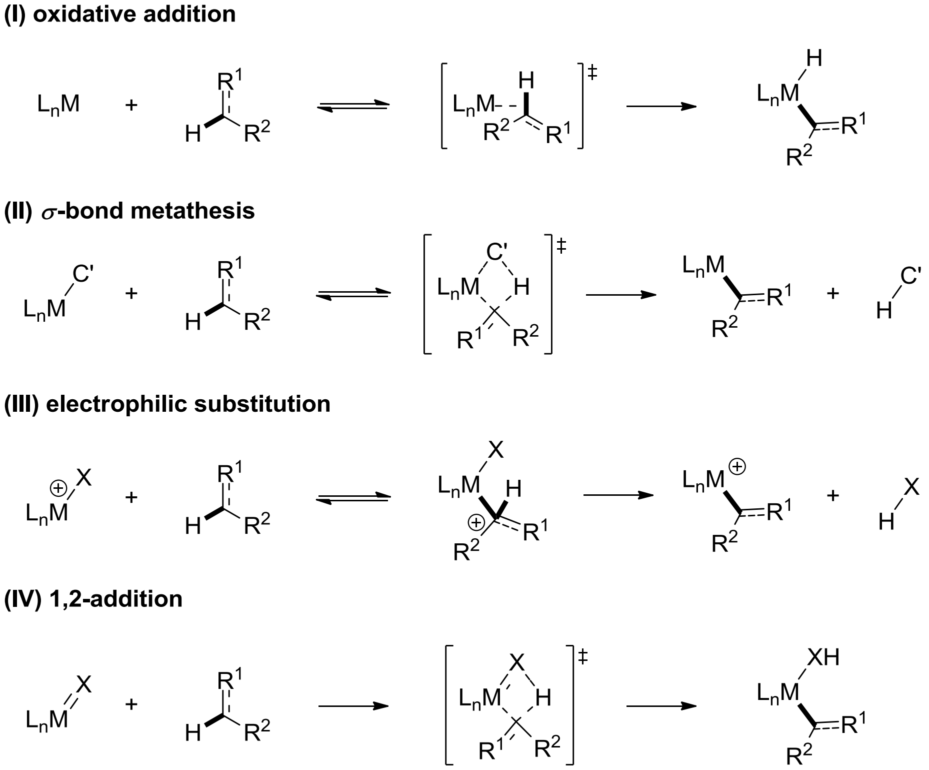


Figure 1.7. X-ray structure of compound 1.29.

1.4.5 Mechanistic considerations

The present work is the first example of intermolecular transition metal-catalyzed carbonylative direct arylation. Thus, the elucidation of the mechanism is a complex subject.

Intensive research efforts paved the way for a deeper understanding of the transition metal catalyzed C−H bond cleavage. Ample research articles and reviews comprehensively summarize various aspects that ought to be scrutinized to characterize the event of C−H bond activation.[7] The advent of C−H bond activation can be classified according to four different processes (Scheme 1.23).



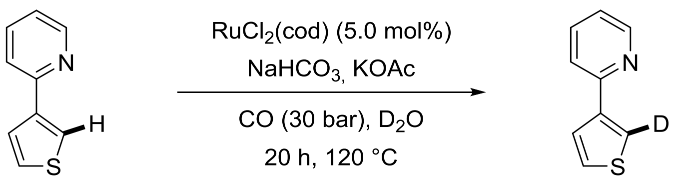
Scheme 1.23. Schematic representation of the different mechanisms for C−H bond activation.

Oxidative addition (**I**) is described as the most common mechanism. The oxidative addition consists of two steps: (1) coordination of the Lewis-basic C−H bond and (2) actual cleavage of the C−H bond to form the new M−C bond (Scheme 1.23). The net increase of the oxidation state of the transition metal by two units is accompanied by a change of geometry of the complex upon formation of two new σ-bonds. This mechanism is most commonly observed for electron-rich, low-valent complexes of the late transition metals (Re, Fe, Ru, Os, Ir, Pt) for which the higher oxidation state of the metal in the addition product and the necessary change in geometry upon formation of the two new bonds are not energetically penalizing. For early transition metals (groups 3 and 4, lanthanides and actinides) with d_0 electronic configuration, an oxidative process is not possible, and the preferred mechanism is σ-bond metathesis (**II**) usually involving an alkyl or a hydride complex (Scheme 1.23). The essential aspect of the σ-bond metathesis mechanism is the concerted formation (M−C and C′−H) and breaking (M−C′ and C−H) of bonds at the transition state. Late- or post-transition metals (Pd^{2+}, Pt^{2+} or Pt^{4+}, Hg^{2+}) in a strongly polar medium in which the metal center only acts as Lewis acid, a putative intermediate is formed by electrophilic attack of the metal to the substrate. The hydrogen atom of the substrate is formally substituted by the metal center. Hence, this mechanism has been formally classified as electrophilic substitution (**III**). Finally, the C−H bond can add across an unsaturated M−X bond in a 1,2 addition (**IV**). This mechanism resembles σ-bond metathesis except that the newly formed X−H bond does not lead to release of XH because the M−X σ-bond is still present in the product. The functional groups X leading to such reactivity are generally amido and alkylidene complexes of early to middle transition metals, but alkoxy and alkylidyne complexes have also been shown to activate C−H bonds.

Despite seemingly large differences among the various mechanisms that can be anticipated, there are three fundamental aspects to consider: (1) How is the C−H bond brought into the proximity of the metal, (2) How is the C−H bond cleaved in the metal coordination sphere and (3) what is the thermodynamic stability of the organometallic product featuring the new M−C bond. These questions ought to be addressed in the last section of this chapter.

In well-comprehended palladium-catalyzed traditional cross-coupling reactions as well as in direct arylations, the oxidative addition of the electrophile to the metal center depicts the first step within the catalytic cycle, and notably precedes the insertion of the metal into a C−H bond. In contrast, applicability of ruthenium catalysts in traditional bi(hetero)arenes through traditional cross-coupling reactions have been elusive.[41] Yet, versatile ruthenium direct arylations strategies have been discovered.[42] *Oi* and *Inoue* were the first who postulated that the cyclometalation precedes the oxidative addition of the electrophile to the metal-center and is nowadays the generally accepted reaction pathway.[43]

In the present system, a successful C−H bond cleavage was evident by full H/D-exchange when 2-(thiophen-3-yl)pyridine **1.8** was subjected to the standard reaction conditions in D_2O in the absence of an electrophile. The C-2 deuterated 2-(thiophen-3-yl)pyridine **D-4a** was isolated from the reaction mixture in 60% yield with an H/D-exchange rate of >95% (Scheme 1.24). This result provides strong evidence for a reversible C−H bond insertion step.



1.8 60% ***d*-1.8**

Scheme 1.24. C-2 Deuteration of 2-(thiophen-3-yl)pyridine 1.8.

Furthermore, experimental results suggested that the C−H bond insertion is promoted both by the nitrogen-containing directing group and acetate-assistance. Generally higher yields have been obtained in the presence of carboxylate additives (Table 1.1). Hence, carboxylate-assistance in the C−H bond cleavage is suggested. Furthermore, the Lewis basicity of the *N*-directing group appeared to be especially important for a successful C−H bond cleavage event. An electron donating methoxy group in 5-position of the pyridine slightly enhanced the reactivity of the system, whereas electron withdrawing substituents, such as bromine or fluorine, significantly attenuated the process relative to the unsubstituted pyridyl group (Figure 1.8). A hydroxyl group in 5-position prohibits the involvement of the *N*-heterocycle in the C−H bond cleavage event. Under basic reaction conditions, 5-hydroxypyridine isomerizes to the zwitterionic pyridium form resulting in complete loss of its Lewis basic character.[39]

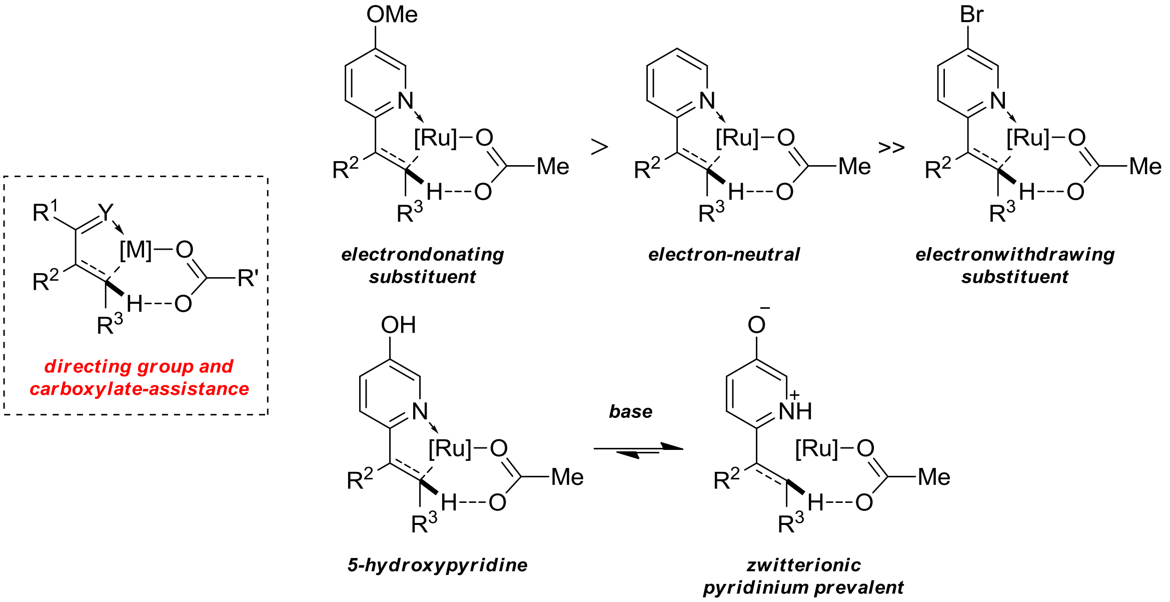
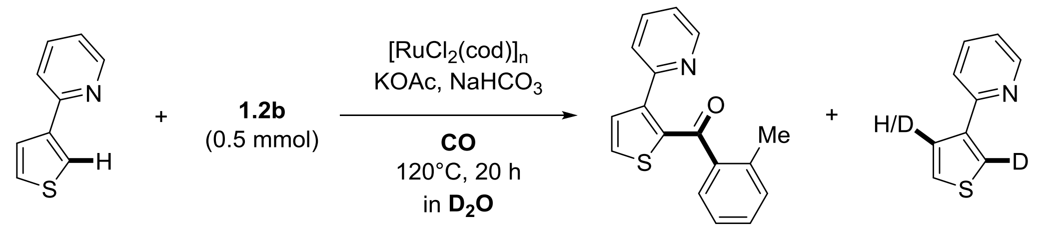


Figure 1.8. Influence of substituents on the *N*-directing group.

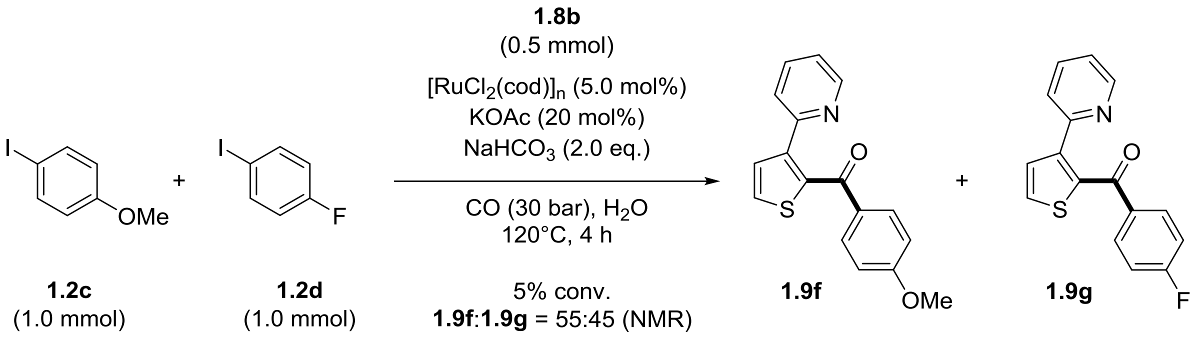
In the following, a number of mechanistic experiments targeting the key steps of the ruthenium-catalyzed carbonylative direct arylation have been conducted. Initially the reversibility of the C−H bond cleavage by using 3-(2'-pyridyl)thiophene (**1.8**) was contemplated. Concerning this matter, the reaction between **1.8** and 2-iodotoluene (**1.2b**) was conducted in D_2O under otherwise unaltered reaction conditions (Scheme 1.25). The process was stopped after 3 h and 65% deuterium incorporation at the 2-position of ***d*-1.8** was determined by ^{1}H NMR spectroscopy. After 20 h full consumption of the electrophile was observed and the H/D-exchange at the 2-position corresponded to 95% deuterium incorporation and 15% at C4. The H/D-exchange at the 4-position in product **1.9a** accounted for less than 7%. This observation is a strong evidence for the reversibility of the ruthenium-catalyzed C−H bond cleavage.



1.8 (1.0 mmol)		**1.9a** **Yield of 3ab**	***d*-1.8** **H/D exchange at C-2**
	after 3 h:	28% (NMR)	65%
	after 20 h:	91% (isol.)	95%

Scheme 1.25. H/D exchange at C2 of 1.8.

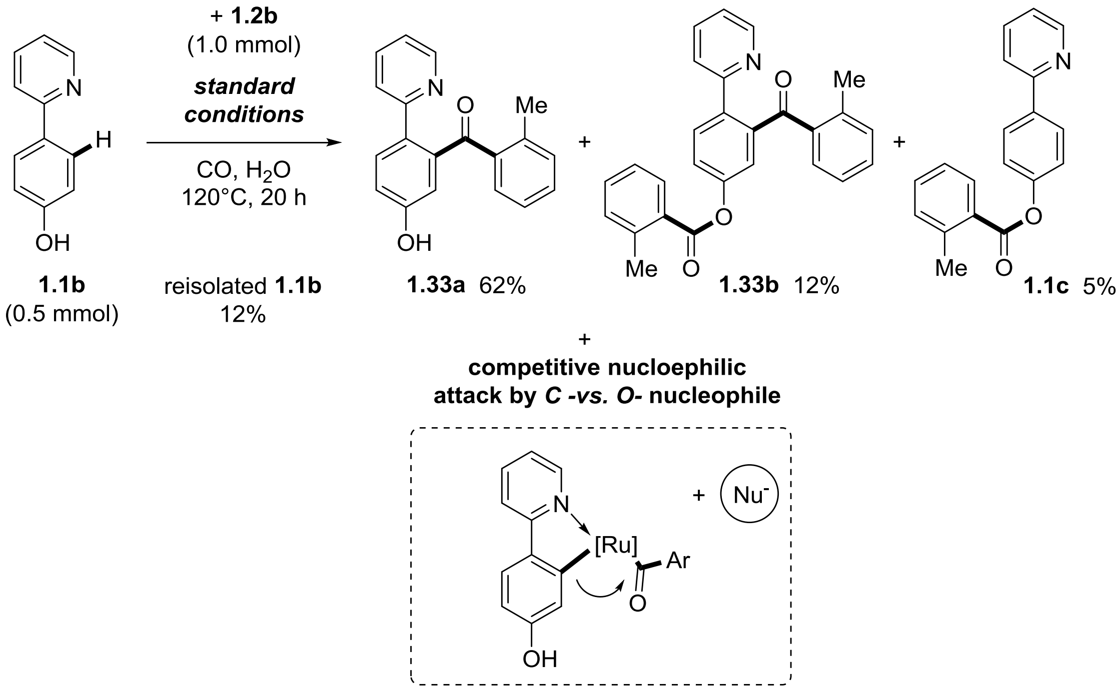
The influence of the electronic nature of the electrophile on the rate of the oxidative addition was probed by an intermolecular competition experiment between electron-rich 4-methoxyiodobenzene (**1.2c**) and electron-poor 4-fluoroiodobenzene (**1.2d**) (Scheme 1.26). The substrates were employed in a 1:2:2 ratio that corresponds to an eightfold excess of electrophile relative to the optimized reaction conditions (with nucleophile **1.2** as the limiting reactant). The reaction was quenched after 4 h in order to secure low conversion. The product distribution of **1.9f** and **1.9g** in a 1.2:1.0 ratio according to ^{1}H NMR spectroscopy. Consequently, the oxidative addition should not represent the rate-determining step in the catalytic cycle.



Scheme 1.26. Intermolecular competition experiment between electron-rich and poor electrophiles.

The metalated arene which is formed in course of the C–H bond can be contemplated as nucleophile which attacks an electrophilic metal-acyl species to generate a new C–C bond. The carbon based nucleophile might face competition from stronger nucleophiles such as hydroxyl groups or amines.

From a reaction between 4-(pyridin-2-yl)phenol (**1.1b**) and 2-iodotoluene (**1.2b**) it was indeed evident that the phenol is indeed capable to attack the metal-acyl species. From the analysis of the crude mixture of products the occurrence of two side-products **1.33b** and **1.1c** have been observed. The benzoylation of the phenol indicated that (1) the phenol competes in the in abstraction of the acyl species *via* intermolecular attack and (2) the carbon monoxide-insertion in the ruthenium-aryl bond of the electrophile subsequent to the oxidative addition is relatively fast. However, the combined product yield for the desired carbonylative direct arylation accounted for 74% isolated yield. Thus, (3) the formally intramolecular insertion of the carbon nucleophile is the privileged pathway.



Scheme 1.27. Competitive attack of *C*- and *O*-nucleophiles.

Eventually, a plausible catalytic cycle for the ruthenium-catalyzed carbonylative direct arylation is proposed as illustrated in Figure 1.9. The C−H bond is brought into the proximity of the metal by coordination of the nitrogen lone-pair of the directing group (**A**). Subsequently, the C−H bond is cleaved in the metal coordination sphere (**B**). In the following, the electrophile oxidatively adds to the chelated ruthenium species (**C**) to form **D**, which in turn readily reacts with carbon monoxide to form of Ru-acyl complex (**E**). Eventually, the second C(sp^2)−C(sp^2) bond formation proceeds *via* reductive elimination and extrusion of the coupling product along with regeneration of the active Ru(II)-catalyst (**F**).

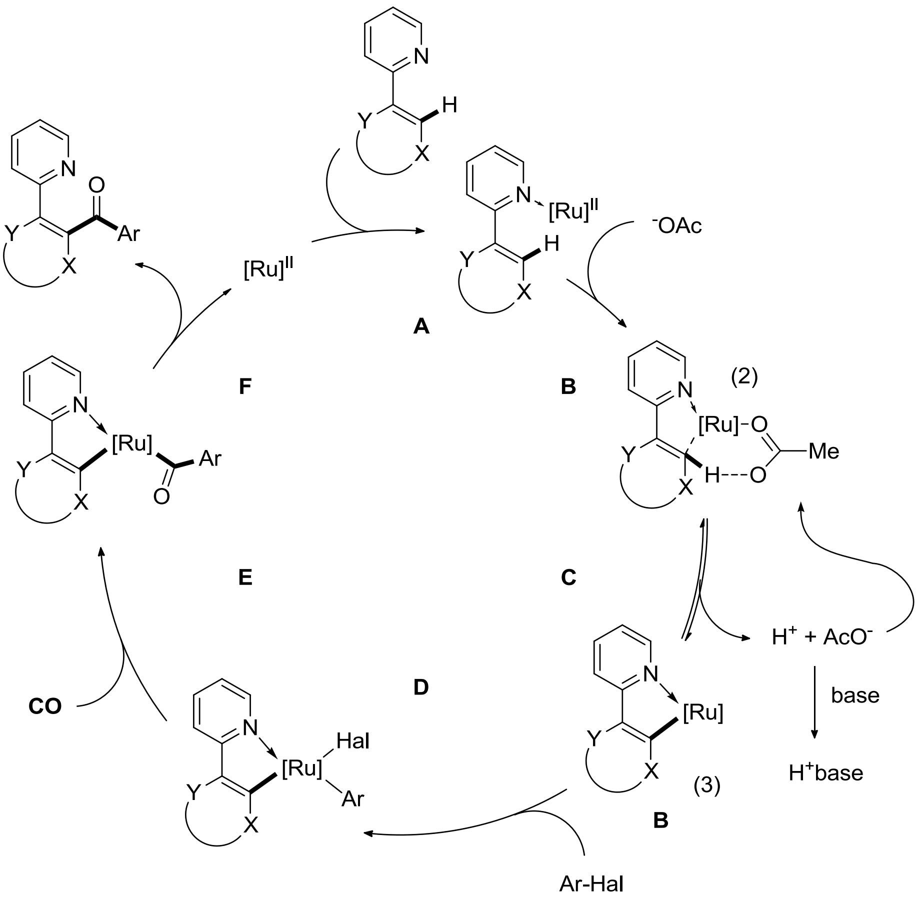


Figure 1.9. Proposed mechanism for the carboxylate-assisted carbonylative direct arylation (hetero)arenes bearing an *N*-directing group.

1.5 Conclusion and outlook

In summary, we have developed the first ruthenium-catalyzed carbonylative direct arylation of (hetero)arenes by means of C−H bond activation. This facile three component synthesis of complex aryl-heteroaryl ketones *via* successive twofold C(sp^2)−C(sp^2) bond formation in water describes a conceptually new path for the construction of benzophenone derivatives.

Starting with simple phenylpyridine derivatives, this chemistry could be extended to the preparation of aryl-heteroarylketones including examples with cleavable directing groups. The synthetic applicability of the developed methodology has been demonstrated in the streamlined synthesis of an analog of the top-selling selective estrogen receptor modulator Raloxifene (Evista®) and the gram-scale synthesis of a key intermediate of marinopyrroles and pyoluteorin.

2 Rhodium(II)-catalyzed enantioselective masked formylation of push-pull carbenes with 1,3,5-trioxane

2.1 Preface

A significant drawback of reactions applying gaseous carbon monoxide as C1-building block is the necessity to operate with special apparatuses, such as autoclaves, high-pressure and multi-vessel glassware, in addition to imperative safety restrictions that come into play when compared to classic bench chemistry. In this chapter the development of an operational methodology for the enantioselective introduction of an inexpensive, crystalline C1-building block, 1,3,5-trioxane by means of rhodium(II)-catalyzed C–H insertion, will be outlined and discussed.

2.2 Project outline

Intensive studies by *Doyle*,[44] *Davies*[45] and others have established dirhodium(II) carbene chemistry as a useful means for site- and stereoselective functionalization of sp^3C–H bonds. It has been shown that the choice of the dirhodium(II) catalyst in combination with appropriate carbene precursors is pivotal to trigger the desired reactivity (C–H bond insertion *vs*. cyclopropanation *vs*. ylide formation), which can be accomplished even in highly functionalized substrates. In this respect, it has been demonstrated that donor/acceptor dirhodium(II) carbene complexes permit intermolecular insertion into sp^3-C–H bond. A comparison of the relative rates of the C–H bond insertion, shown in Figure 2.1, highlights the superior reactivity of secondary C–H bonds which can best stabilize a positive charge build up during the C–H bond cleavage event, e.g. C–H bonds in allylic position and/or in the vicinity of a heteroatom.[2a]

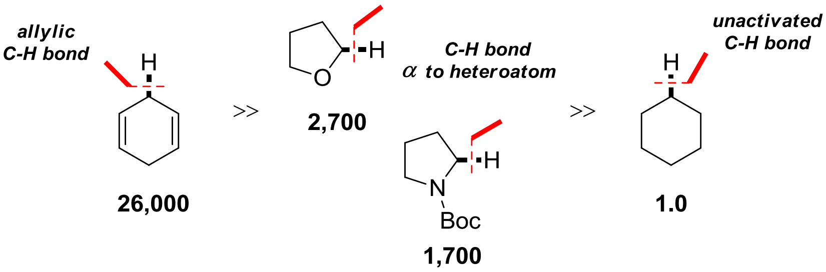
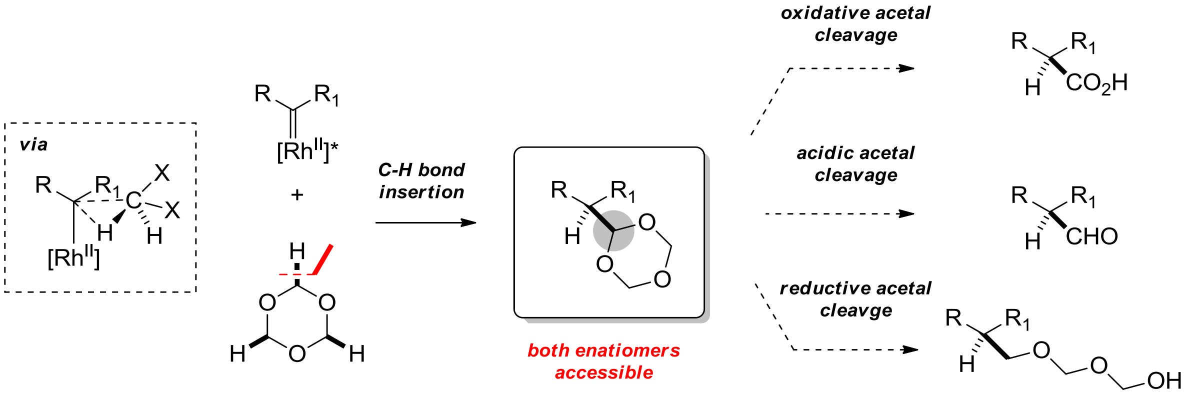


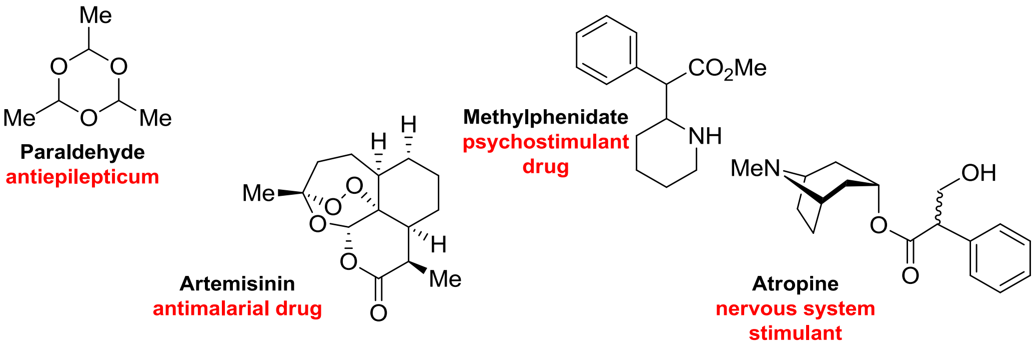
Figure 2.1. Relative rates of reactivity for rhodium carbene C−H functionalization.[45a]

This project was outlined to investigate the functionalization of 1,3,5-trioxane as alternative C1 building block by means of dirhodium(II) carbene chemistry, derived from diazo compounds, for the stereoselective implementation of a versatile masked formyl functionality (Scheme 2.1). 1,3,5-Trioxane, a solid, easily handled formaldehyde surrogate, combines several features which suggest advantageous for an efficient sp^3C–H bond functionalization. Six chemically equal C–H bonds are positioned in α-position to two oxygen heteroatoms. Additionally, the cyclic structure minimizes the steric congestion, thus rendering the targeted reaction site conveniently accessible.[3] Subsequent cleavage of the acetal, under oxidative, acidic or reductive conditions, respectively, ought to grant access to optically active carboxylic acids, aldehydes and readily protected primary alcohols.



Scheme 2.1. Rhodium(II)-catalyzed enantioselective masked formylation of push-pull carbenes with 1,3,5-trioxane.

Cyclic ethers are broadly appreciated for their non-peptidic hydrogen binding abilities and ring flexibility in pharmaceutical chemistry and other life sciences.[46,47] In addition, 2-aryl-2-(1,3,5-trioxan-2-yl)acetates are structurally closely related to biologically active methylphenidates and atropine yet providing orthogonal hydrogen-bonding abilities (Scheme 2.2). Providing access to this class of compounds is likely to contribute to expand the current tool box in medicinal chemistry.



Scheme 2.2. Selected pharmaceuticals and natural products containing cyclic ethers and α-arylpropionic acid derivatives, respectively.

2.3 Background

2.3.1 1,3,5-Trioxane in organic synthesis

1,3,5-Trioxane or *s*-trioxane has been employed as clean and convenient anhydrous source of formaldehyde. Trioxane is of very low toxicity following single-dose administration. The oral LD_{50} values for rats ranges from 7.7 to 9.5 g/kg body weight. Single dermal treatment of rabbits with 4.0 or 15 g/kg does not cause irritation or any clinical signs of toxicity.[48] In combination with hexamine, trioxane can be compressed to solid fuel bars, used as outdoor stove fuels. Furthermore, 1,3,5-trioxane is used as restorative chemical for the conservation of postmortem tissue. 1,3,5-Trioxane is formed from formaldehyde under thermolysis or acid-mediated cyclotrimerisation (Figure 2.2).[49]

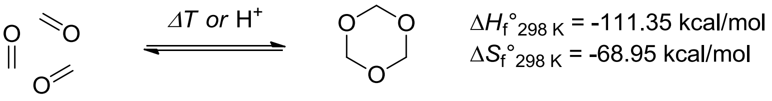


Figure 2.2. Formation of 1,3,5-trioxane by cyclotrimerisation of formaldehyde.

Although the 1,3,5-trioxane congener paraldehyde (Figure 2.3) is long known as central nervous system depressant for the treatment of acute status epilepticus, the 1,3,5-trioxane motif is essentially absent in medicinal chemistry. A related yet structurally off 1,2,4-tiroxanyl motif is found in the antimalarial Artemsinin.[50] The reason for the limited appearance of 1,3,5-trioxane rings is likely caused due to the lack of methods to append the trioxanyl motif into drug-like scaffolds. Accordingly, very few chemical transformations for its installation are reported in the literature.[51] Such examples almost exclusively describe the installation of the trioxane onto sp^2-hybridized carbons *via* radical chemistry.[52] Hence, these approaches inherently do not allow for generation of a stereogenic centers.

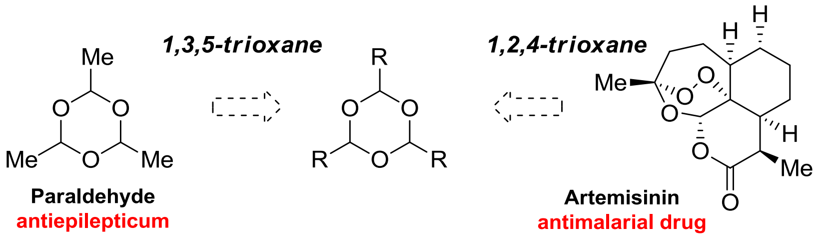
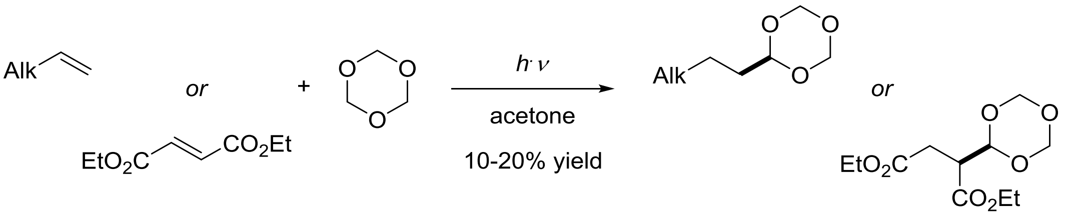


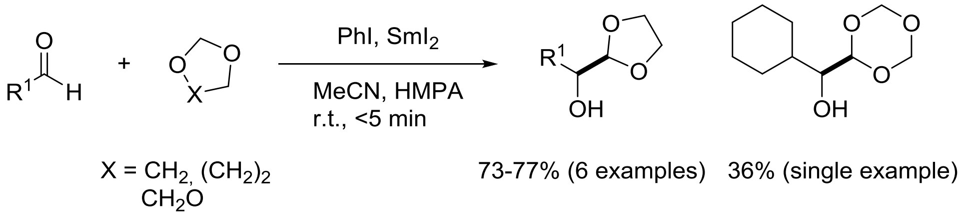
Figure 2.3. Pharmaceuticals bearing a trioxane motif.

Early examples for the functionalization of trioxane can be found in the midst of the scope of a protocol for the photoalkylation of cyclic ethers described by *Rosenthal* and *Elad* in 1968 (Scheme 2.3).[51a] However, the yields of alkyltrioxacyclohexanes were poor accounting only for 10-20% yield.



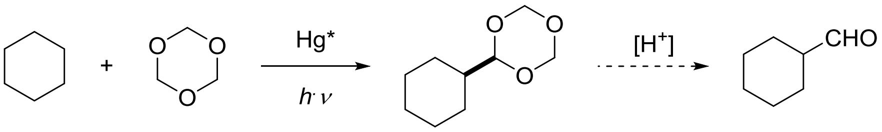
Scheme 2.3. Ketone-initiated photoaddition of olefines to cyclic ethers.

Almost twenty years later, the group of *Inanaga* reported a SmI_2-induced masked formylation of carbonylcompounds. *α*-Hydroxyacetals were attained by the reduction of iodobenzene with SmI_2 in a solution of 1,3-dioxolane-MeCN-HMPA (20:2:1) in the presence of carbonyl compounds.[51b] However, the substitution of 1,3-dioxolane with 1,3,5-trioxane gave rise to the corresponding adducts only in poor yields (Scheme 2.4).



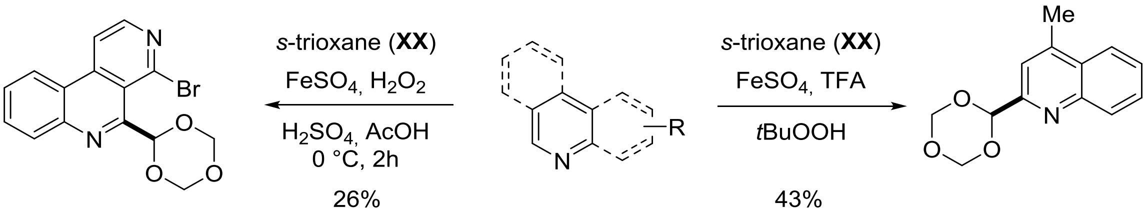
Scheme 2.4. SmI_2-induced masked formylation of carbonyl compounds.

Crabtree and *Brown* particularly emphasized the synthetic high value of the trioxanyl moiety as a masked formyl group. In their studies the authors described the functionalization of cyclohexane by mercury-photosensitized cross-dehydrodimerization which generated 2-cyclohexyl-1,3,5-trioxane (Scheme 2.5).[53] They stressed the opportunity to cleave the acetal upon hydrolysis, however the report is lacking further details concerning this transformation.



Scheme 2.5. Alkane functionalization by mercury-photosensitized cross-dimerization.

A fourth reaction in which the 1,3,5-trioxane motif is fully implemented into a molecular scaffold is the Minisci-type functionalization of *N*-heterocycles such as chinoline[52b] or benzonaphthyridine (Scheme 2.6).[52a]

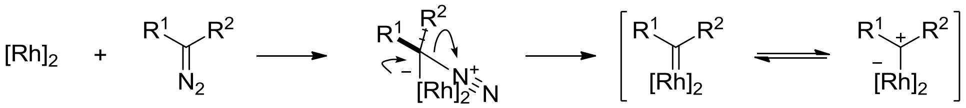


Scheme 2.6. Minisci-type functionalization of heterocycles using 1,3,5-trioxane.

Besides the above mentioned examples, in the vast majority of reactions with 1,3,5-trioxane, the *O*-heterocycle is used as formaldehyde source. Practical applications are aldol reactions,[54] Blanc chloromethylation,[55] Pictet-Spengler-cyclization[56] or Eschweiler-Clarke aminomethylations and Mannich reactions.[27]

2.3.2 C–H Bond functionalization by means of rhodium carbenoid insertion

The C−H bond functionalization by a metal-bound carbene, nitrene or oxo species has become a powerful branch in the field of C−H bond functionalization methodologies in recent years.[57] In particular, chiral catalysis using dirhodium(II) catalysts has experienced immense growth since the discoveries in the early 1980’s.[58] Dirhodium(II) carboxylate complexes are inherently stable to heat, moisture and can be handled and stored under ambient atmosphere. They are highly reactive catalysts for the decomposition of diazo compounds (Scheme 2.7).



Scheme 2.7. Rhodium(II)-mediated decomposition of diazo compounds.

The resulting rhodium carbenoids are exceptionally versatile in their reactivity, while displaying high selectivities in reactions such as C–H bond insertions, cyclopropanation/propenation reactions and ylide formation, cycloadditions[59] and cross-coupling reactions.[60] This section will highlight selected examples of rhodium(II)-catalyzed C–H bond insertion reactions with an emphasize on the application in small molecule activation.

The reactivity is particularly dependent on the stability of the carbenoid and C−H bond strength of the reaction partner. Variation of the electron demand of the substituents on the carbene precursor proved particularly helpful to affect the chemoselectivity (Figure 2.4). A wide array of experimental data displayed considerably enhanced chemo- and stereoselectivity when donor/acceptor rhodium carbenoids where employed in cyclopropanation[61] and C−H bond insertion reactions. A computational study conducted by *Hansen*, *Autschbach* and *Davies* demonstrated that stabilized donor/acceptor rhodium carbenoids display significantly higher potential energy activation barriers which *vice versa* leads to an increased selectivity due to lower reactivity compared to the traditionally used acceptor carbenoids derived from unsubstituted diazo esters.[57b]

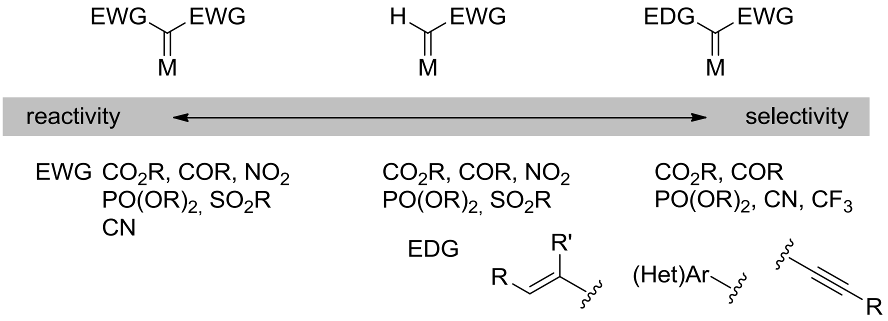


Figure 2.4. Classification of carbenoid intermediates.

The C−H bond functionalization by donor/acceptor rhodium carbenes is a powerful method that has impacted profoundly on complex chemical synthesis. Amongst the most notable developments in this field is the highly site and stereoselective intermolecular direct functionalization of unactivated sites in a multitude of molecules. This has proven advantageous to streamline the synthesis of numerous natural products and pharmaceutical targets.

Chiral rhodium-prolinate complexes, initially invented by *McKervey*[62] and further developed by the group of *Davies*,[63] display excellent catalytic activity in intra- and intermolecular C−C bond forming reactions *via* C−H bond insertion of donor-acceptor carbenoids in a highly stereoselective fashion. The highest stereoinduction was commonly achieved in apolar solvents. However, *McKervey*'s $Rh_2(S\text{-BNP})_4$ catalyst was poorly soluble in this medium. Introducing a dodecyl side-chain significantly enhanced the solubility and broadened the applicability of the catalyst system (Figure 2.5). The *S*-DOSP (dodecylsulfonylprolinate) backbone of $Rh_2(S\text{-DOSP})_4$ is synthesized from chiral pool amino acid *S*-proline and dodecylsulfonyl chloride. Dodecylsulfonyl chloride is accessed from sodium dodecylsulfonate which is a bulk chemical commonly used as surfactant and constitutes a major component in laundry detergent.[64] Hence, this powerful catalyst consists of inexpensive and abundant commodities. Irrespective of the substitution pattern, the carboxylate ligands undergo thermal ligand exchange with the acetate ligands of $Rh_2(OAc)_4$ to form the corresponding rhodium(II) carboxylate complex.

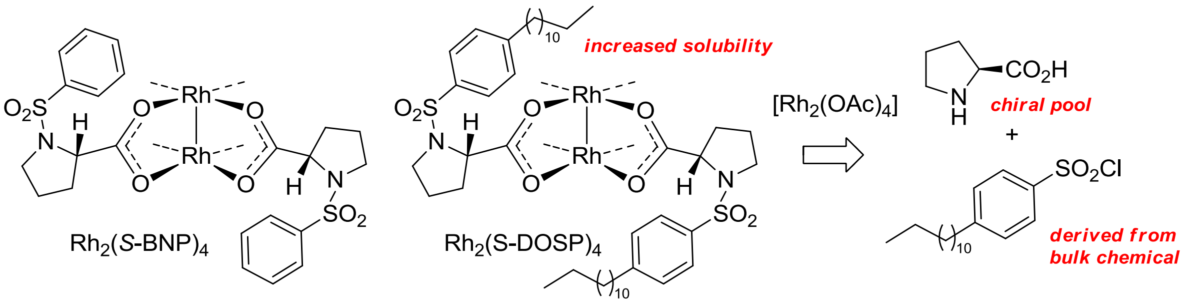


Figure 2.5. Chiral rhodium(II)-prolinate complexes $Rh_2(S\text{-BNP})_4$ (left) and $Rh_2(S\text{-DOSP})_4$ (middle).

$Rh_2(S\text{-DOSP})_4$ is arguably the most widely applied chiral rhodium catalysts and has been used in a multitude of enantioselective C−H bond insertion reactions. The site selectivity is controlled by a delicate balance of steric and electronic effects. Highly substituted sites are electronically favored as they stabilizes build up of the positive charge at the carbon centre during the C−H insertion event. Nonetheless this contribution is counterbalanced by the steric demands of the carbene complex. Thus, dirhodium tetraprolinate catalyst $Rh_2(S\text{-DOSP})_4$ operate most efficiently in C−H bond functionalization reactions at secondary C−H bonds, although a few examples of functionalization of sterically accessible tertiary C−H bonds[45b,57c] and electronically activated primary C−H bonds have been reported.[65]

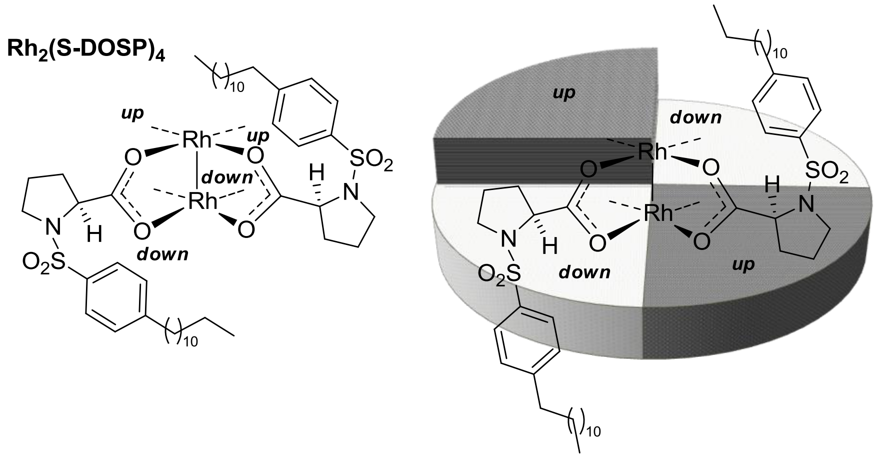


Figure 2.6. Simplified model of the dirhodium prolinate complex Rh_2(*S*-DOSP)$_4$.

Kinetic studies have demonstrated that only one of the two metal atoms is catalytically competent while the other metal center functions as an electron sink to stabilize the carbenoid structure.[66] The selectivity of the chiral dirhodium(II) paddlewheel carboxylate can be illustrated as depicted in Figure 2.6. The core of the complex is represented as a disc-like shape. The dirhodium(II) complex can be separated into quadrants, defined by the O−Rh−O bonds. In the Rh_2(*S*-DOSP)$_4$ model, tetraprolinate DOSP is thought to reside in a D_2-symmetric conformation. An alternating up-down arrangement minimizes the net dipole induced by the *N*-sulfonyl groups.[67] The donor/acceptor carbenoid arranges itself in a way that the donor group (e.g. aryl or vinyl moiety) is in the plane of the rhodium bound carbene, whereas the electron withdrawing group (e.g. alkyl ester) adopts an arrangement perpendicular to the plane of the carbene. The stereo-electronic demand of the ester shields an additional quadrant. Hence, the incoming substrate has merely one possible trajectory to approach the carbenoid. These features dictate the stereochemistry of the resulting coupling product (Figure 2.7). Calculations at a B3LYP/6-31G*[Rh-RSC+4f] level of theory suggested that the C−H bond insertion is highly asynchronous for activated C−H bonds. In these cases, the formation of the new C−H bond slightly precedes the C−C bond formation between the carbenoid and the substrate. This is also evident in a 165° C−H−C angle in the optimized transition state geometry. Hence, the substrate penetrates the metal carbenoid in an almost orthogonal trajectory as illustrated in Figure 2.6. The Newman projection, as shown below, serves as good model for the prediction of the stereochemical outcome of the reaction.

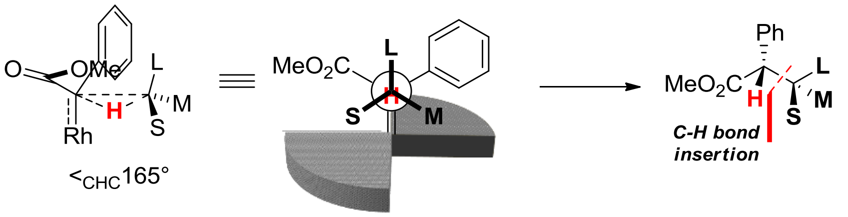
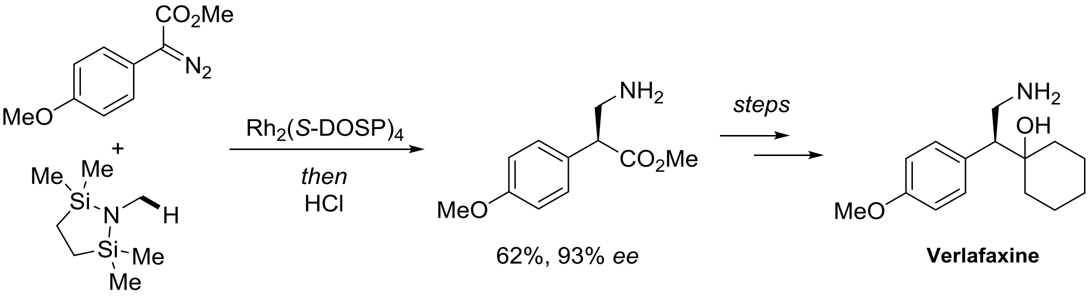


Figure 2.7. Newman projection as predictive model for the stereoselective C−H bond insertion.

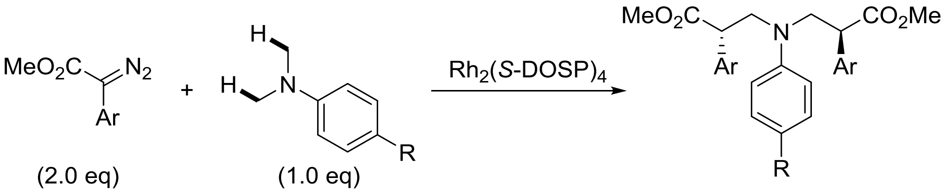
Noteworthy, small molecule activation, naturally depending on its definition, is relatively scarce in rhodium-carbenoid catalysis. Examples that provide a formal C1 extension of the carbenoid are even less widespread.

Two examples in this area have been studied and published by the group of *Davies*. In the first example, stereoselective insertion of methylphenyl diazoacetates into the methyl group of silyl-protected methylamine was accomplished in the presence of $Rh_2(S\text{-DOSP})_4$ (Scheme 2.8). The corresponding chiral *β*-amino esters were synthesized in good yields and high enantiomeric excess. Acidic treatment eventually liberated the free amine. This reaction was applied to a rapid enantioselective synthesis of the antidepressant venlafaxine (Scheme 2.8).[68]



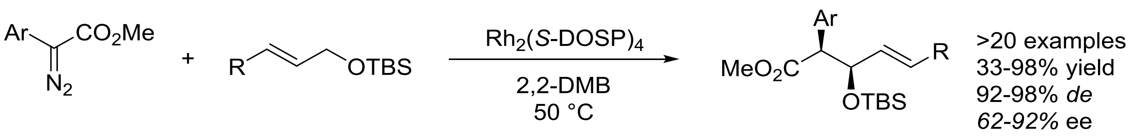
Scheme 2.8. C‑H functionalization strategy for the preparation of venlafaxine.

The C–H functionalization of a primary center alpha to the nitrogen atom of *N*,*N*-dimethylanilines was further applied to the preparation of C_2-symmetric anilines, by using an excess of methyl aryldiazoacetate in reported yields of 41-60% and 85-95% *ee* (Scheme 2.9).[65a] Blocking of the *para*-position of the aniline arene was mandatory to avoid site-product formation by competing electrophilic aromatic substitution.



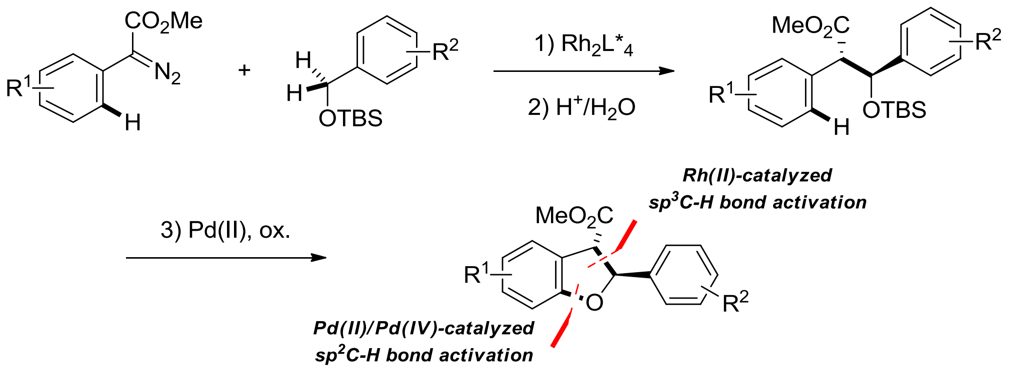
Scheme 2.9. Double C‑H activation strategy for the asymmetric synthesis of C_2-symmetric anilines.

Besides these two examples for the stereoselective activation of formal C1-building blocks, the broad applicability of stereoselective C−H bond insertion by means of rhodium(II) carbenoid chemistry has certainly been showcased. In particular, the site-selective activation of C−H bonds α to heteroatoms proved to be a fruitful pathway to create valuable architectures and supplies alternative strategies to traditional synthetic routes. For example, *β*-hydroxy esters, traditionally prepared by an aldol reaction have been stereoselectively accessed by α-C–H functionalization of silyl ethers (Scheme 2.10).[69]



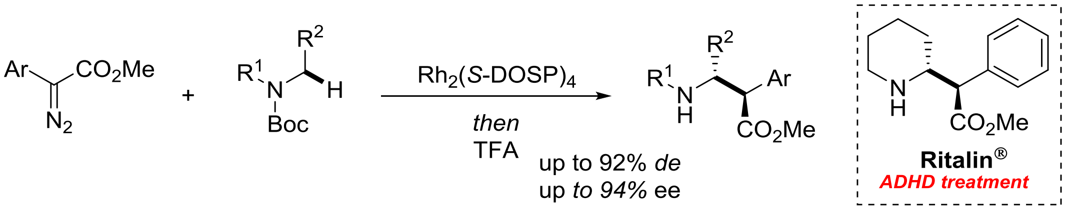
Scheme 2.10. Catalytic asymmetric C–H activation α to oxygen as a surrogate to the aldol reaction.

Almost one decade later, in 2003, this approach was implemented in the sequential synthesis of functionalized 2,3-dihydrobenzofurans based on C−H bond functionalization in a collaborative project jointly published by the groups of *Huw Davies* and *Jin-Quan Yu* (Scheme 2.11).



Scheme 2.11. Sequential C−H functionalization reactions for the enantioselective synthesis of highly functionalized 2,3-dihydrobenzofurans.

Similarly, *β*-amino esters, products of the Mannich reactions, are obtained by C–H activation *α* to nitrogen.[70] This reaction provided access of *threo*-methylphenidates, the active form of the psychostimulant drug Ritalin® (Scheme 2.12).



Scheme 2.12. Catalytic asymmetric C–H activation α to nitrogen as a surrogate to the Mannich reaction.

A strategically surrogate for the Claisen condensation has been proposed by the insertion of donor-acceptor substituted carbenoids into C–H bonds of acetals (Scheme 2.13).[71] The resulting protected *β*-keto esters were formed in up to 65% yield and maximum 91% *ee*. However, the average yields and enantiomeric excesses were moderate.

Scheme 2.13. Asymmetric C–H insertion of Rhodium(II) stabilized carbenoids into acetals.

In line with these examples, we aimed to exploit small molecule-activation by means of rhodium(II)-catalyzed C−H bond activation to provide an equivalent for asymmetric formylation outside the range of thoroughly studied hydroformylations.

2.4 Results and discussion

The direct functionalization of inexpensive, crystalline, and safe to handle cyclic ether 1,3,5-trioxane by means of enantioselective rhodium(II) carbenoid insertion into one of six chemically equivalent C−H bonds is presented. The applied method allowed for the unprecedented implementation of stable, chiral trioxanyl acetals.

2.4.1 Optimization and catalyst screening

Methyl phenylacetate **2.1a** was used as standard substrate for the optimization of the reaction conditions for the rhodium-catalyzed stereoselective insertion into 1,3,5-trioxane **2.2** (Table 2.1). The conversion to the desired product was determined by ^{1}H NMR analysis of the crude mixtures after evaporation of the solvent. Mesitylene was used as an internal standard. Isolated yields are shown in parenthesis. Where appropriate, the enantiomeric excess was determined by chiral HPLC analysis (*ee* of (*S*)-enantiomer). The stereochemistry was assigned according to the predictive model for Rh$_2$(*S*-DOSP)$_4$ C−H bond insertion as described in Figure 2.7. Later the prediction was confirmed by x-ray analysis of an enantiomerically pure probe and cross-checked with its chiral HPLC trace and optical rotation values.

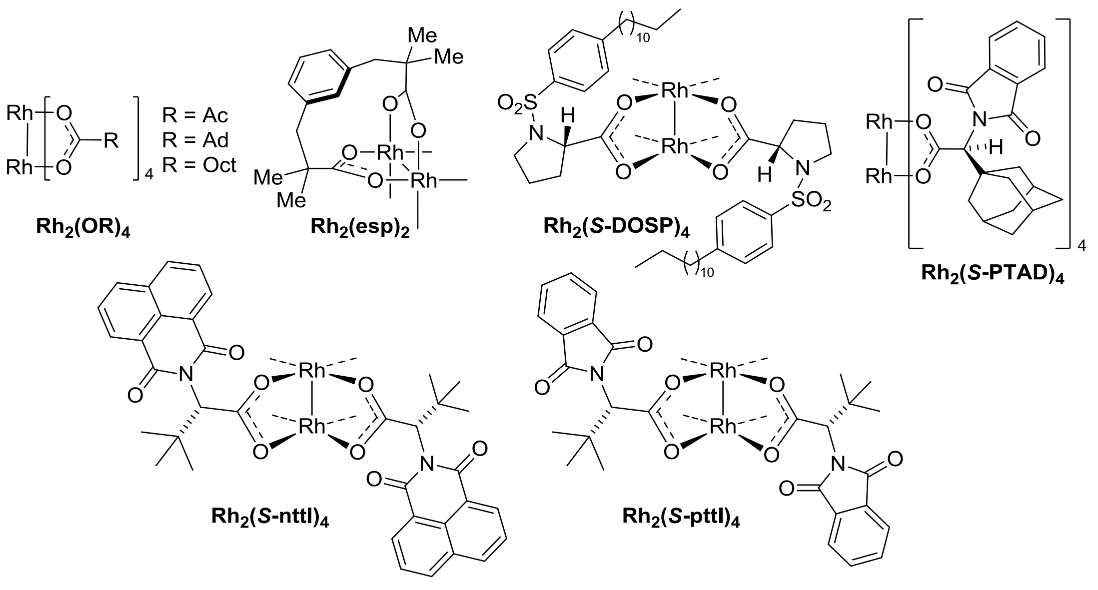
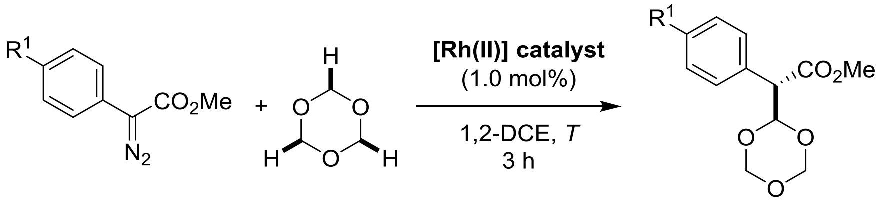


Figure 2.8. Tested achiral and chiral rhodium carboxylate complexes.

Although most tested chiral rhodium(II) carboxylate complexes, Rh$_2$(*S*-ptad)$_4$, Rh$_2$(*S*-pttl)$_4$, Rh$_2$(*S*-nttl)$_4$ (Figure 2.8) efficiently catalyzed the C−H bond insertion of phenyl acetate derived carbenoids into 1,3,5-trioxane (Table 2.1, entry 13-22). Rh$_2$(*S*-DOSP)$_4$ imparted both the highest selectivity for the productive C–H insertion pathway and highest enantioselectivity amongst the chiral catalysts tested (36% isol. 92% *ee* (*S*), yield of **2.3a**; Table 2.1, entry 18). The modest yields owing to the high reactivity of diazoesters, which are prone to participate in side reactions such as dimerization, in expense of product yield. For instance, (2*Z*,2'Z)-dimethyl 2,2'-(hydrazine-1,2-diylidene)bis(2-phenylacetate) was formed and isolated in 18% yield as major side product (Table 2.1, entry 12).

None-the-less, a higher yield of 54% and improved enantioselectivity (99% *ee*, (*R*)) was observed when methyl 4-bromophenyldiazo acetate **2.1b** was used as the substrate (entry 23). Thus, after an exploratory screening, optimal results were obtained when a solution of methyl phenyl diazoacetate **2.1** in 1,2-dichloroethane was added dropwise to a styrring solution of the $Rh_2(S\text{-DOSP})_4$ (1.0 mol%) and 1,3,5-trioxane (**2.3**) in 1,2,-dichloroethane over the course of 90 min.

Table 2.1. Optimization and catalyst screening.[a]



2.1 **2.2** **2.3a** (R^1 = H) **2.3b** (R^1 = Br)

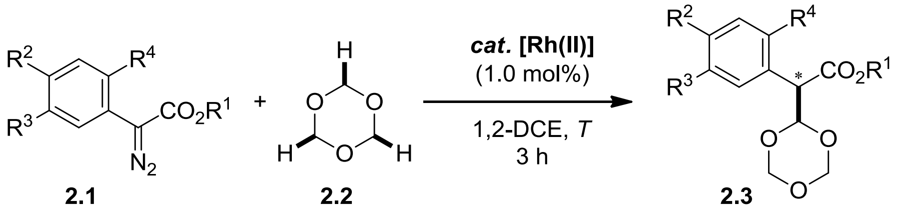
entry	R^1	Rh(II) cat.	*T* [°C]	solvent	yield (%)[a]	*e.r.* (*ee*)[b]
1	Ph	$Rh_2(OAc)_4$	40	1,2-DCE	<5	
2	Ph	$Rh_2(esp)_2$	40	1,2-DCE	(25)	
3	Ph	$Rh_2(esp)_2$	r.t	1,2-DCE	33	
4	Ph	$Rh_2(esp)_2$	0	1,2-DCE	12	
5	4-BrPh	$Rh_2(O_2CAd)_4$	40	1,2-DCE	50 (45)	
6	4-BrPh	$Rh_2(esp)_2$	r.t.	1,2-DCE	23	
7	**4-BrPh**	**$Rh_2(esp)_2$**	**40**	**1,2-DCE**	**60 (54)**	
8	4-BrPh	$Rh_2(esp)_2$	60	1,2-DCE	44 (42)	
9	4-BrPh	$Rh_2(esp)_2$	40	$CHCl_3$	51 (53)	
10	4-BrPh	$Rh_2(esp)_2$	40	PhMe	9	
11	4-BrPh	$Rh_2(esp)_2$	40	EtOAc	0	
12	4-BrPh	$Rh_2(esp)_2$	40	*n*-heptane	35	
13	Ph	$Rh_2(S\text{-PTAD})_4$	40	1,2-DCE	27	58:42 (16)
14	Ph	$Rh_2(S\text{-PTAD})_4$	r.t.	1,2-DCE	28	59:41 (18)
15	Ph	$Rh_2(S\text{-PTAD})_4$	0	1,2-DCE	7	*n.d.*
16	Ph	$Rh_2(S\text{-DOSP})_4$	40	1,2-DCE	25	91:9 (82)
17	Ph	$Rh_2(S\text{-DOSP})_4$	r.t.	1,2-DCE	35	93:7 (86)
18	**Ph**	**$Rh_2(S\text{-DOSP})_4$**	**0**	**1,2-DCE**	**37 (36)**	**96:4 (92)**
19	4-BrPh	$Rh_2(S\text{-nttl})_4$	0	1,2-DCE	18	70:30 (40)
20	4-BrPh	$Rh_2(S\text{-pttl})_4$	40	1,2-DCE	41	60:40 (20)
21	4-BrPh	$Rh_2(S\text{-pttl})_4$	0	1,2-DCE	15	59:41 (18)
22	4-BrPh	$Rh_2(S\text{-pttl})_4$	0	1,2-DCE	25	64:36 (27)
23	**4-BrPh**	**$Rh_2(S\text{-DOSP})_4$**	**0**	**1,2-DCE**	**54 (45)**	**>99:1 (99)**

Reaction conditions: A 1M solution of **2.1** (0.5 mmol, 1.0 eq.) was added dropwise to a stirred solution of the Rh catalyst (1.0 mol%) and **2.2** (5 mmol, 10 eq.) in the indicated solvent (5.0 mL) within 90 min. [a] Determined by ^1H NMR analysis of the crude mixture. Mesitylene was used as internal standard, isolated yields in parentheses.

2.4.2 Scope of the transformation

The electronic nature of the substituents on the phenyl ring had a crucial impact for the efficiency of the reactions. The reactivity of the substrates correlated well and can be predicted with corresponding Hammett values.[72] Substrates with positive $\sigma_{m/p}$ values proved to benefit from the product-forming C–H insertion pathway, whereas substituents with negative $\sigma_{m/p}$ values gave less satisfying results in terms of product yields. Thus, the scope of this reaction could be explored in a predictable manner, comprising a reasonably broad variety of functional groups, including halides (Table 2.2, entries 2-5), sulfonates (entries 6-7) and cyclopropylcarbonyl (entry 8) in moderate yields and excellent enantiomeric excesses (91-99% *ee*). The stereochemistry of all products was assigned according to their optical rotation in comparison with the confirmed configuration of (*R*)-**2.3b** (entry 3) which is in analogy with the stereochemistry of the predictive model for chiral $Rh_2(DOSP)_4$ catalysts.

Table 2.2. Scope of the reaction: *para*-substituted phenyl diazo acetates (2.1).



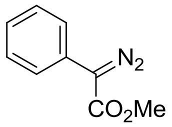
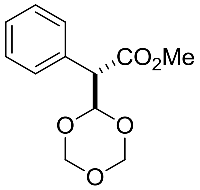
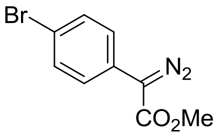
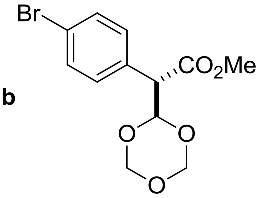
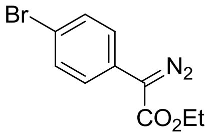
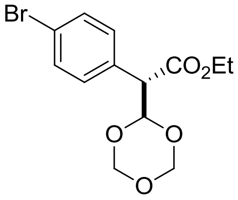
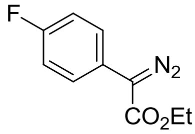
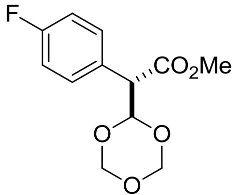
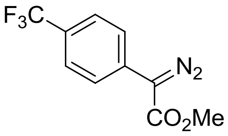
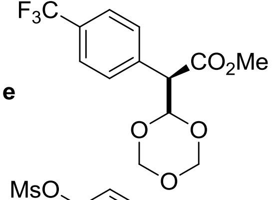
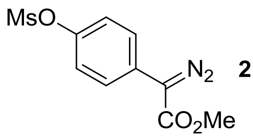
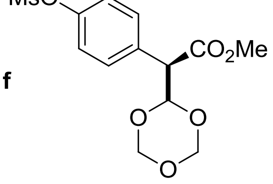
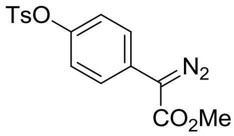
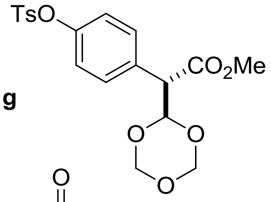
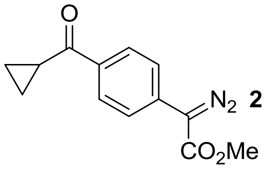
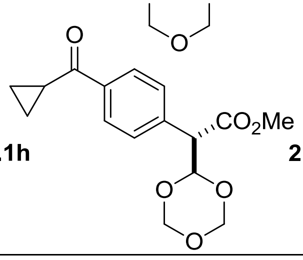
entry	substrate		product		yield (%)^a	*ee* (%)^b
1		**2.1a**		**2.3a**	**A** 37 (36) **B** 39 (37)	92% *ee* (*S*)
2		**2.1b**		**2.3b**	**A** 44 (42) **C** 54 (44) **B** 60 (54)	95% *ee* (*S*) 99% *ee* (*R*)
3		**2.1c**		**2.3c**	**A** 42 (38) **B** 37 (32)	99% *ee* (*S*)
4		**2.1d**		**2.3d**	**A** 42 (41) **B** 58 (55)	95% *ee* (*S*)
5		**2.1e**		**2.3e**	**C** 40 (36) **B** 50 (44)	94% *ee* (*R*)
6		**2.1f**		**2.3f**	**C** 48 (38) **B** 55 (52)	91% *ee* (*R*)

Table 2.2. (continued) Scope of the reaction: *para*-substituted phenyl diazo acetates (2.1).

7		**2.1g**		**2.3g**	**A** 60 (54) **B** 56 (61)	95% *ee* (*S*)
8		**2.1h**		**2.3h**	**A** 26 (23) **B** 38 (34)	91% *ee* (*S*)

Reaction conditions: A solution of methyl phenyl diazoacetate **2.1** (0.5 mmol, 1.0 eq.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a stirred solution of (**A**) $Rh_2(S\text{-}DOSP)_4$, (**B**) $Rh_2(esp)_2$ or (**C**) $Rh_2(R\text{-}DOSP)_4$ (1.0 mol%) and **2.2** (5 mmol, 10 eq.) in 1,2-dichloroethane (5.0 mL) in the course of 90 min. [a] Determined by ^1H NMR. [b] Determined by chiral HPLC. Absolut configuration of the major isomer is given in parentheses.

In the presence of meta-substituents the isolated yields of racemic products (method **B**) were comparable with those obtained for *para*-substituted phenyldiazoacetates (Table 2.3, entries 1-5). The corresponding enantioenriched products were formed in comparably lower yields (21-35%) and moderate enantiomeric excess (67-77% *ee*, entries 1-4).

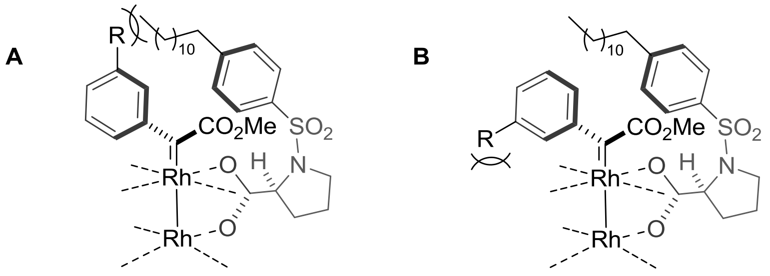
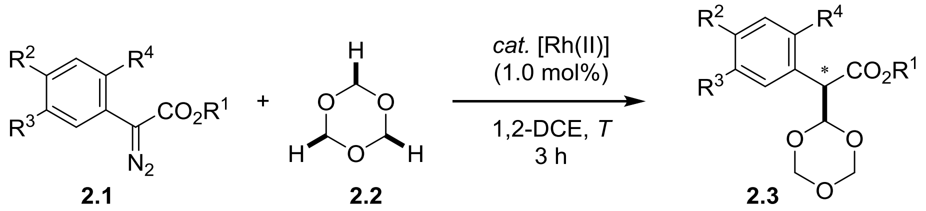
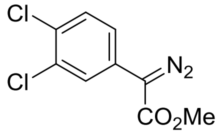
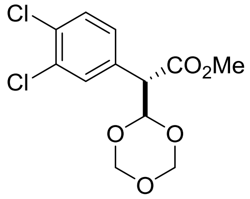
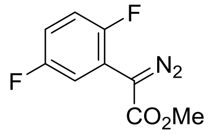
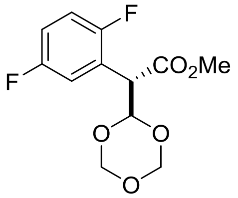
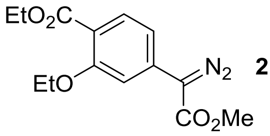
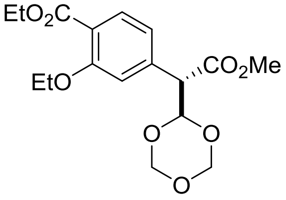
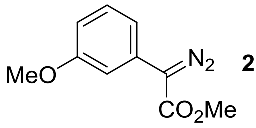
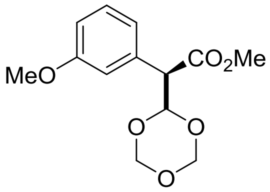
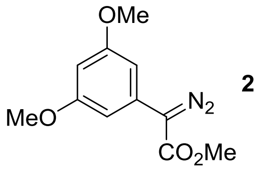
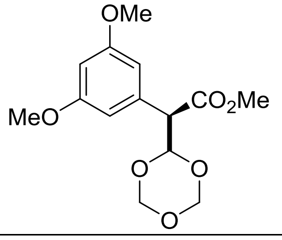


Figure 2.9. Conformers A and B of $Rh_2(S\text{-}DOSP)_4$ carbenoids bearing a *meta*-substituent.

The diminished enantiomeric excess ought to originate from either one of two possible conformations of the corresponding rhodium carbenoid species, **A** or **B** (Figure 2.9). As illustrated, an adverse steric repulsion between the substrate and the ligand backbone are conceivable in both instances, which might lead to an out-of plain-bend of the phenyl ring. Thus, the usually unfavorable C−H insertion from the quadrant that is shielded by the ester group is now permitted. This disadvantageous steric repulsion is even more pronounced when the methyl 3,5-dimethoxyphenyldiazoacetate is used and the corresponding product (*R*)- was isolated in a low yield (17%), when compared to its racemate (56%), and in lower enantioselectivity (53% *ee*, entry 5).

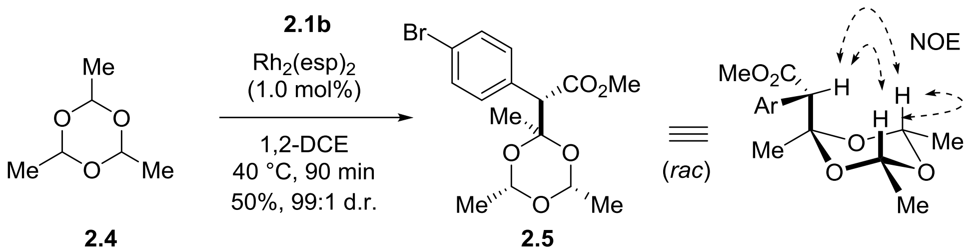
Table 2.3. Scope of the reaction: *meta*-substituted phenyl diazo acetates.



entry	substrate		product		yield (%)[a]	*ee* (%)[b]
1		**2.1i**		**2.3i**	**A** 38 (35) **B** 58 (52)	77% *ee* (*S*)
2		**2.1j**		**2.3j**	**A** 21 (21) **B** 59 (53)	70% *ee* (*S*)
3		**2.1k**		**2.3k**	**A** 40 (34) **B** 62 (55)	67% *ee* (*S*)
4		**2.1l**		**2.3l**	**A** 26 (20) **B** 51 (48)	76% *ee* (*R*)
5		**2.1m**		**2.3m**	**A** 20 (17) **B** 59 (56)	53% *ee* (*R*)

Reaction conditions: A solution of methyl phenyl diazoacetate **2.1** (0.5 mmol, 1.0 eq.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a stirred solution of (**A**) Rh_2(*S*-DOSP)$_4$, (**B**) $Rh_2(esp)_2$ or (**C**) Rh_2(*R*-DOSP)$_4$ (1.0 mol%) and **2.2** (5 mmol, 10 eq.) in 1,2-dichloroethane (5.0 mL) in the course of 90 min. [a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC. Absolut configuration of the major isomer is given in parentheses.

Gratifyingly, the structurally related yet more sterically congested acetaldehyde trimer, paraldehyde (**2.4**), was an equally eligible coupling partner, showcased in Scheme 2.14. In this sequence, methyl 2-(4-bromophenyl)-2-((4*R*,6*S*)-2,4,6-trimethyl-1,3,5-trioxan-2-yl)acetate (**2.5**), bearing an acetal-protected ketone quaternary center, was isolated in a 50% yield as racemic mixture of the (4*R*,6*S*)-diastereomer, in excellent diastereoselectivity (99:1). When chiral Rh_2(S-DOSP)$_4$ was used, formation of the desired product accounted for 11% (NMR-yield) only led to unsatisfactory low yields with we attribute to disfavourable steric repulsion between paraldehyde **2.4** and the bulky chiral DOSP-ligands.



Scheme 2.14. Formation of a quaternary carbon center by regioselective insertion of 1b into the α-C−H bond of paraldehyde.

It is noteworthy to mention, that in most related reports, the purification of the C−H insertion products have been difficult to achieve and yields were often documented as calculated yield from a crude mixtures of products.[73] In the present work, all products were isolated and almost exclusively obtained as colorless, crystalline material. Yields are given for the analytically pure material. In two cases, crystals suitable for x-ray analysis were attained (Figure 2.10). This instance was pivotal to unambiguously support the successful enantioselective C−H bond insertion and the absolute configuration of the formed products. The stereochemistry could be assigned from the crystal structure of enantiomerically pure (-)-(*S*)-ethyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate (**2.3b**) from the reaction of ethyl 2-(4-bromophenyl)-2-diazoacetate (**2.1b**) and 1,3,5-trioxane (**2.2**) in the presence of chiral Rh$_2$(*S*-DOSP)$_4$. Subsequently, the enantiomerically pure crystal was subjected to HPLC analysis to confirm that it represents the major component. Another crystal structure of racemic methyl 2-(2,5-difluorophenyl)-2-(1,3,5-trioxan-2-yl)acetate (**2.3j**) could be resolved.

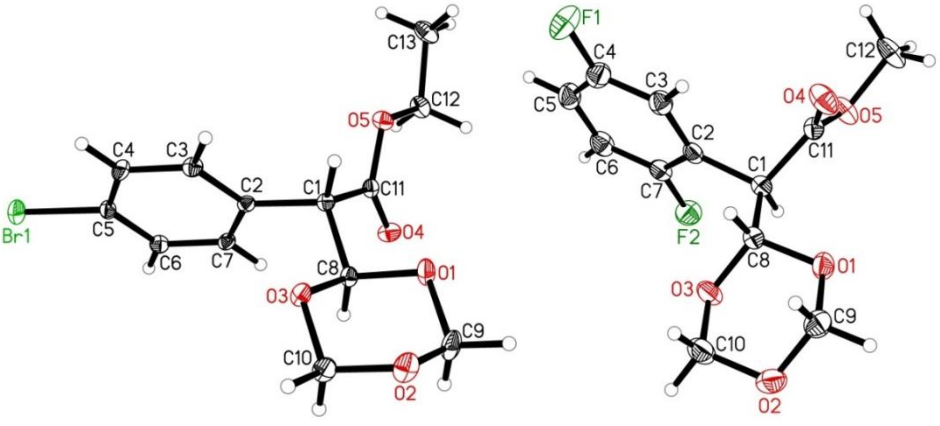


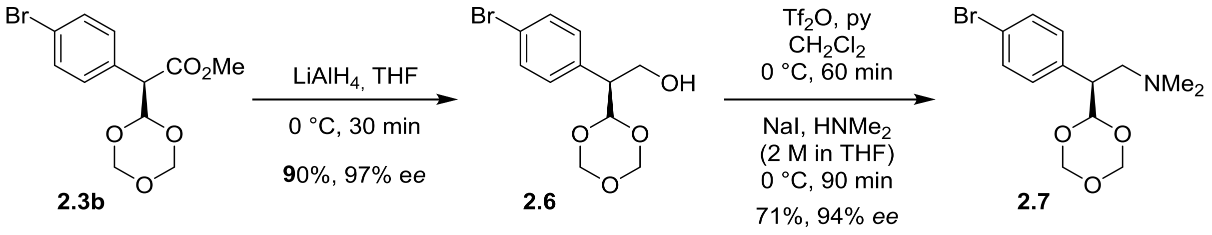
Figure 2.10. X-ray structures of (-)-(*S*)-ethyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate 2.3b and (*rac*)-methyl 2-(2,5difluorophenyl)-2-(1,3,5-trioxan-2-yl)acetate 2.3j.

2.4.3 Product derivatization

Methyl 2-aryl-2-(1,3,5-trioxan-2-yl)acetates **2.3** were found to be surprisingly robust compounds. The high stability of the trioxane moiety could be exploited in terms of product derivatization. For this purpose a sufficient amount of starting material was required. 2-(4-bromophenyl)-2-diazoacetate (**2.1b**) was chosen as substrate for a gram-scale synthesis of (*R*)-methyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate ((*R*)-**2.3b**) as it is easily accessible and proved more stable than the parent 2-

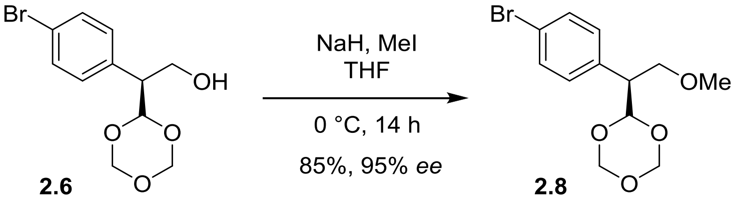
phenyl-2-diazoacetate (**2.1a**). The corresponding coupling product of diazo **2.1b** and 1,3,5-trioxane (**2.2**) catalyzed by Rh_2(*R*-DOSP)$_4$ was obtained in 39% isolated yield comparable to the outcome of the small scale reaction. With enough material in hand, we turned our attention to further transformations.

Ester **2.3b** was efficiently reduced by lithium aluminium hydride. Alcohol **2.6** was obtained in a 90% isolated yield with full retention of the absolute configuration. Subsequent functionalization of the free alcohol allowed for the synthesis of (*S*)-2-(4-bromophenyl)-*N*,*N*-dimethyl-2-(1,3,5-trioxan-2-yl)ethanamine (**2.7**) in 71% isolated yield and 94% *ee* over two steps (Scheme 2.15).



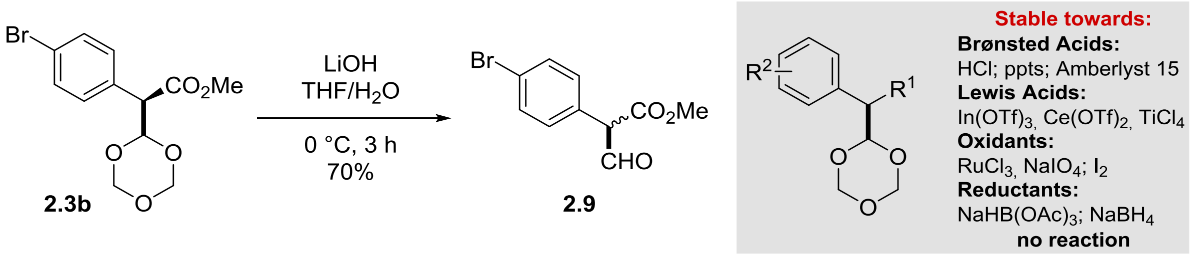
Scheme 2.15. Reduction of (*R*)-methyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate and synthesis of phenethylamine 2.7.

Treatment of alcohol **2.6** with sodium hydride and iodomethane yielded methyl ether **2.8** in 85% yield (Scheme 2.16). Hence, alcohol **2.6** serves as valuable building block which can be treated either as nucleophile or pre-electrophile.



Scheme 2.16. Synthesis of chiral ether 2.8.

As previously mentioned, methyl 2-aryl-2-(1,3,5-trioxan-2-yl)acetates **2.3** proved to be rather stable. A number of conditions listed in Scheme 2.17 were tested in order to cleave the trioxanyl acetal. In contrast to commonly used acetals that are cleaved at low pH, 1,3,5-trioxane is exceedingly stable under acidic conditions. Methyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate (**2.3b**) can be stored in 10% HCl in THF for several days (>7 days) without any evidence of degradation.[74] Furthermore, ester **2.3b** proved to be stable under reflux in several solvents (MeOH, THF, 1,4-dioxane/MeOH, H_2O/MeOH/THF) in the presence of concentrated hydrochloric acid, pyridinium *p*-toluenesulfonate (ptts) and amberlyst 15. Also other conditions that are usually applied for the cleavage of acetal groups did not affect the degradation of the cyclic ether (Scheme 2.17).[75] This unexpected behavior arguably originates from a conformational stabilization due to the *syn*-periplanar alignment of the oxygen lone pairs. Moreover, the 5-oxygen ought to significantly alter the electronic nature of the acetal oxygens, rendering them less prone to protonation. Alternatively, treatment of ester **2.3b** with lithium hydroxide in THF/H_2O led to rapid cleavage of the *O*-heterocycle selectively yielding the free aldehyde **2.9** in a 70% isolated yield. However, under these alkaline conditions it was noted that (*R*)-methyl 2-(4-bromophenyl)-3-oxopropanoate (**2.9**) readily racemizes. Nevertheless, the corresponding alcohol **2.6** and ether **2.8** derivative of **2.3b** were stable under the same reaction conditions. Notably, *in situ* reduction of the aldehyde with $NaBH_4$ could not prevent the racemization. This result indirectly substantiates that the aldehyde-enol tautomerization is faster compared to the reduction step.



Scheme 2.17. Cleavage of the trioxanyl acetal 2.3b.

Indeed, the apparently anomalous behavior of 1,3,5-trioxane compared to 1,3-dioxane has been previously reported in a related context. *Jenkins* and co-workers studied the reaction of *tert*-butoxyl radicals with cyclic ethers by the radical trapping technique.[76] They have evaluated 14 cyclic alkanes and cyclic ethers in terms of their reactivity pattern and relative rate of abstraction of *tert*-butoxyl radicals. It was observed that oxygen α to C−H strongly enhances the abstraction, whereas oxygen located β to C−H generally retards the abstraction. According to this supposition, the reactivities of 1,3,5-trioxane and of 1,3-dioxane are comparable, and arguably enhanced in case of the trioxane. However, the hydrogen atoms exhibited much reduced reactivity, accounting for less than half compared to 1,3-dioxane. By comparison of the bond lengths of both cyclic ethers from x-ray data (co-crystallized with a zinc porphyrin complex)[77] no significant dissimilarities in the C−H bond lengths was observed. Conversely, it was hypothesized that the differences ought to be of electronic origin. The obvious difference between 1,3,5-trioxane and 1,3-dioxane is the 5-oxygen *versus* 5-methylene substituent. Thus, whereas each methylene group of the trioxane is subjected to electron withdrawal by two flanking oxygen atoms, the analogous methylene of the dioxane experiences a slightly electron donation by the trimethylene chain. In *Jenkins* study it is comprehensible that a reduced accumulation of electron density results in a reduced rate of hydrogen abstraction by the (electrophilic) *tert*-butoxyl radical (Figure 2.11., left).

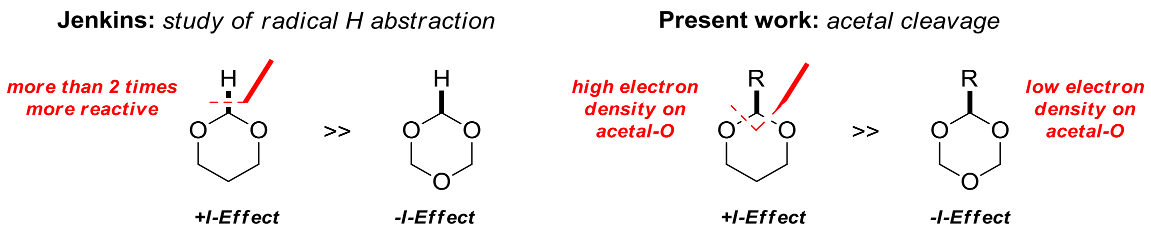


Figure 2.11. Comparison of 1,3-dioxane and 1,3,5-trioxane in radical hydrogen abstraction and acetal cleavage of 2-(1,3-dioxanyl) and 2-(1,3,5-trioxanyl) acetals.

Extrapolated to the objected acetal cleavage, the electronic influence of the oxygen atom in the backbone of the 1,3,5-trioxanyl acetal has a similarly perturbing effect (Figure 2.11, left). The acetal oxygens possess a diminished electron density compared to the 1,3-dioxanyl acetal oxygen atoms. Hence, protonation is excessively more difficult. In addition, the oxygen atoms in trioxane seem also less eligible to interact with Lewis-acids which ought to facilitate the cleavage.

2.5 Stereoelectronic effects in 1,3,5-trioxane: The Perlin effect

“The longer C–H bond has the lower one-bond C–H coupling constants”

Saul Wolfe et al., Department of Chemistry, Queen's University, Ontario, Canada.

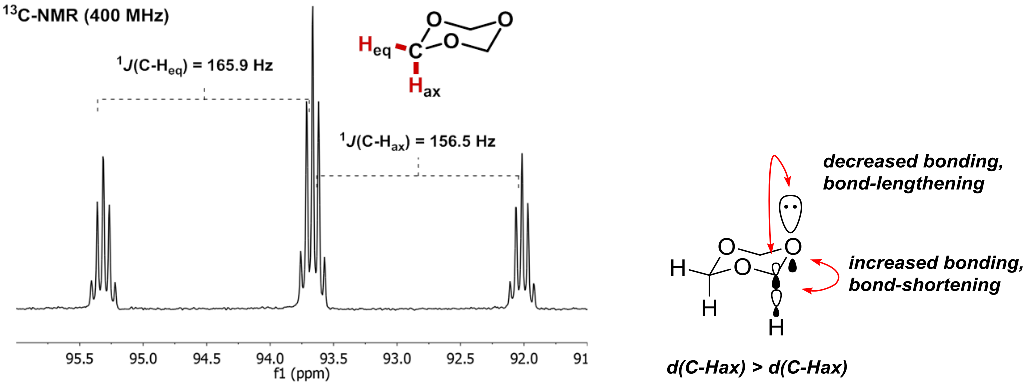
(Can. J. Chem. ***1990****, 68, 1051–1062.)*

2.5.1 Background

The stereochemical non-equivalence of axial and equatorial bonds in cyclohexane derivatives in the chair conformation manifests itself in a number of ways, and is particularly evident in the NMR spectra. Typically, the chemical shift of axial protons is 0.1-0.7 ppm upfield compared to the equatorial protons ($^{3}J_{\mathrm{H(ax)/H(ax)}} = 8$-10 Hz, while $^{3}J_{\mathrm{H(eq)/H(eq)}} = 2$-3 Hz). The C−H bond length and strength and therefore, the chemical reactivity is reflected by its coupling constant and chemical shift in the NMR spectrum and is significantly influenced upon its stereochemical relationship to vicinal electron lone pairs. In cyclohexanes and derived saturated heterocycles having one or more first row heteroatoms attached to the carbon of interest, the $^{1}J_{\mathrm{C-H(eq)}}$ coupling constant is always larger than the axial one ($^{1}J_{\mathrm{C-H(ax)}} < {}^{1}J_{\mathrm{C-H(eq)}}$). In literature this effect is generally referred to as *Perlin Effect*.[78] This interrelation is reminiscent of an infrared effect known as Bohlmann bands. The magnitude of a one-bond C−H coupling constant expectedly varies inversely with the bond length, i.e. the longer, thus weaker, the C−H bond exhibits a smaller one-bond coupling constant. This correlation has been confirmed due to numerous experimental studies and has been rationalized by quantitative perturbational molecular orbital (PMO) theory. $^{1}J_{\mathrm{C-H}}$ values from undecoupled ^{13}C NMR spectra are commonly addressed to determine the anomeric configuration in carbohydrate derivatives (Scheme 2.18).

2.5.2 Stereoelectronic effects in 1,3,5-trioxane

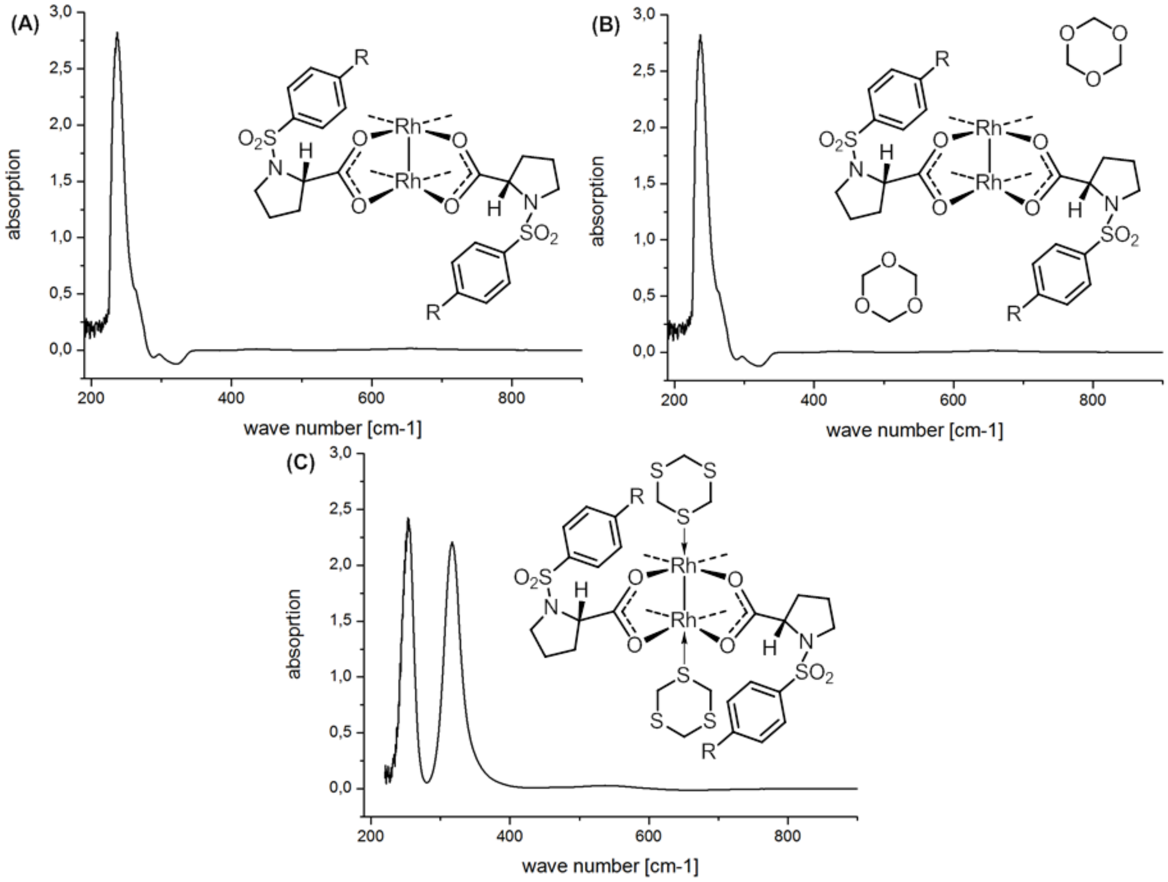
1,3,5-Trioxane is a 6-membered heterocycle consisting of three alternating -CH_2O- units. All axial oxygen lonepairs of the C_3-symmetric molecule are arranged in a 1,3-*syn*-periplanar fashion. This interrelation stabilizes the chair structure of the heterocycle. Moreover, the axial lone-pairs perturb the contiguous axial C−H bonds *via* $n_O \rightarrow \sigma^*_{C–H}$ interactions. As a result, the axial C−H bond is weakened while the C−O bonds are strengthened and thus shortened. These geometric features ought to lead to a superior reactivity of the axial C−H bond and enhanced stabilization of the carbenium intermediate which is formed during the rhodium-carbenoid triggered C−H bond-cleavage.



Scheme 2.18. (A) Decoupled and (B) undecoupled ^{13}C-NMR spectra of 1,3,5-trioxane (2.2).

In contrary, a reverse Perlin-effect for all C−H bonds is met in 1,3-dithiane ($^1J_{C–H(ax)} > {}^1J_{C–H(eq)}$) suggesting the existence of a dominant $\sigma_{C–S} \rightarrow \sigma^*_{C–H}$ stereoelectronic interaction which leads to a weakening of the equatorial C−H bond in this heterocycle. A similar stereoelectronic relation can be assumed to be present in 1,3,5-trithiane.

When 1,3,5-trithiane was tested in the catalytic reaction with methyl phenyldiazo acetate **2.1a** no product formation could be observed. Instead a color change from green to purple was noticed when 1,3,5-trithiane was added to a solution of Rh_2(*S*-DOSP)$_4$ which most likely originates from ligation of the sulfur lone-pairs to the vacant axial position of the rhodium complex. Scheme 2.19 shows the UV-vis spectra of solutions of (**A**) Rh_2(*S*-DOSP)$_4$, (**B**) Rh_2(*S*-DOSP)$_4$ and 1,3,5-trioxane and (**C**) Rh_2(*S*-DOSP)$_4$ and 1,3,5-trithiane in 1,2-dichloroethane ($5x10^{-4}$ M). Spectra **A** shows an absorption maxima at 237 cm^{-1} which is unaffected by the presence of 1,3,5-trioxane. In the presence of 1,3,5-trithiane UV-vis spectra shows two maxima at 243 cm^{-1} and 317 cm^{-1} strongly shifted towards higher wave numbers which clearly supports a strong substrate-catalyst interaction in the presence of sulfur containing-heterocycles. A similar catalyst deactivating effect is encountered when urotropin was tested as coupling partner in the rhodium-mediated C−H bond insertion, emphasizing the well-known lone-pair donor binding affinity of nitrogen atoms to the rhodium metal center.

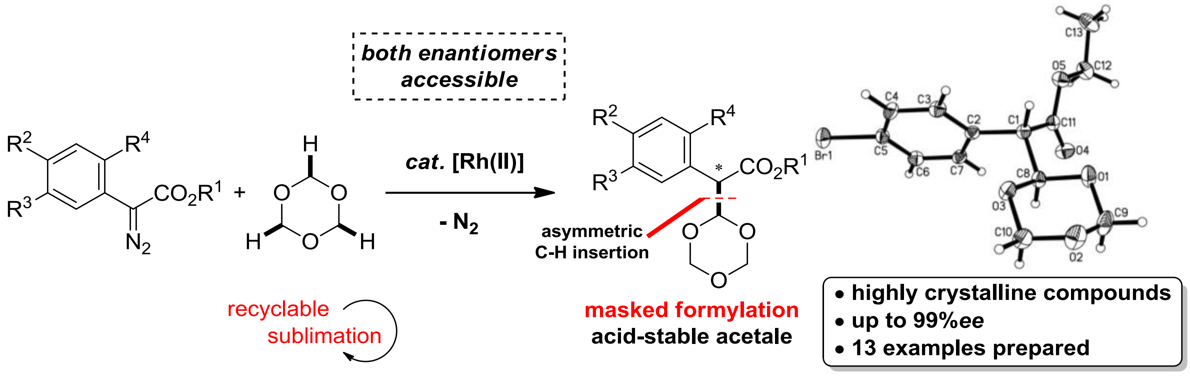


Scheme 2.19. UV-vis spectra of (A) Rh_2(*S*-DOSP)$_4$, (B) Rh_2(*S*-DOSP)$_4$ and 1,3,5-trioxane and (C) Rh_2(*S*-DOSP)$_4$ and 1,3,5-trithiane in 1,2-dichloroethane ($5x10^{-4}$ M).

2.6 Conclusion and outlook

The developed methodology for the enantioselective masked-formylation of push-pull carbenes by means of rhodium(II) carbenoid mediated C–H bond insertion provides access to a new substance class of chiral alkyl 2-phenyl-2-(1,3,5-trioxan-2-yl)acetates (Scheme 20). This scaffold is the first of its kind in which a 1,3,5-trioxane moiety is attached to an optically active sp^3-hybridized carbon atom. Owing to the structural relation to naturally occurring arylpropionates such as atropine and artificial methylphenidates, this substance class holds great promise to be used as valuable building blocks for medicinal chemistry. The demonstrated high stability of the *O*-heterocycle towards strong acidic conditions is advantageous in view of oral administration of potential drug candidates.

However, the selective cleavage of the 1,3,5-trioxanyl acetal remains an explicit goal. Liberation of the free aldehyde while maintaining the optical purity would provide a formylation strategy beyond traditional asymmetric hydroformylation chemistry.



Scheme 2.20. Enantioselective masked formylation of rhodium(II) carbenoids using 1,3,5-trioxane.

3 Rhodium(II)-catalyzed annulation of azavinyl carbenes through ring-expansion of 1,3,5-trioxane: Rapid excess to 9-membered heterocycles

3.1 Preface

Besides donor-acceptor substituted carbenes that have been studied in depth, 1-sulfonyl-1,2,3-triazoles depict another promising class of carbene precursors. This section describes the decomposition of 1-sulfonyl-1,2,3-triazoles in the presence of rhodium(II) catalysts and the reactivity of the corresponding azavinyl carbenes with 1,3,5-trioxane.

3.2 Project outline

Intermolecular insertions of highly reactive metalbound carbenes have emerged as a powerful strategy for the functionalization of seemingly inert sp^3 C−H bonds and activated and unactivated alkanes.[5a,45a,79] However, although diverse C−H bonds have been successfully functionalized, this strategy has been mainly limited to donor-acceptor substituted rhodium(II) carbenes derived from phenyl or vinyl diazoesters (Figure 3.1).

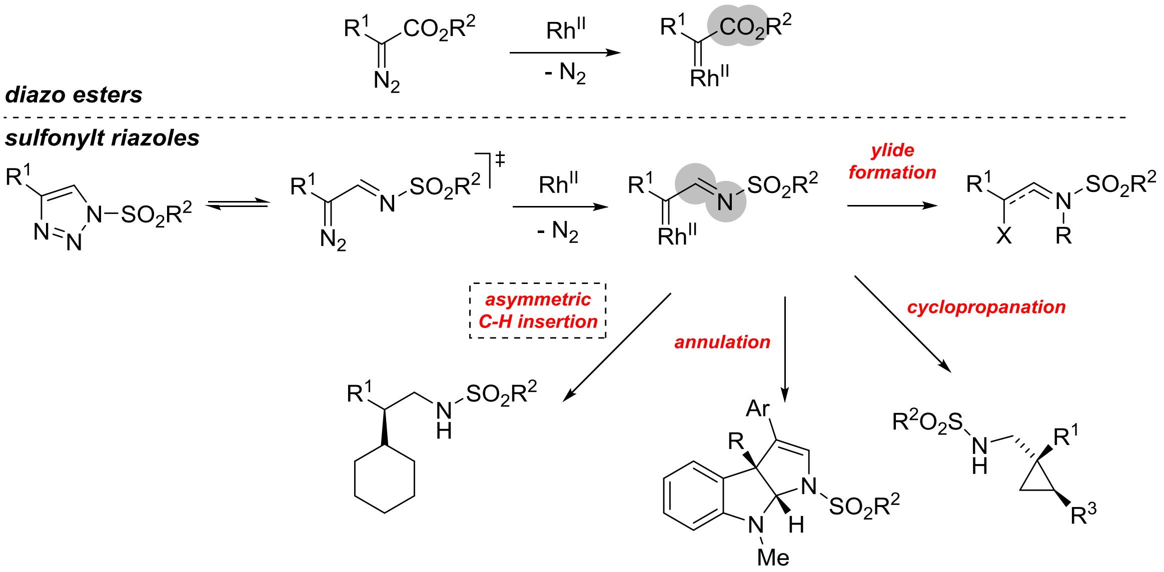
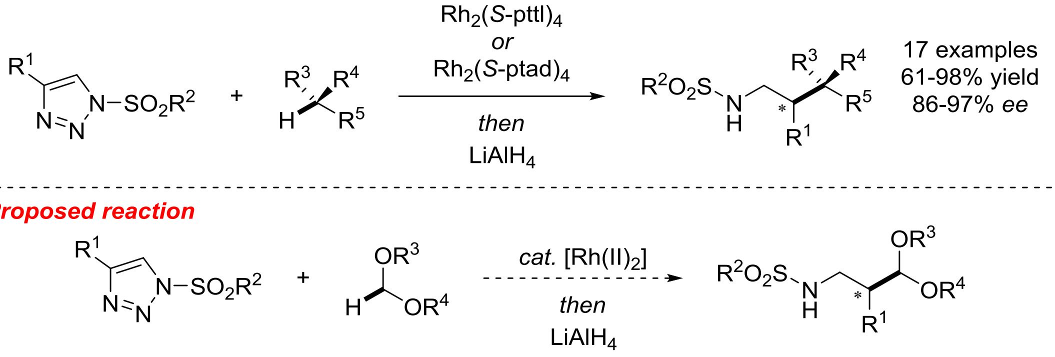


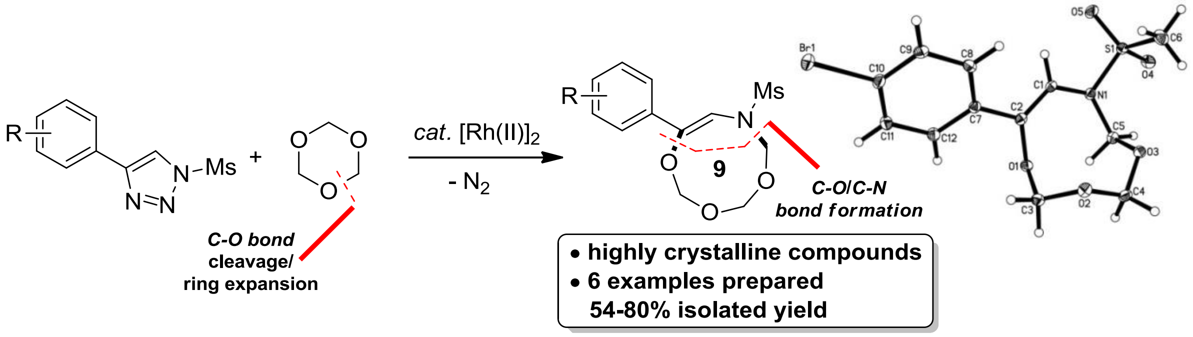
Figure 3.1. Overview of the reactivity of rhodium-carbenoids derived from 1-sulfonyl-1,2,3-triazoles.

The group of *Valery Fokin* has strikingly demonstrated that 1-sulfonyl-1,2,3-triazoles can serve as direct precursors to azavinyl carbenes in the presence of rhodium(II) catalysts in the transannulation of nitriles.[80] Azavinyl carbenes are electronically closely related to donor-acceptor substituted carbenes and share many reactivity features. Subsequent to the seminal discovery that 1-sulfonyl-1,2,3-triazoles serve as formidable carbene precursor, triazoles were tested in a variety of reactions that have been previously reserved to diazo acetates, such as cyclopropanation, dimerization, insertion, dipolar addition, ylide generation, and rearrangement reactions (Figure 3.1).[81] The most important precedence to this end was the reactivity of azavinyl carbenes derived from 1-sulfonyl-1,2,3-triazoles towards unactivated C−H bonds. In 2011, *Fokin* and *Chuprakov* published a protocol on a highly enantioselective C−H insertion into unactivated alkanes that allowed for the synthesis of various chiral *β*-sulfonamides (Scheme 3.1).[57e]



Scheme 3.1. Catalytic asymmetric C−H insertions of Rhodium(II) azavinyl carbenes into unactivated alkanes.

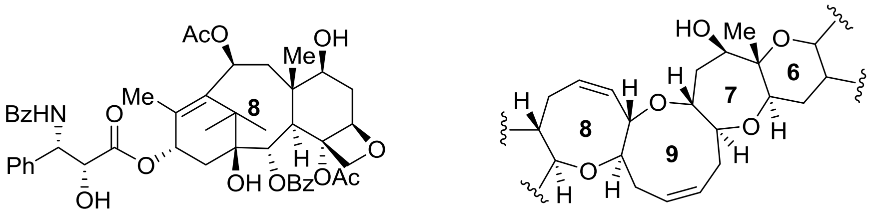
Based on these findings and to further explore the synthetic potential of 1,3,5-trioxane, we envisioned to study the rhodium(II)-catalyzed decomposition of 1-sulfonyl-1,2,3-triazoles in the presence of 1,3,5-trioxane. The C−H insertion of the azavinyl carbene into 1,3,5-trioxane would supply direct to chiral protected *β*-amino carbonyl compounds derived from phenethylamines. However, in this reaction, ylide formation of the oxygen-heterocycle with the Rh-carbenoid species outcompetes the C−H bond functionalization pathway (Scheme 3.2). Successful optimization of the reaction condition allowed for the one-pot preparation of a seemingly illusive nine-membered 1,3,5,7-trioxazonine ring.



Scheme 3.2. Rhodium(II)-catalyzed decomposition of *N*-sulfonyl-triazoles in the presence of 1,3,5-trioxane.

3.3 Background

The formations of medium-sized rings depict a synthetic challenge since their synthesis is often impeded by adverse entropic or unfavorable transannular interactions.[82] However, their synthesis gains considerable attention, not least because of the broad abundance of medium-sized rings natural products and the huge therapeutic success of agents derived from that substance class, such as taxol[83] or a number of polycyclic ethers shown in Figure 3.2.[84] 7- to 11-membered cyclic structures are most frequently obtained *via* macrocyclization,[85] fragmentation, ring expansion and ring-closing metathesis reactions.[86]



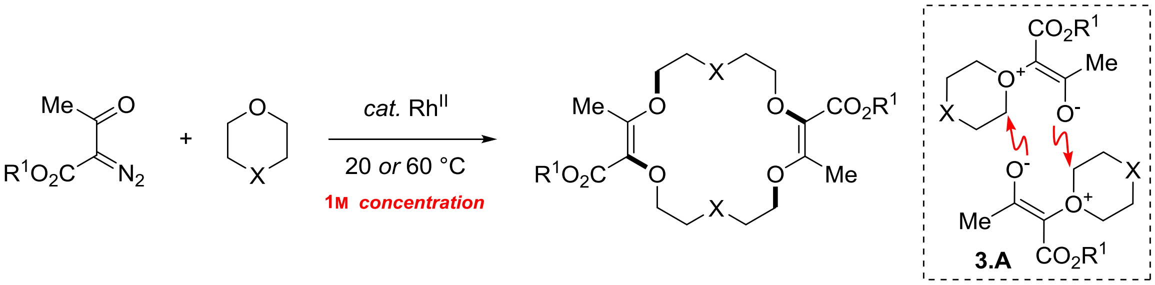
(-)-Taxol
anticancer agent

***E,F,G,H*-rings of Ciguatoxin**
marine polyther

Figure 3.2. Natural products containing medium-sized rings, (-)-taxol and E,F,G,J-rings of Ciguatoxin.

The influence of ethers upon carbenes has been investigated both experimentally and computationally. Whereas phosphonium ylides[87] and sulfur ylides[88] are readily formed and widely used in organic synthesis, depending on the electrophilic nature of the carbene, oxygen ylides between carbenes and ether oxygen atoms are reputed to undergo rather weak interactions.[89] More nucleophilic carbenes, e.g. derived from push-pull diazo compounds, are associated with interactions of C–H bonds of carbon α to oxygen atoms. However, reactive electrophilic carbenes such as azavinyl carbenes are known to form oxygen ylide intermediates that are prone to undergo C–O bond insertion reactions.[90]

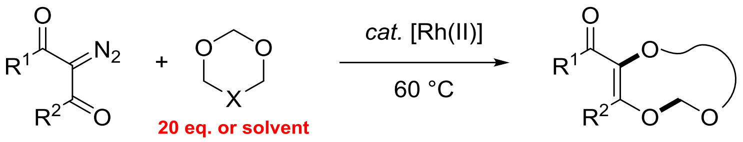
In 2010, the group of *Lacour* and co-workers observed that the transition-metal-catalyzed decomposition of diazo compounds in the presence of cyclic ethers is a powerful method for the regioselective condensation of two *α*-diazo-*β*-ketoesters and two cyclic ethers to yield functionalized 16- to 18-membered macrocycles in up to 75% yield (Scheme 3.3).[91]



Scheme 3.3. Rhodium(II)-catalyzed synthesis of functionalized polyether macrocycles.

According to Baldwin's rule, the intramolecular 5-*endo-tet* cyclization of the ylide intermediate **3.A** is disfavored.[92] The authors suggested that the key step of the proposed mechanism involves a synchronous "concerted" dimerization of two oxonium ylide intermediates **3.A** (Scheme 3.3).[93] The developed methodology was later further expanded to the non-templated macrolactonization of methyl diazoacetoacetates and substituted ethers.[94]

In 2012, again the group of *Lacour* demonstrated that α-diazo β-ketoesters and diketones react with cyclic acetals yielding polyoxygenated 8- and 9-membered, which was unprecedented at that time (Scheme 3.4).[95]



Scheme 3.4. Synthesis of medium-sized rings versus macrocycles through rhodium-catalyzed ring-expansion reactions of cyclic acetals.

The synthesis of medium-sized rings *versus* macrocycles proceeded with perfect regioselectivity. The standard reaction conditions stipulate a 20-fold excess of cyclic acetal. Of particular interest, 1,3,5-trioxane was also was also used as a substrate, yielding the corresponding insertion products in 34-85% yield. The authors proposed a mechanistic rational in direct application of Baldwin's rules. Accordingly, the reaction pathway encompasses the formation of an oxonium ylide (**A**), its transformation into an electrophilic unsaturated acyclic oxocarbenium intermediate and subsequent intramolecular nucleophilic attack. This reaction had precedence and was previously reported in 1999 by *Tollari* and co-workers for the synthesis of polyoxygenated coumarins.[96]

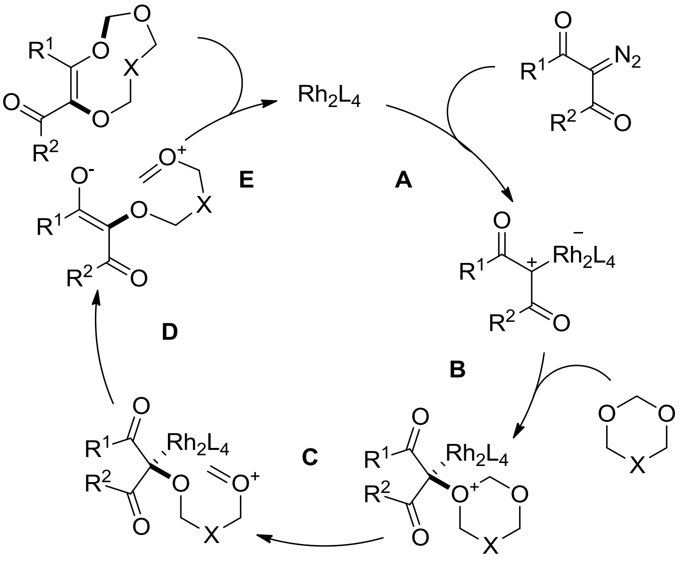
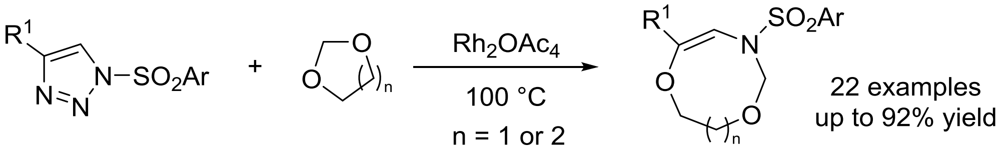


Figure 3.3. Proposed catalytic cycle for the rhodium-catalyzed medium-sized ring synthesis from diazo acetoacetates and cyclic acetals.

After we have started to investigate the rhodium-catalyzed decomposition of 1-sulfonyl-1,2,3-triazoles in the presence of 1,3,5-trioxane, the group of *Lacour* published a closely related work on the insertion of 1-arylsulfonyl-1,2,3-triazoles into cyclic acetals, 1,3-dioxane and 1,3-dioxolane (Scheme 3.5).[97]

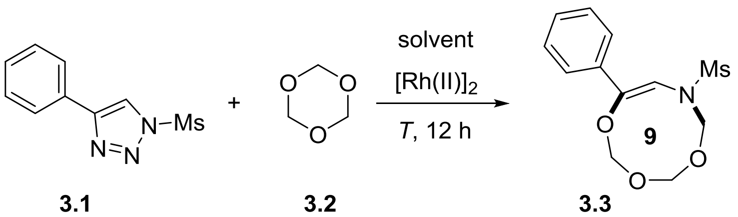


Scheme 3.5. One-step synthesis of nitrogen-containing medium-sized rings *via* α-imino diazo intermediates.

3.4 Results and discussion

At the outset of our studies of the rhodium(II)-catalyzed decomposition of sulfonyl-triazoles in the presence of 1,3,5-trioxane a number of achiral rhodium(II) catalysts were screened to evaluate their catalytic activity (Table 3.1, entry 1-6). $Rh_2(Opiv)_4$ gave the best result and a coupling product was obtained in 60% isolated yield in 1,2-dichloroethane (entry 3). A brief solvent screening revealed that the yield could be enhanced to 70% in chloroform (entry 9). Hence, the best results for the annulation of 1-(methylsulfonyl)-4-phenyl-1*H*-1,2,3-triazole **3.1** with 1,3,5-trioxane **3.2** was obtained at 40 °C in the presence $Rh_2(Opiv)_4$ using chloroform as a solvent (entry 3). Under these reaction conditions the corresponding product (*Z*)-7-(methylsulfonyl)-9-phenyl-6,7-dihydro-1,3,5,7-trioxazonine **3.3** was isolated in 70% yield after flash chromatography. Increasing the temperature to 60 °C and 80 °C did not lead to significant increase of the product yield (entry 16 and 17, respectively). Thus, the scope was explored at 40 °C.

Table 3.1. Optimization of reaction conditions.



entry	Rh(II) cat.	solvent	*T* [°C]	yield (%)[a]
1	$Rh_2(OAc)_4$	1,2-DCE	40	10
2	$Rh_2(esp)_2$	1,2-DCE	40	45
3	$\mathbf{Rh_2(Opiv)_4}$	**1,2-DCE**	**40**	**65 (60)**
4	$Rh_2(tpa)_4$	1,2-DCE	40	<5
5	$Rh_2(oct)_4$	1,2-DCE	40	<5
6	$Rh_2(OAd)_4$	1,2-DCE	40	55
7	$Rh_2(Opiv)_4$	1,2-DCE	40	65 (60)
8	$Rh_2(Opiv)_4$	CH_2Cl_2	40	10
9	$\mathbf{Rh_2(Opiv)_4}$	$CHCl_3$	**40**	**71 (70)**
10	$Rh_2(Opiv)_4$	heptane	40	<5
11	$Rh_2(Opiv)_4$	cyclohexane	40	15
12	$Rh_2(Opiv)_4$	PhMe	40	54
13	$Rh_2(Opiv)_4$	$CHCl_3$	0	<5
14	$Rh_2(Opiv)_4$	$CHCl_3$	r.t.	31
15	$Rh_2(Opiv)_4$	$CHCl_3$	40	71 (70)
16	$Rh_2(Opiv)_4$	$CHCl_3$	60	67
17	$Rh_2(Opiv)_4$	$CHCl_3$	80	73

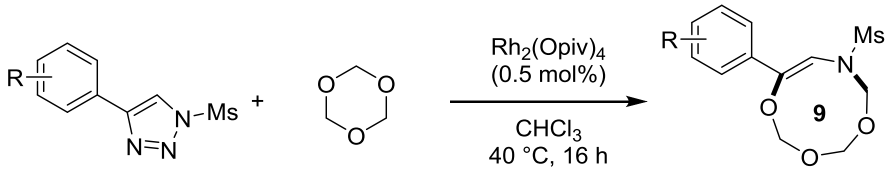
Reaction conditions: **3.1** (0.5 mmol), **3.2** (2.5 mmol), cat. [Rh(II)] (0.5 mol%), solvent (1.5 mL). [a]GC-yield is shown. Isolated yields in parentheses.

Owing to the unusual atomic constitution of the molecule, structural elucidation on the basis of ^1H-NMR spectroscopy proved challenging. Gratifyingly, the structure of the 9-membered *N*,*O*-heterocycle could be unambiguously assigned by help of X-ray analysis of compounds **3.3b** and **3.3d** (Figure 3.4).

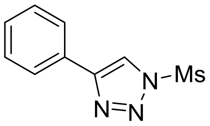
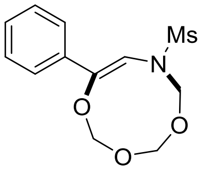
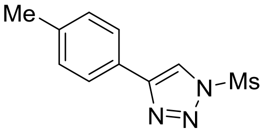
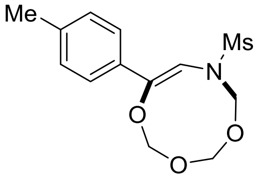
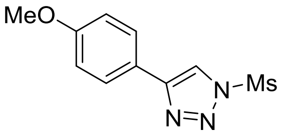
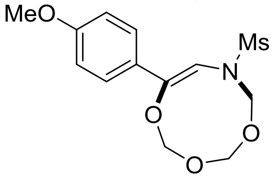
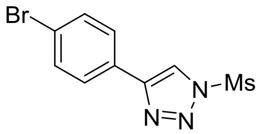
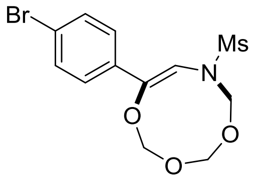
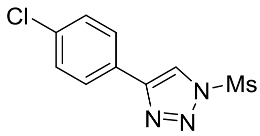
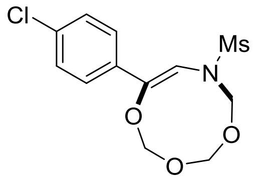
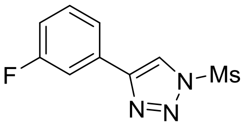
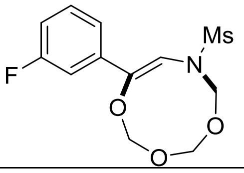
3.4.1 Scope and limitations

Having assessed a practical protocol for the rhodium-catalyzed ring expansion of 1,3,5-trioxane **3.2**, we studied the scope of 1-(methylsulfonyl)-4-phenyl-1*H*-1,2,3-triazole **3.1** derivatives that could be used under these conditions (Table 3.2).

Table 3.2. Scope of the Rhodium(II)-catalyzed ringexpansion of 1,3,5-trioxane (3.2).



3.1 **3.2** **3.3**

entry	substrate		product		yield (%)[b]
1		**3.1a**		**3.3a**	72%
2		**3.1b**		**3.3b**	72%
3		**3.1c**		**3.3c**	60%
4		**3.1d**		**3.3d**	70%
5		**3.1e**		**3.3e**	65%
6		**3.1f**		**3.3f**	80%

Reaction conditions: [a] **3.1** (0.5 mmol) and **3.2** (2.5 mmol) were dissolved in $CHCl_3$ (2 mL), $Rh_2(Opiv)_4$ (0.5 mol%) was added and the reaction mixure was stirred at 40 °C for 16 h. [b] isolated yields are shown.

All reactions proceeded smoothly at 40 °C with different aryl-substituted 1,4-disubstituted 1-sulfonyl-1,2,3-triazoles **3.1** in good yields (60-80%). Hereby, the outcome was largely unaffected by the electronic nature of the substituents on the aromatic ring of the triazole. The structure of the obtained compounds is unusual to say the least and may appear illusive at first sight. Yet, we found that these compounds are highly stable and without exception obtained as colorless crystalline solids. Hence, we were grateful for obtaining crystals that were suitable for crystal structure analysis. This technic enabled us to unambiguously assign the configuration of the heterocycle. The reaction products shown in Figure 3.4 are composed of a nine-membered heterocycles consisting of two sp^2-hybridized carbon atoms, respectively, along with an alternating carbon-heteroatom chain following a *N-C-O-C-O-C-O-* sequence. The 9-position of 6,7-dihydro-1,3,5,7-trioxazonine **3.3** core harbors the aryl substituents of the former 4-aryl-1,2,3-triazol.

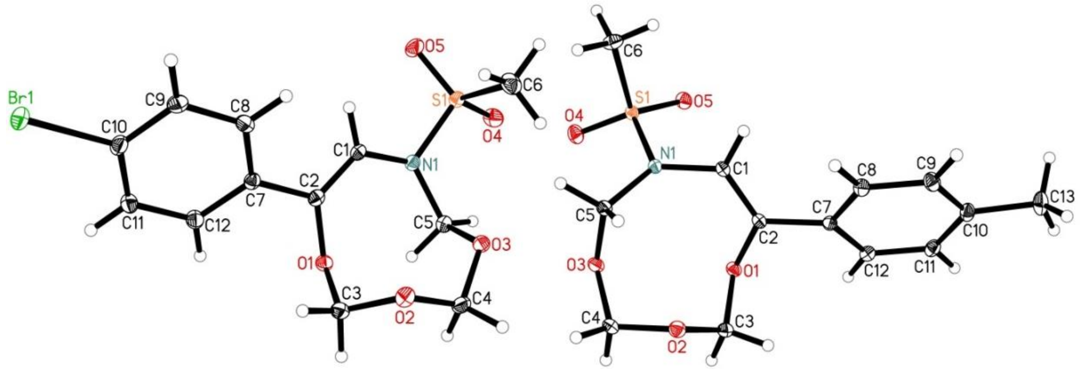
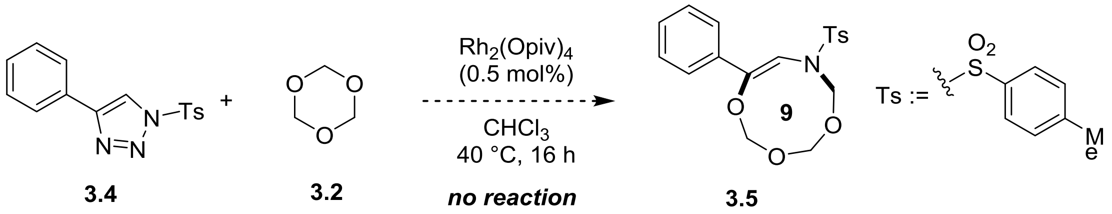


Figure 3.4. X-ray structures of compounds 3.3d and 3.3b.

The reaction was optimized for 1-(methylsulfonyl)-4-phenyl-1*H*-1,2,3-triazoles (**3.1a**). However, one major drawback of 1-(methylsulfonyl)-1*H*-1,2,3-triazoles **3.2** is the relatively high sensitive towards hydrolysis. The free 1*H*-1,2,3-triazole strongly binds to the vacant axial positions of the dirhodium complex and is thus poisonous for the catalytic activity. Therefore, it is especially important to operate with pure starting material to supply with good reactivity.



Scheme 3.6. Reaction of *N*-1-tosyl-1,2,3-triazole with 1,3,4-trioxane.

Noteworthy, the corresponding 1-tosyl-1,2,3-triazoles **3.4** displayed no reactivity in the transformation with 1,3,5-trioxane (Scheme 3.6), demonstrating that the presented reaction is orthogonal to the recently published protocol by *Lacour*.[97] To this end the reaction scope is rather limited and sensitive to substituents other than aryls. However, the reaction product depicts a novel class of organic compounds that possesses a unique arrangement of carbon and heteroatoms.

3.4.2 Mechanistic considerations

The encountered reaction pathway seems particularly intriguing with regard to the energy profile of ring-opening *versus* degradation of 1,3,5-trioxane. The energy required for the ring-opening event accounts for ca. 80 kcal/mol, considerably higher compared to the activation energy required to initiate the thermal decomposition with 49.1 kcal/mol.[98] Quantum chemical calculation suggest that the thermal fragmentation of 1,3,5-trioxane into three formaldehyde molecules proceeds through a concerted mechanism. Thus, the unimolecular decomposition pathway to formaldehyde ought to be both entropically and kinetically favored. Nonetheless, the ring expansion products, 6,7-dihydro-1,3,5,7-trioxazonine **3.3**, have been obtained in high yields under mild reaction conditions.

An reasonable explanation for the different reactivity of cyclic ethers that preferentially form 16- and 18-membered macrocycles[91,94] *versus* the selective formation of medium-sized rings in the presence of acetals,[95,97] was provided by the group of *Lacour* and co-workers.

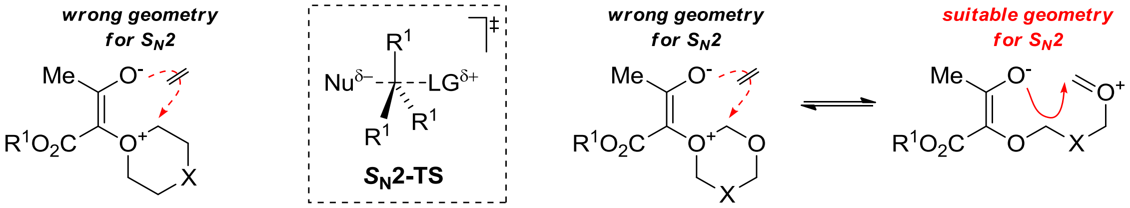


Figure 3.5. Mechanistic explanation for macrocyclization *versus* medium-sized ring synthesis.

S_N2 reactions whether inter- or intramolecular proceed *via* a transition state in which the incoming nucleophile and the leaving group are concerted in a trajectory somewhat close to 180°. Both cyclic ethers and cyclic acetals form reactive ylide intermediates with electrophilic carbenes. In the case of acetylacetonate derived carbenes an enolate species is formed. However, in ylides derived from cyclic ethers the geometry prohibits a nucleophilic attack on the electrophilic α carbon atom (Figure 3.5). In these species the chemical tension is released upon dimerization of two ylides. *Oxygen*-ylides formed from cyclic acetals, on the other hand, are mesomerically stabilized. The ring opening of the ether to the carbenium intermediate provides a scenario that allows for nucleophilic attack of the oxygen nucleophile on the electron-deficient carbon to form 8- and 9-membered *oxygen*-heterocycles, respectively.

An equal situation is encountered in azavinyl carbenes. The acetal ylide is similarly stabilized by its open-chain mesomer. The negative charge of the zwitterion is located on the sulfony amine which is in the right angle to attack the carbenium cation to form 6,7-dihydro-1,3,5,7-trioxazonine **3.3** (Figure 3.6).

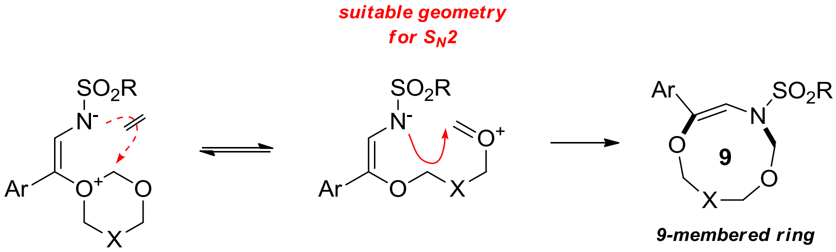
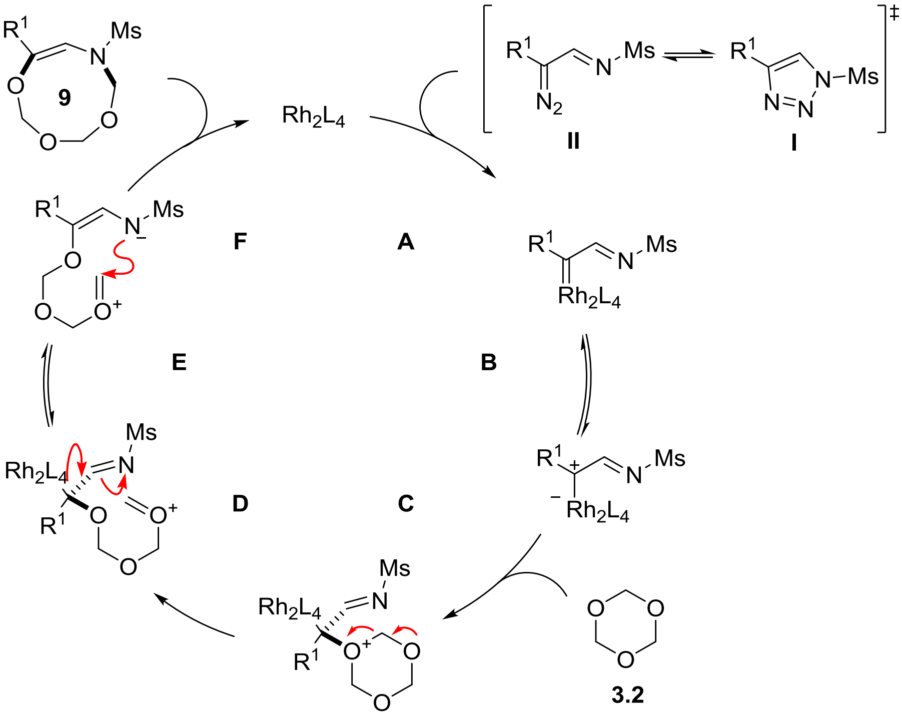


Figure 3.6. Rational for 9-membered ring synthesis from 1-sulfonyl-triazoles and 1,3,5-trioxane.

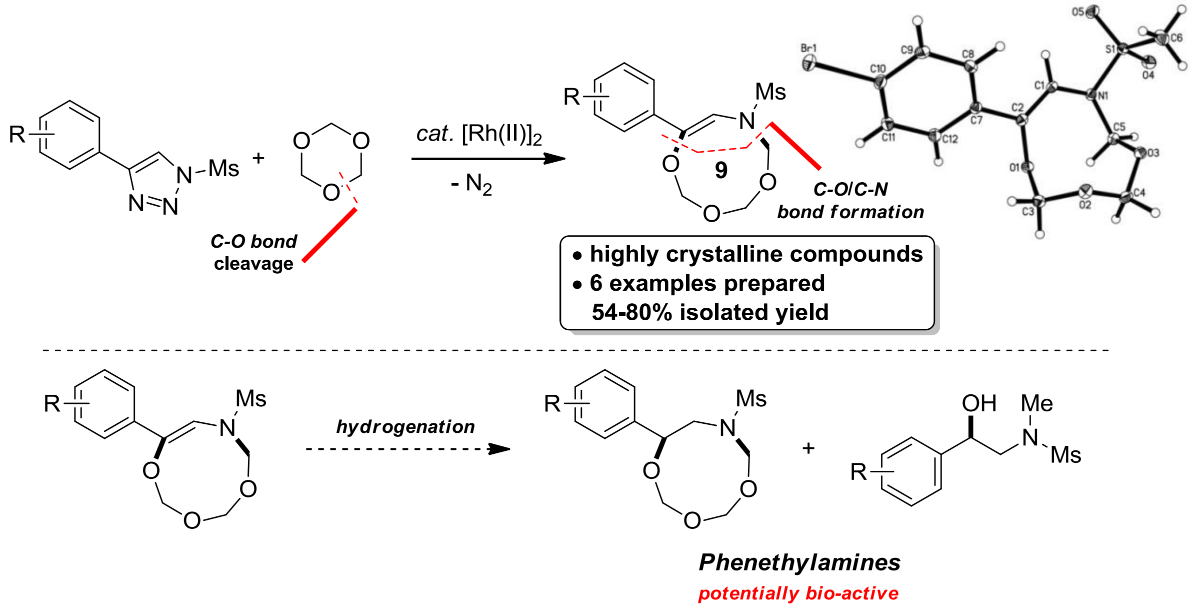
The proposed reaction mechanism is depicted in Scheme 3.7, below. The catalytic cycle commences with the decomposition of the triazole **I** from its open-chain isomer **II** (**A**). In the following, the reaction pathway involves the generation of an electrophilic metal carbenoid (**B**). Nucleophilic attack of an oxygen atom from 1,3,5-trioxane generates the corresponding oxonium ylide (**C**). Electron-shift of one adjacent oxygen lone-pair forms a trigonal sp^2-hybridized carbon center which is amenable to intramolecular nucleophilic attack from the sulfonyl amine (**E**) that accommodated negative charge in course of the extrusion of the rhodium catalyst. This rational supplies an adequate explanation for the synthesis of the 6,7-dihydro-1,3,5,7-trioxazonine and the complete regioselectivity.



Scheme 3.7. Proposed catalytic cycle.

3.5 Conclusion and outlook

In summary, we have developed a methodology for the rhodium(II)-catalyzed annulation of azavinyl carbenes derived from 1-(methylsulfonyl)-1,2,3-triazoles through ring-expansion of 1,3,5-trioxane. This examples further highlights the synthetic value of 1,3,5-trioxane as building block in organic chemistry apart from its role as a formaldehyde surrogate. Thus, unlike the common sense, this study could further invigorate the strength and stability of trioxane. The chemical structure of the product is unprecedented. The further functionalization of the nine-membered 1,3,5,7-trioxazonine rings and the evaluation of their stability under certain reaction conditions depict a field of future research. Notably, hydrogenation of the double bond ought to grant access to potentially bio-active phenethylamines.



4 Rhodium(II)-catalyzed alkoxylation-acetalization of donor-acceptor-substituted diazo compounds: One-step synthesis of highly functionalized quaternary carbon centers

4.1 Preface

This chapter summarizes the development of a new strategy for the rapid build-up of densely functionalized quaternary carbon centers from inexpensive chemical commodities. A rhodium(II)-catalyzed alkoxylation-acetalization of donor-acceptor-substituted diazo compounds by trimethyl orthoformate has been discovered and is the subject of the following section. This reaction allows for the one step synthesis of quaternary centers holding an alkene or arene, alkoxy, aldehyde and ester functionality.

4.2 Project outline

Encouraged by our previous results, we were intrigued to further expand the logic of implementing a C1-building block by means of rhodium(II)-catalyzed C−H bond insertion of carbenes. An initial survey of a suitable precursor drew our attention to trimethyl orthoformate.

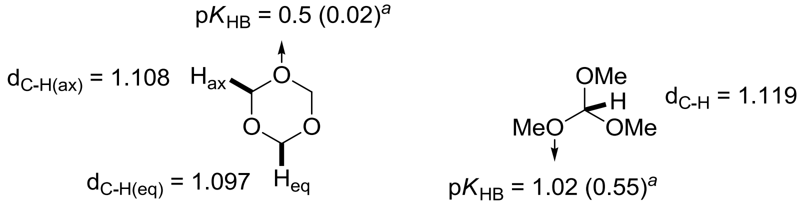
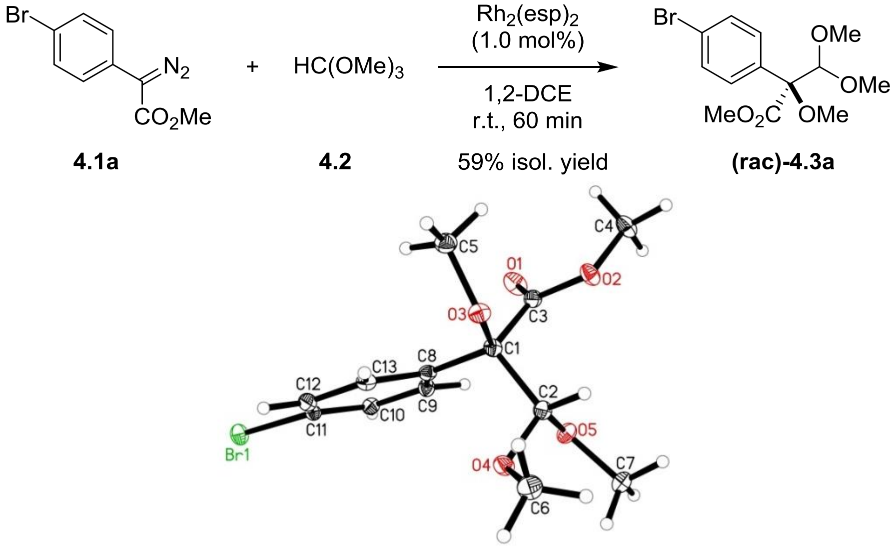


Figure 4.1. C−H bond length and *O*-basicity in 1,3,5-trioxane and trimethyl orthoformate. [a] Hydrogen bond basicity, statistically corrected value is shown in parenthesis.[46a]

In chapter 2, the bond-weakening effect of the oxygen lone-pairs in 1,3,5-trioxane has been discussed. In further expansion of this effect, *a priori*, the C−H bond insertion ought to be even more pronounced when an additional lone-pair impairs the bond strength. However, a significantly different hydrogen bond affinity and thus higher nucleophilicity of the oxygen atoms in these structures may contribute to a deviant reactivity of 1,3,5-trioxane and the trimethyl orthoester.

An initial experiment of the reactivity of trimethyl orhoformate (**4.2**) and 4-bromophenyl diazoacetate (**4.1a**) in the presence of $Rh_2(esp)_2$ yielded a product with suitable spectroscopic and mass spectrometric data, suggesting the successful incorporation of trimethyl orhoformate into the rhodium carbenoid species. However, based on the analytic data, ambiguous assignment of the molecular structure of the reaction product proved difficult. Gratifyingly, crystals suitable for X-ray analysis elucidated a surprising structure featuring a quaternary center holding an alkane or arene, alkoxy, aldehyde and ester functionality.



Scheme 4.1. Rhodium(II)-catalyzed reaction of 4-bromophenyl diazo acetate 4.1a and trimethyl ortho formate 4.2.

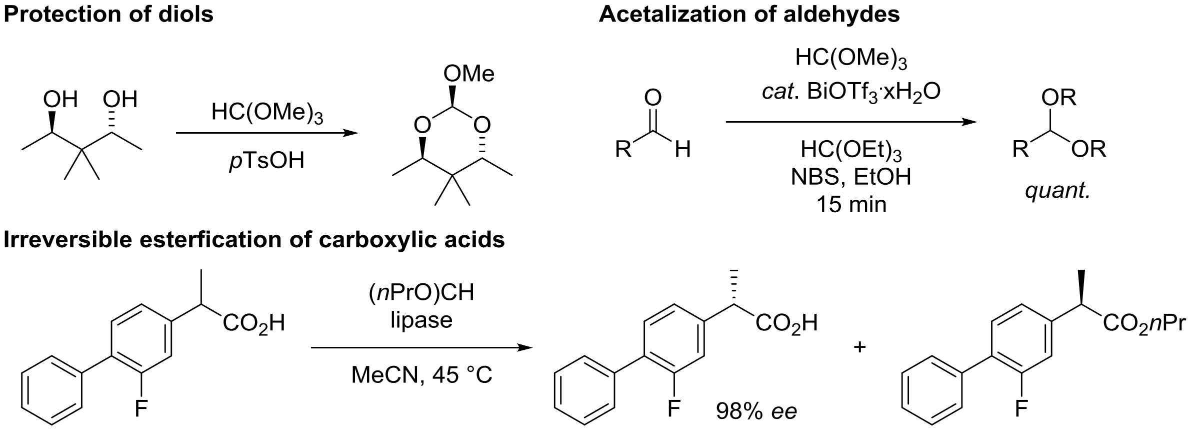
This unexpected reaction outcome could be rationalized *via* a ylide formation/[1,2]rearrangement mechanism. To the best of our knowledge, this transformation is the first reaction of trimethylortho formate in which a simultaneous C−C and C−O bond formation has been observed. The extrusion of nitrogen as a sole by-product and otherwise full atom-economy renders this process particularly valuable and environmentally benign. The optimization of reaction conditions, scope and limitations and mechanistic investigation will be discussed after a preceding overview of relevant related transformations involving orthoesters and related applications of rhodium(II) catalysis.

4.3 Background

4.3.1 Trialkyl orthoesters in organic synthesis

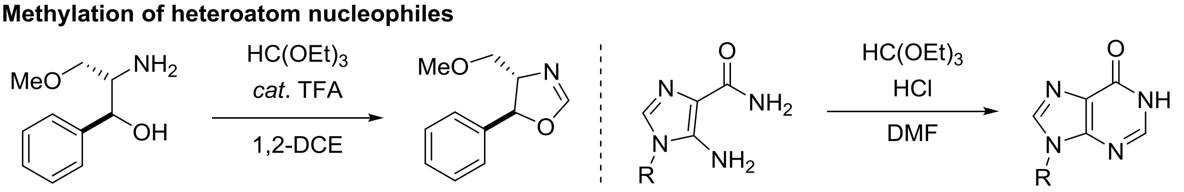
Trimethyl orthoformate or trimethoxymethane is the simplest orthoester. It is a versatile reagent widely used in synthetic organic chemistry.[99] Orthoformates are bench-stable, yet highly reactive compounds. Reactions of orthoesters can be classified in reactions which result in (1) carbon−oxygen bond formation, (2) carbon−heteroatom bond forming transformations and (3) carbon−carbon bond formation.

Typical examples for C−O bond forming reactions with trialkyl orthoformates are protection of diols,[100] acetalization of carbonyl compounds,[101] and esterification of acids (Scheme 4.2). The conversion of orthoformate to formate is energetically favored. Hence, trialkyl orthoformates are excellent esterification reagents as they function both as a water scavenger and as a source of alcohol for the esterification. This dual role limits reaction reversibility. Thus, trialkyl formats are especially useful in lipase-catalyzed kinetic resolution of racemic carboxylic acids wherein orthoesters allow for enhanced enantiomeric excess of the resolved acids relative to alternative protocols.[102] A similar effect accounts in acetalization reactions, allowing the formation of acetals under exceedingly mild conditions, making the additional use of acids obsolete. Thus, irrespective of the great number of different reaction condition for the acetalization of aldehydes, common features are high yields over a broad range of substrates, high selectivities for aldehydes *versus* ketones and tolerance of acid-sensitive functionalities.



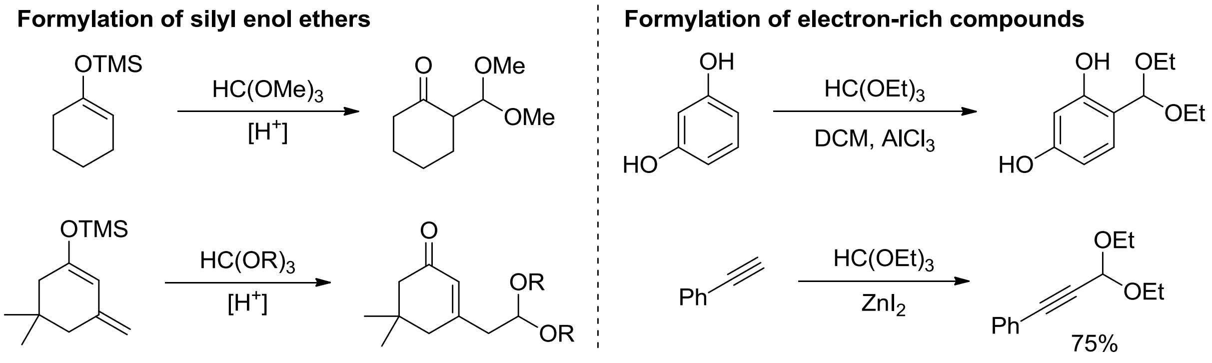
Scheme 4.2. Reactions of orthoformates in which C−O bonds are formed.

One of the most common applications of trialkyl orthoformates is in the condensation with 2-amino alcohols or vicinal diamines to afford heterocycles.[103] Two representative examples include facile acid-catalyzed preparation of asymmetric 2-oxazolines from chiral amino alcohols (Scheme 4.3),[103d] as well as high yielding conversion of substituted *ortho*-phenylenediamines to benzamidazoles or 2-aminophenols to benzoxazoles catalyzed by ytterbium triflate under solvent-free conditions (Scheme 4.3). Noteworthy, the ytterbium catalyst can be recycled and is reusable without loss of activity.



Scheme 4.3. Reactions of orthoformates in which C−heteroatom bonds are formed.

C−C bond forming reactions with trialkyl orthoformates encompass formylation of carbanions,[104] formylation of electron-rich species, such as arenes and alkynes (Scheme 4.4).[105] These reactions are synthetically particularly interesting as they add molecular complexity to simple carbon frameworks and supply with a useful handle for further transformations.

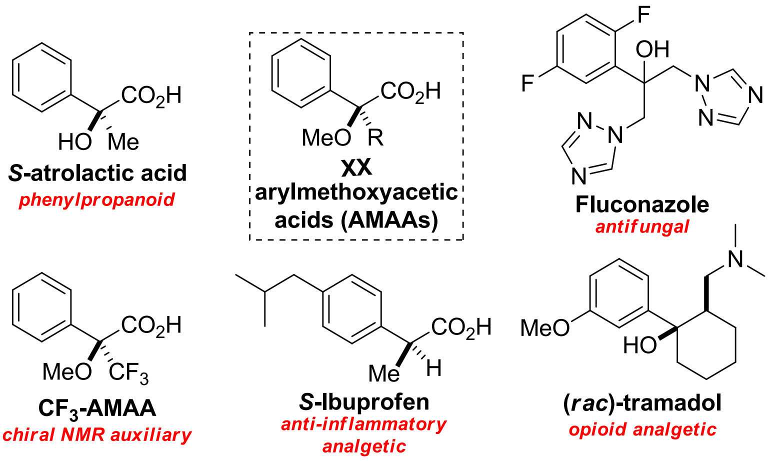


Scheme 4.4. Reactions of orthoformates in which C−C bonds are formed.

Besides applications of trialkyl orthoformates in organic synthesis, they are also used in inorganic and organometallic chemistry. For instance, trimethyl orthoformate is often used as dehydrating reagent in the synthesis of transition metal complexes.[106]

4.3.2 Synthesis of arylmethoxyacetic acid derivatives

Arylmethoxyacetic acids (AMAAs) represent a versatile class of synthetic intermediates and serve as potent precursor for a plethora of highly valuable pharmaceuticals (Scheme 4.5).

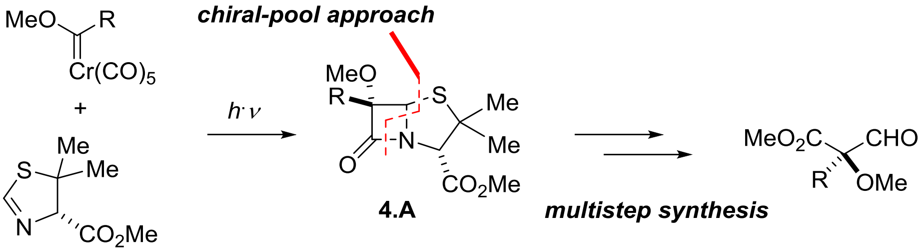


Scheme 4.5. Arylhydroxy acetic acids and derivatives.

Arylmethoxyacetic acids are employed as auxiliary reagents for the determination of the absolute configuration of organic compounds by NMR as chiral derivatisation reagents.[107] Phenylpropionic acid derivatives, ibuprofen and naproxen, are immensely appreciated as non-steroidal analgesic and non-steroidal anti-inflammatory agents.[108] Moreover, α-carbonyl-α-hydroxy arylpropionic acids have the potential to revise current syntheses of essential drugs, such as powerful antifungal fluconazole[109] and severe pain-relieving agent tramadol.[109,110]

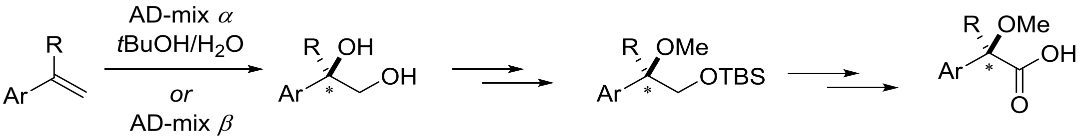
There are basically no straightforward procedures known that supply synthetic excess to α-carbonyl-α-hydroxy arylpropionic acids. In practice, commonly reported procedures require a multistep reaction sequence. Hence, build-up of this substance class remains a challenge within the synthetic community.

Hegedus and co-workers followed a chiral-pool approach for the generation of optically active quaternary carbon centers.[111] Photoaddition of stoichiometric chromium-alkoxycarbene complexes to optically active valine-derived thiazolines generated penam intermediate **4.A**. Alcoholysis of the *β*-lactam followed by solvolysis of the thiazolidine ring produced highly functionalized optically active quaternary centers holding an alkane or arene, alkoxy, aldehyde and ester functionality. However, this approach demanded a tedious synthesis of the chiral thiazoline precursor that was only reliably produced on large scale.



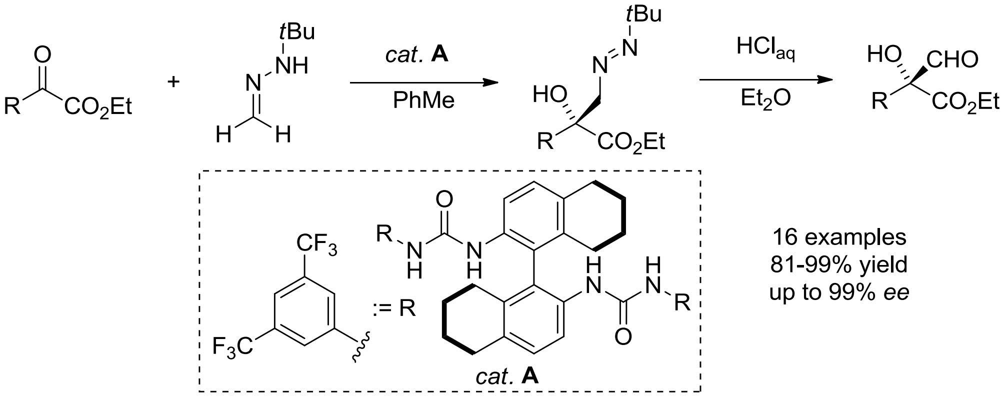
Scheme 4.6. Synthesis of optically active carbon centers from photoaddition of chromium-alkoxycarbene complexes and chiral thiazolines.

Another approach for the preparation of arylmethoxyacetic acids by the group of *Massanet* involves a sequence of asymmetric dihydroxylation and further oxidation of the resulting glycol with TEMPO/NaClO/NaClO$_2$, concerted around a tedious protection/deprotection sequence (Scheme 4.7).[112]



Scheme 4.7. Sequential enantioselective synthesis of arylmethoxyacetic acid derivatives from α-styrenes.

An interesting organocatalytic approach was reported by *Fernandez*, *Lassetta* and co-workers. Therein, they investigated an asymmetric formal carbonyl-ene reaction of formaldehyde *tert*-butyl hydrazone with *α*−keto esters by dual activation by bis-urea catalysts.[113] The corresponding tertiary carbinols were obtained in excellent yields and high to excellent regioselectivities (Scheme 4.8).

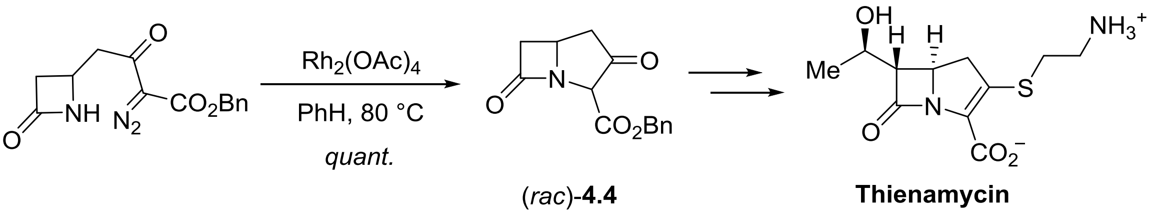


Scheme 4.8. Asymmetric formal carbonyl-ene reactions of formaldehyde *tert*-butyl hydrazone with α-keto esters: dual activation by bis-urea catalysts.

4.3.3 Rhodium(II) catalysis: Ylide formation and C−X/C-C bond forming reactions

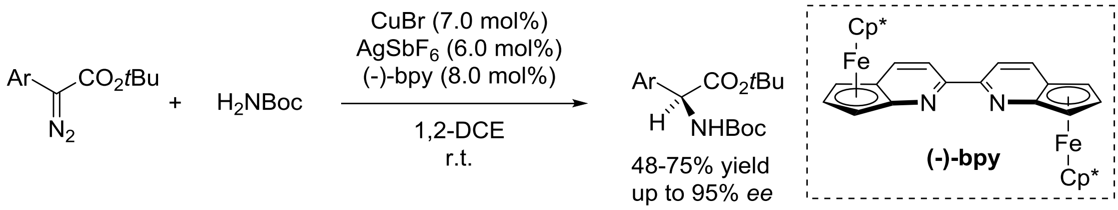
The carbenoid intermediate formed in the course of transition metal catalyzed decomposition of diazo compounds are highly electrophilic in nature and readily react with various heteroatom nucleophiles.[114] The corresponding ylides are eligible to undergo a wide variety of transformations, ranging from simple proton transfer to more complex [2,3]-sigmatropic rearrangement, [1,2]-Stevens-rearrangement and 1,3-cycloaddition reactions.[58,79,114c]

Since their discovery in the 1970s, dirhodium carboxylates have been applied as highly efficient catalysts in the carbenoid O–H and N–H insertion reactions.[115] The most notable industrial application of this reaction is the $Rh_2(OAc)_4$-catalyzed intramolecular insertion into a *β*–lactam N–H bond, a key step in MERCK's thienamycin synthesis (Scheme 4.9).[116] The cyclic ketoester **4.4** was formed in quantitative yield.



Scheme 4.9. Rhodium-catalyzed N–H insertion step in MERCK's thienamycin synthesis.

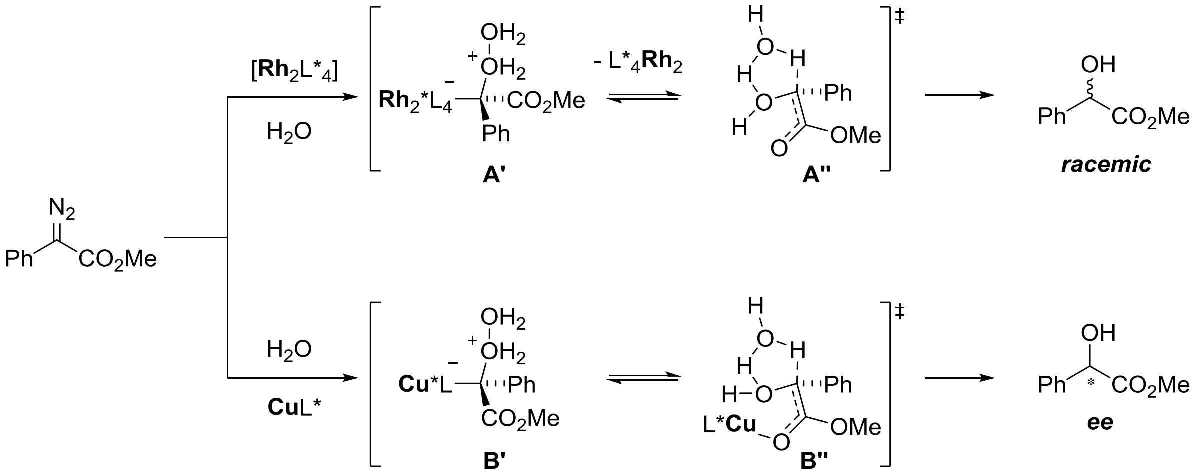
However, the excellent level of stereoinduction of chiral dirhodium catalyst that has been achieved in asymmetric cyclopropanation and C–H insertion reactions could not be translated to asymmetric O–H and N–H insertion reactions.[117] The reaction of phenyldiazoacetates with alcohols was catalyzed by various chiral dirhodium catalysts in excellent yield, however exclusively as racemic mixtures.[118] Better results in terms of stereoselectivity have been achieved by *Fu* and co-workers who applied a copper/planar-chiral ligand (-)-bpy* catalyst system that accomplished N–H insertion of carbamate with a wide range of aryldiazoacetates in good yields and enantioselectivities (Scheme 4.10).[17b] This logic could further be extended to *O*-nucleophiles, supplying efficient excess to chiral *α*-amino and *α*-hydroxy acids, respectively.[119]



Scheme 4.10. Asymmetric copper-catalyzed N–H insertion of aryldiazoacetates and *tert*-butyl carbamate.

The orthogonal selectivity of rhodium versus copper carbenoids was later addressed by *Yu* and co-workers by application of density functional theory (DFT).[120] In both cases a water-catalyzed [1,2]-

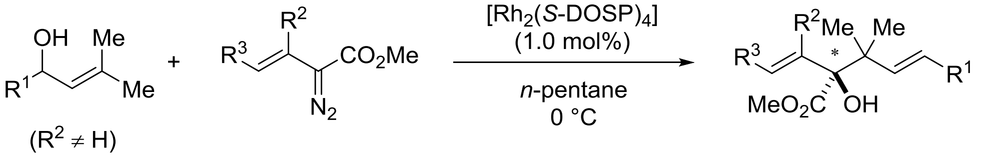
proton shift process was found to be much more energetically favored over a direct [1,2]-proton shift. However, while the copper-associated ylide **B'** is the reactive species for the [1,2]-proton shift in the copper-catalyzed O–H insertion, the Rhodium(II)-catalyzed O–H insertion operates *via* free ylide **A''** (Scheme 4.11).



Scheme 4.11. Rhodium(II) and Cu(I) catalyzed O–H insertion.

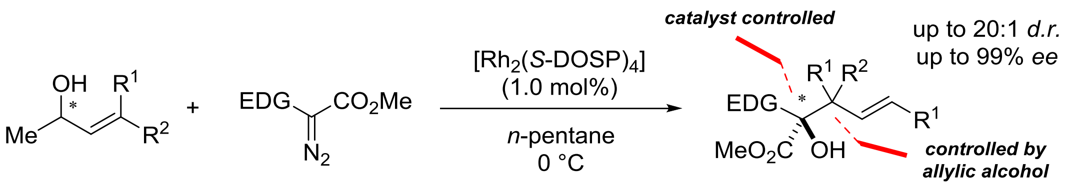
Mechanistically, the presented rhodium(II)-catalyzed alkoxylation-acetalization of donor-acceptor-substituted diazo compounds by trimethyl orthoformate features an ylide formation and a subsequent rearrangement resulting in concomitant C–O and C–C bond formation. This type of reactivity has precedence in rhodium(II) catalysis and has been exploited to create a number of interesting transformations and molecular frameworks.[114c,121]

A tandem ylide formation/[2,3]-sigmatropic rearrangement between methyl phenyldiazoacetates and methyl styryldiazoacetates was discovered and studied by *Huw Davies* and co-workers (Scheme 4.12). The two-step ylide formation and rearrangement competes favorably with the conventional O–H insertion under the premise that highly substituted allyl alcohols are used. Tertiary *α*–hydroxycarboxylate derivatives were synthesized in 53-70% isolated yield and >98% *ee* with dirhodium tetraprolinate $Rh_2(S\text{-DOSP})_4$.[122]



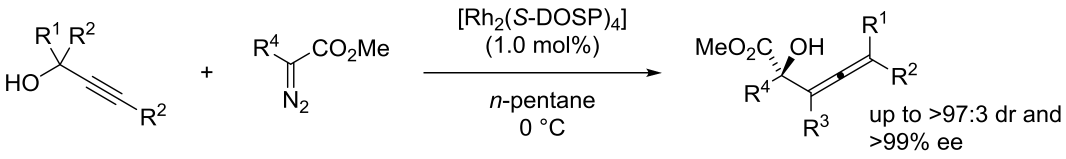
Scheme 4.12. Tandem oxonium ylide formation/[2,3]-sigmatropic rearrangement between donor/acceptor carbenoids and allylic alcohols.

The same group succeeded in synthesizing tertiary *α*–hydroxycarboxylate containing vicinal stereo centers.[123] They found that the stereochemistry of the tertiary alcohol is governed by the configuration of the catalyst, whereas the adjacent stereocentre is controlled by the chirality of the allylic alcohol (Scheme 4.13).



Scheme 4.13. Stereoselective C−C Bond formation by rhodium-catalyzed tandem ylide formation/[2,3]-sigmatropic rearrangement between donor/acceptor carbenoids and chiral allylic alcohols.

The same catalytic system was used for the stereoselective synthesis of allene derivatives. These substances arose when propagylic alcohols were used in conjunction with push-pull carbenes (Scheme 4.14).[124] A considerably broad substrate scope could be created by this strategy. Furthermore, chiral resolution of racemic propagylic alcohols could be achieved, leading to an enantioenrichment of the unreactive enantiomer of 65-95%. Computational studies reveiled that a highly organized transition state structure contributes to the excellent enantiodiscrimination.



Scheme 4.14. Tandem oxonium ylide formation/[2,3]-sigmatropic rearrangement between donor/acceptor carbenoids and propargylic alcohols.

Donor-acceptor substituted rhodium-carbenoids are electrophilic at the carbon atom. However, in the case of vinyl derivatives two mesomeric structures can be postulated possessing divergent reactive sites. In the preceding section reactivity was exclusively observed on the α-carbon, however, the reactivity can be altered towards a favorably vinylogous reactivity (Figure 4.2).[125]

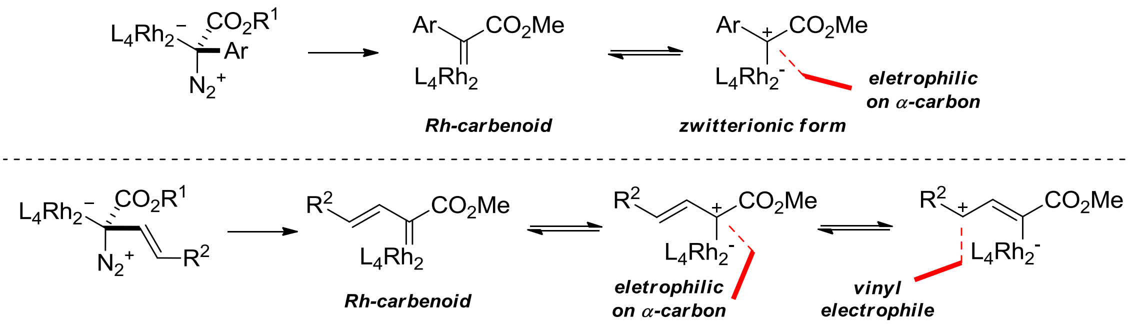
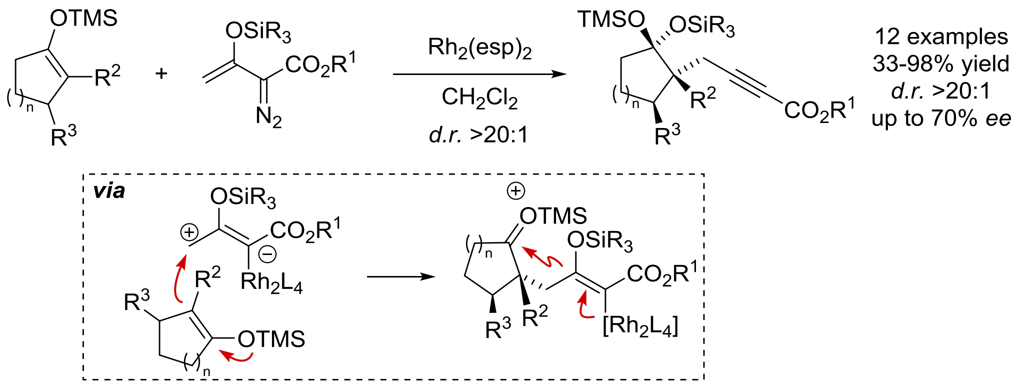


Figure 4.2. Electrophilic sites in aryl- and vinyl push-pull carbenes.

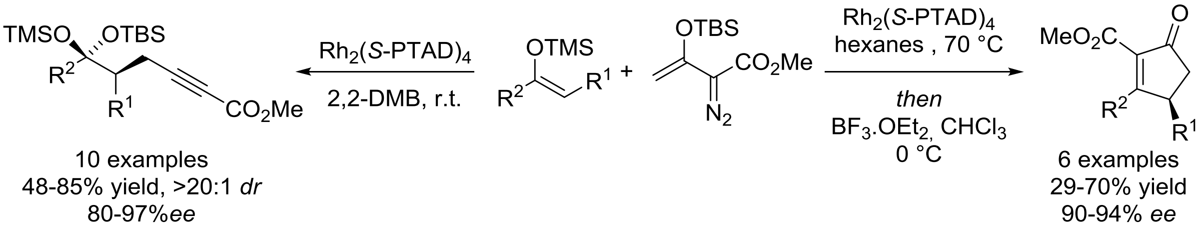
In many cases the vinylogous reactivity of rhodium carbenoids was only observed when the vinylic position of the carbenoid is unsubstituted.[126] Other factors to favor vinylogous reactivity were electron-deficient dirhodium catalysts, polar solvents, and bulky esters on the carbenoid. Recently, the group of *Davies*[127] and others[128] have studied the vinylogous reactivity in a variety of transformations. It was found that chiral bulky dirhodium catalysts could enhance vinylogous reactivity, especially in combination with sterically demanding nucleophiles.[129]

One example for the vinylogous functionalization of diazo compounds, published by *Davies* and co-workers, is the highly diastereoselective methodology for the rapid access to functionalized 2-alkynoates in a single step using cyclic silyl enol ethers and siloxy vinylcarbenoids under rhodium(II) catalysis (Scheme 4.15).[130] It has been clearly shown that bulky *tert*-butyl esters in conjunction with sterically demanding silyl protecting groups on the diazo compound was advantageous for a high yielding functionalization in *γ*-position of the vinyl ester. An exploratory study concerning the enantioselectivity of the reaction was conducted. However, only moderate levels of enantiomeric excess of up to 70% *ee* could be achieved.



Scheme 4.15. Alkynoate synthesis through the vinylogous reactivity of rhodium(II) carbenoids

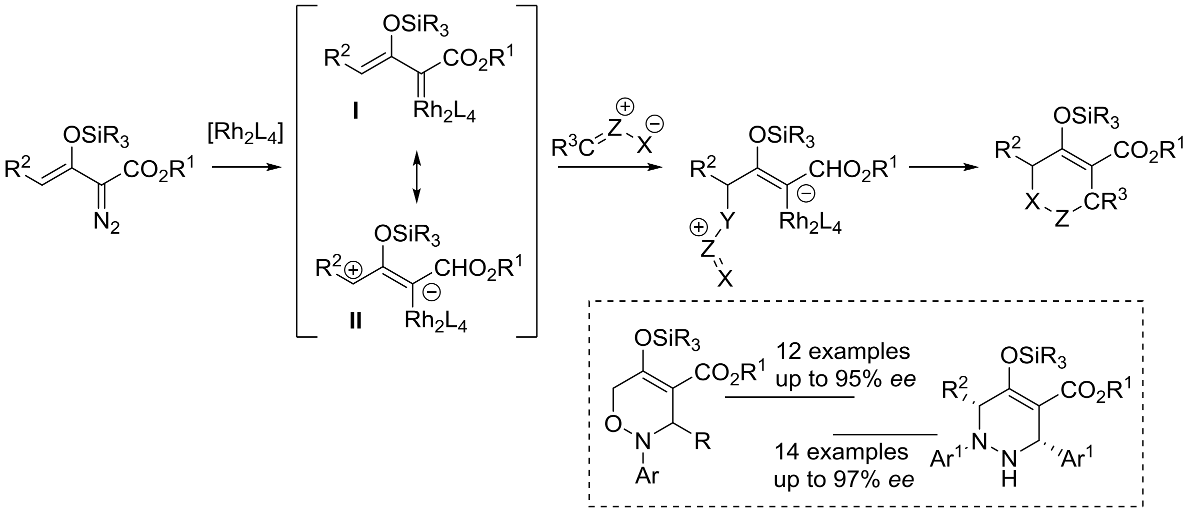
As an extension to this protocol, the same group later published an asymmetric vinylogous addition of acyclic silyl enol ethers to siloxyvinyldiazoacetate (Scheme 4.16).[127d] The reaction proceeds through a diastereoselective 1,4-siloxy group migration event and the products were obtained in up to 97% *ee*. The reaction pathway proved to be dependent on the steric congestion of the silyl enol ether. In this instance, bulky silyl enol ether provoked an enantioselective formal [3+2] cycloaddition.



Scheme 4.16. Asymmetric vinylogous addition of acyclic silyl enol ethers to siloxyvinyldiazo acetate.

There are manifold examples of formal [3+3] cycloaddition reactions employing vinyldiazo aceates and 1,3-dipols.This reaction pattern has been exploited for the synthesis of a number of heterocycles. These reactions feature concomitant C−C/C−heteroatom bond formations which is conterminous with the presented reaction.

In this context, *Doyle* and co-workers have developed a direct formal [3+3] cycloaddition that provides an effective access to bicyclic and tricyclic 1,2,3,6-tetrahydropyridazine derivatives.[128d] The reaction sequence is triggered by rhodium(II)-catalyzed dinitrogen extrusion from enol diazoacetates followed by vinylogous addition with *N*-acyliminopyridinium ylides. Intramolecular asymmetric addition of the 1,3-dipol to the zwitterionic vinyl ether complex **II** forms the [3+3] cycloaddition product (Scheme 4.17).



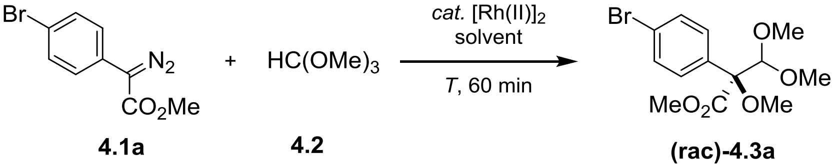
Scheme 4.17. Enantioselective dearomatizing formal [3+3] cycloaddition reactions of *N*-acyliminopyridinium ylides with electrophilic enol carbene intermediates.

4.4 Results and discussion

4.4.1 Optimization of reaction conditions

Starting from the encouraging result of the initial experiment between trimethyl orthoformate (**4.2**) and 4-bromophenyl diazoacetate (**4.1a**) in the presence of $Rh_2(esp)_2$, the influence of crucial reaction parameters was targeted. Other achiral catalyst gave inferior results (Table 4.1, entries 1-6). However, further optimization of the reaction conditions led to improved isolated yields of up to 77% when Rh_2(*S*-pttl)$_4$ was used as catalyst in chloroform (entry 12). Optimal results were achieved by dropwise addition of a 0.2 molar solution of **4.1** in dichloromethane to a stirring solution of **4.2** in dichloromethane in the presence of Rh_2(*S*-pttl)$_4$ (1.0 mol%) at ambient temperature. However, to this end, all products were obtained as racemic mixture. This observation suggests an extrusion of the chiral catalyst to take place prior to the formation of the desired coupling product.

Table 4.1. Optimization of reaction conditions for the rhodium(II)-catalyzed tandem alkoxylation/acetalization of 4.1a with trimethyl orthoformate (4.2).[a]



entry	Rh(II) cat.	solvent	*T* [°C]	yield (%)[a]
1	none	$CHCl_3$	23	0
2	$Rh_2(OAc)_4$	$CHCl_3$	23	0
3	$Rh_2(Opiv)_4$	$CHCl_3$	23	10
4	$Rh_2(OOct)_4$	$CHCl_3$	23	38
5	$Rh_2(OAd)_4$	$CHCl_3$	23	27
6	$Rh_2(tpa)_4$	$CHCl_3$	23	12
7	$Rh_2(esp)_2$	$CHCl_3$	23	49 (41)
8	Rh_2(*S*-DOSP)$_4$	$CHCl_3$	23	48 (45)
9	Rh_2(*S*-meox)$_4$	$CHCl_3$	23	0
10	Rh_2(*S*-mepy)$_4$	$CHCl_3$	23	0
11	Rh_2(*S*-nttl)$_4$	$CHCl_3$	23	28
12	**Rh_2(*S*-pttl)$_4$**	**$CHCl_3$**	**23**	**77 (71)**
13	Rh_2(*S*-ptad)$_2$	$CHCl_3$	23	55
14	**Rh_2(*S*-pttl)$_4$**	**DCM**	**23**	**86 (84)**
15	Rh_2(*S*-pttl)$_4$	DCE	23	86 (74)
16	Rh_2(*S*-pttl)$_4$	PhMe	23	36
17	Rh_2(*S*-pttl)$_4$	PhCl	23	79 (78)
18	Rh_2(*S*-pttl)$_4$	2,2-DMB	23	56
19	Rh_2(*S*-pttl)$_4$	DCM	0	51
20	Rh_2(*S*-pttl)$_4$	DCM	23	**86 (84)**
21	Rh_2(*S*-pttl)$_4$	DCM	40	82 (81)

Reaction conditions: A 0.2 M solution of **4.1a** (0.2 mmol) and **4.2** (1.0 mmol) in the specified solvent was added dropwise (1 h) to a stirring solution of **4.2** (1.0 mmol) and the $[Rh(II)]_2$ catalyst (1.0 mol%) of the same solvent (0.3 mL). [a] GC-yield is shown. Mesitylene was used as internal standard. Isolated yields in parentheses.

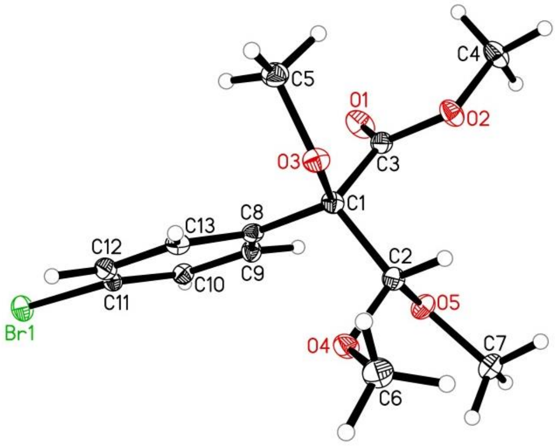


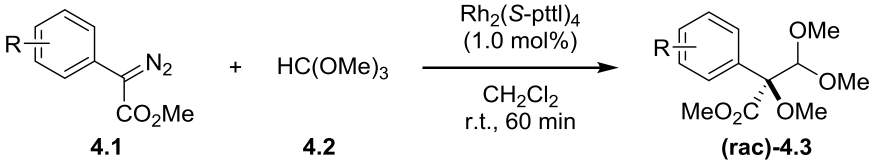
Figure 4.3. Crystal structure of compound 4.3a

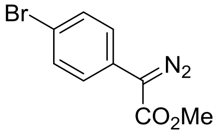
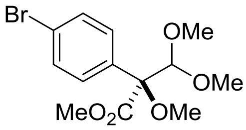
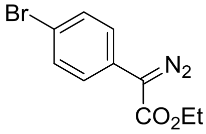
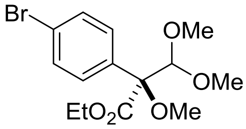
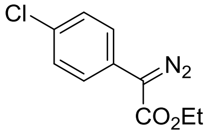
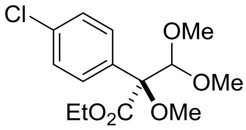
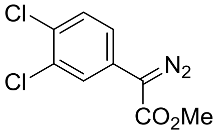
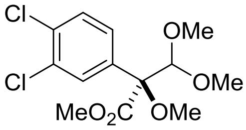
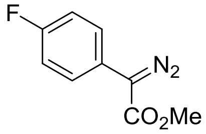
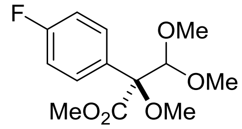
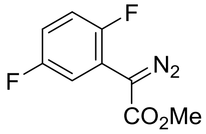
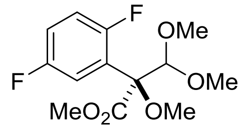
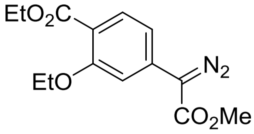
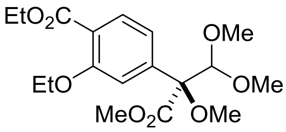
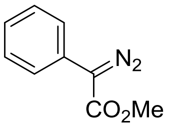
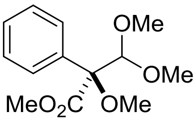
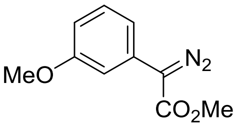
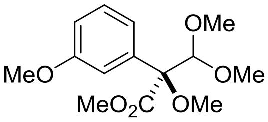
The elucidation of chemical structure of the reaction product was not ambiguous. Gratifyingly, crystals suitable of x-ray analysis could be obtained from the screening product. To our surprise, one of the methoxy groups of the trimethyl orthoformate (**4.2**) was bound to the former carbenoid carbene in 2-position of the methyl 2-(4-bromophenyl)-2-diazoacetate (**4.1a**). In addition, a new C−C bond was formed between C-2 and central carbon atom of **4.1a**. In summary, the coupling product possesses a highly functionalized quaternary center holding an arene, alkoxy, protected aldehyde and ester functionality.

4.4.2 Scope and limitations

Having a practical protocol in hand for the rhodium-catalyzed alkoxy-acetalization of methyl 2-(4-bromophenyl)-2-diazoacetate (**4.1a**), we studied the scope with respect to phenyl-2-diazoacetate **4.1** derivatives under the evaluated reaction conditions. A variety of methyl and ethyl phenyl-2-diazoacetate afforded the corresponding products in high yield. Electron-withdrawing substituents benefit the desired reaction pathway (entries 1-7). Thus, valuable product bearing bromo- (entry 1 and 2), chloro- (entry 3 and 4) and flouro-substituents (entry 5 and 6) as well as ester and alkoxy-functionalities (entry 7) were well tolerated. When ethyl aryldiazo acetates, **4.1b** and **4.1c**, slightly diminished yields of the desired coupling products, **4.3b** and **4.3c**, were obtained. In these cases, intramolecular C–H bond insertion into the ester side-chain yielding a 4-membered lactone, is competitive with the ylide formation pathway. The modest yield of methyl 2,3,3-trimethoxy-2-phenylpropanoate (**4.3h**) from electron-neutral methyl 2-phenyl-2-diazoacetate (**4.1h**) of 40% in dichloromethane at ambient temperature could be increased to reasonable 65% isolated yield when the reaction was conducted in chlorobenzene at 60 °C (Table 4.2, entry 8). Electron-donating substituents are less suitable and resulted in complex mixtures of products. However, versatile alkoxy groups were well tolerated in the *meta*-position in which the negative inductive effect prevails the otherwise dominant positive mesomeric effect (Table 4.2, entry 9).

Table 4.2. Scope of the reaction of rhodium(II)-carbenoids with trimethyl orthoformate (4.2).[a]



entry	substrate		product		yield (%)[a]
1		**4.1a**		**4.3a**	84%
2		**4.1b**		**4.3b**	63%
3		**4.1c**		**4.3c**	68%
4		**4.1d**		**4.3d**	73%
5		**4.1e**		**4.3e**	76%
6		**4.1f**		**4.3f**	83%
7		**4.1g**		**4.3g**	83%
8		**4.1h**		**4.3h**	40% 65%[b]
9		**4.1i**		**4.3i**	72%[c]

Reaction conditions: A 0.2 M solution of **4.1** (0.2 mmol) and **4.2** (1.0 mmol) in CH_2Cl_2 was added dropwise (1 h) to a stirred solution of **4.2** (1.0 mmol) and the Rh_2(*S*-pttl)$_4$ catalyst (1.0 mol%) in CH_2Cl_2 (0.3 mL) at ambient temperature. [a]isolated yields are shown. [b]reaction was conducted in PhCl at 60 °C. [c] isolated yield of the corresponding aldehyde after iodine-mediated acetal-cleavage.

As previously mentioned, donor-acceptor-substituted carbenoids derived from vinyldiazo acetates **4.5** harbor two potential electrophilic reaction sites. Thus, formation of two different products resulting from (**A**) α-functionalization and (**B**) vinylogous addition are conceivable (Figure 4.4).

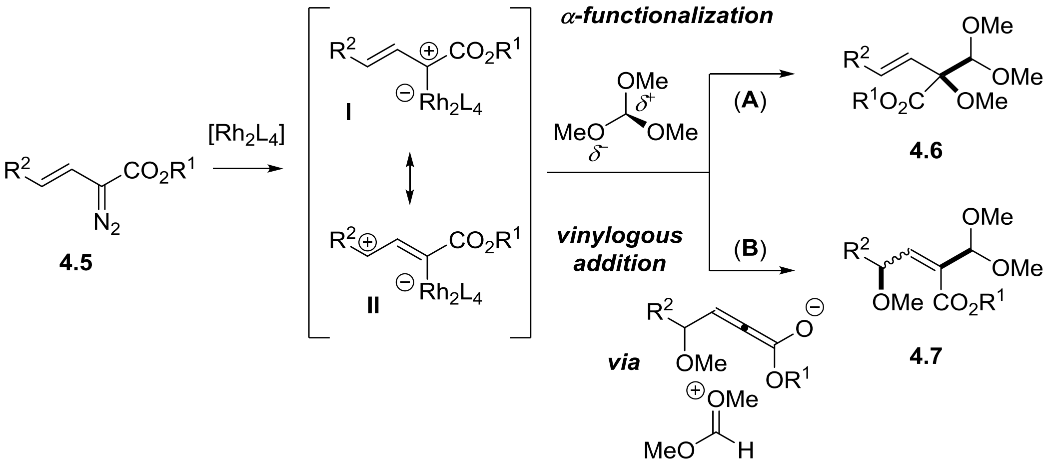
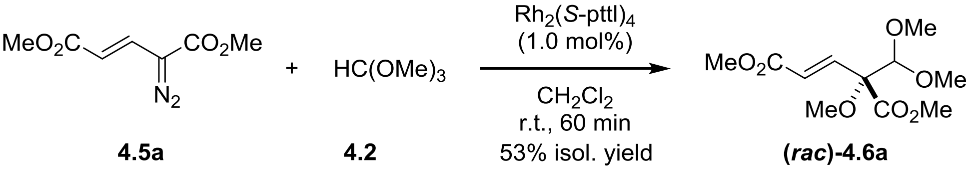


Figure 4.4. α-Functionalization *vs.* vinylogous addition.

We were delighted to find that vinyldiazo acetate **4.5** depicted equally potent coupling partners in the alkoxylation/acetalization reaction sequence. The coupling product of dimethyl glutaconoate **4.5a** was obtained in 53%. According to the ^{1}H NMR spectrum the reaction was judged to proceed *via* the *α*-functionalization mechanism (**A**) evident from the trans-coupling constants of 15.1 Hz.



Scheme 4.18. Rhodium-catalyzed alkoxylation-acetalization of dimethylglutaconoate.

4.4.3 Derivatization of methyl 2-phenyl-2,3,3-trimethoxypropanoates

The crux of the developed methodology lies in the diverse opportunities for the derivatization of the C−C/C−O coupling products. The different functional groups of the molecule possess orthogonal reactivity and can thus be transformed independently from each other (Figure 4.5). The ester group can be selectively reduced, saponificated or manipulated upon nucleophilic attack. A halide, or related functional group, attached to the phenyl moiety can be subjected to a vast number of cross-coupling reactions to trigger C−C bond forming reactions or functionalization with heteroatoms. The probably most valuable reactive site of the molecule is the protected formyl group. The free aldehyde serves as excellent chemical anchor for a myriad of transformations.

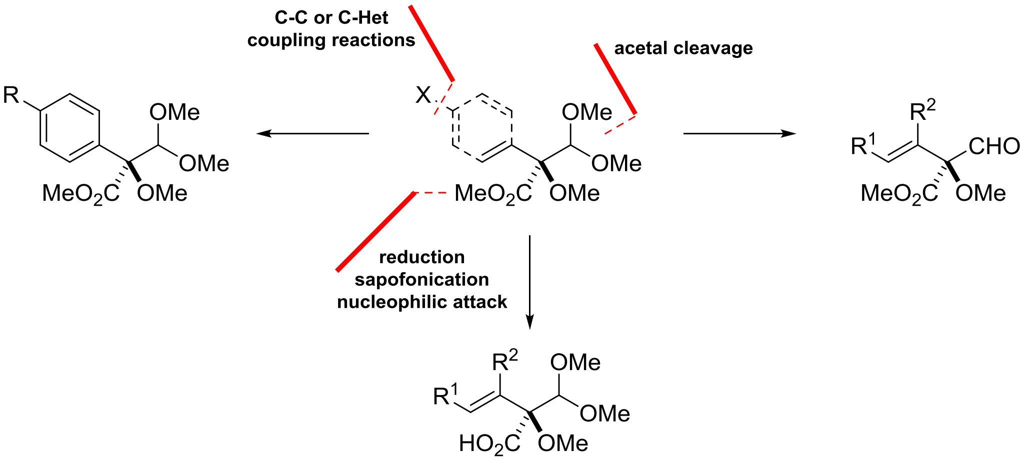
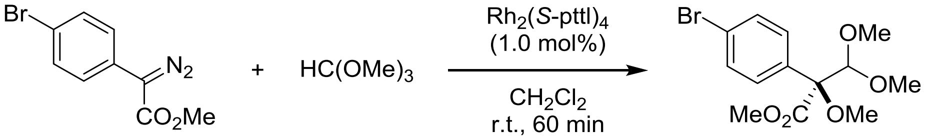


Figure 4.5. Functionalization strategies.

The screening substrate methyl 2-(4-bromophenyl)-2-diazoacetate (**4.1a**) was used as it is easily accessible in high yields. The corresponding coupling product methyl 2-(4-bromophenyl)-2,3,3-trimethoxypropanoate (**4.3a**) is equally straightforward to make and its purification is facile. Thus, **4.3a** was produced in gram-scale from a 5.0 mmol reaction. Analytically pure product was obtained after filtration and recrystallization from Et_2O/*n*-heptane in 76% isolated yield (Scheme 4.19).



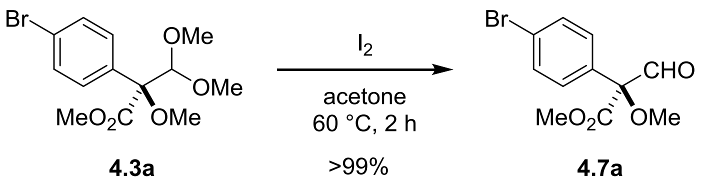
4.1a
(5.0 mmol)

4.2

(rac)-4.3a
76%, 1.26 g

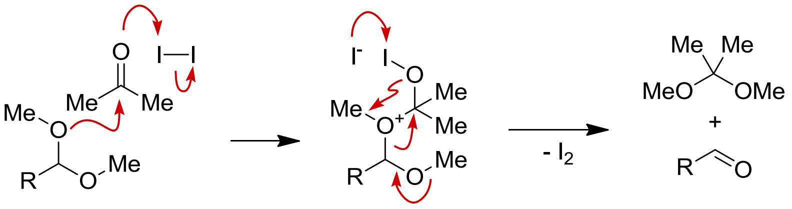
Scheme 4.19. Gramm-scale synthesis of methyl 2-(4-bromophenyl)-2,3,3-trimethoxypropanoate (4.3a).

A convenient and rapid deprotection of the dimetylacetal was achieved under neutral reaction conditions in the presence of iodine (Scheme 4.20).[75e] The corresponding aldehyde **4.7a** was obtained in excellent yield.



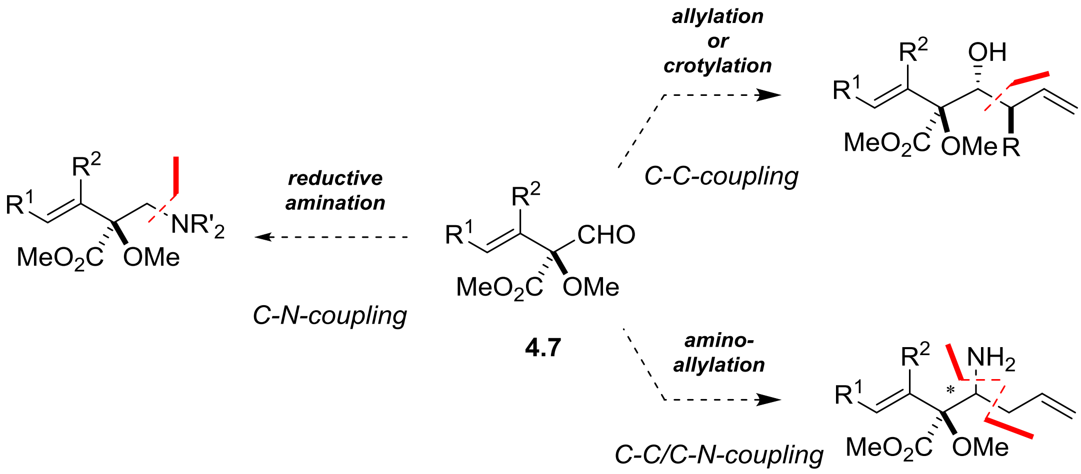
Scheme 4.20. Dimethylacetal cleavage by molecular iodine in acetone.

The general reaction mechanism of the molecular iodine catalyzed deprotection of dialkylacetal cleavage is presumed to go through a substrate exchange mechanism, rather than a hydrolysis mechanism as encountered in acid-catalyzed cleavage. The deprotection initially involves a polarization of the carbonyl group in acetone by molecular iodine. The full mechanism is depicted in Scheme 4.21.



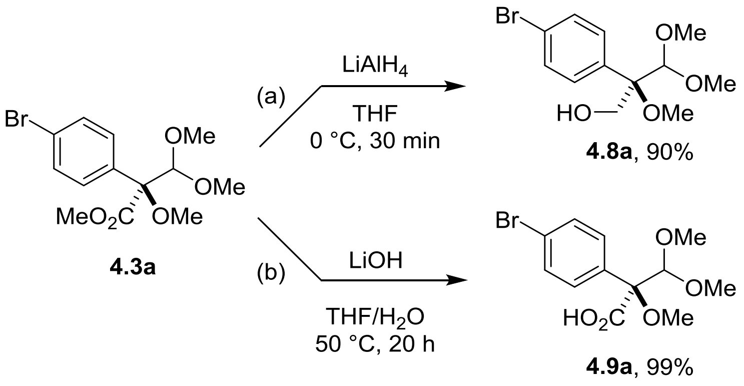
Scheme 4.21. Exemplified mechanism for the iodine-mediated deprotection of acetals.

The free aldehyde **4.7** is an excellent starting point for versatile further functionalization. Just to mention a few opportunities arising at this juncture, the aldehyde is amenable to participate in C–N bond forming reactions such as reductive amination supplying access to phenethylamines,[131] C–C bond generating allylation and crotylation,[132] or combined C–C/C–N bond formation *via* an aminoallylation sequence for the synthesis of homoallylic primary amines (Scheme 4.22).[4f,133]



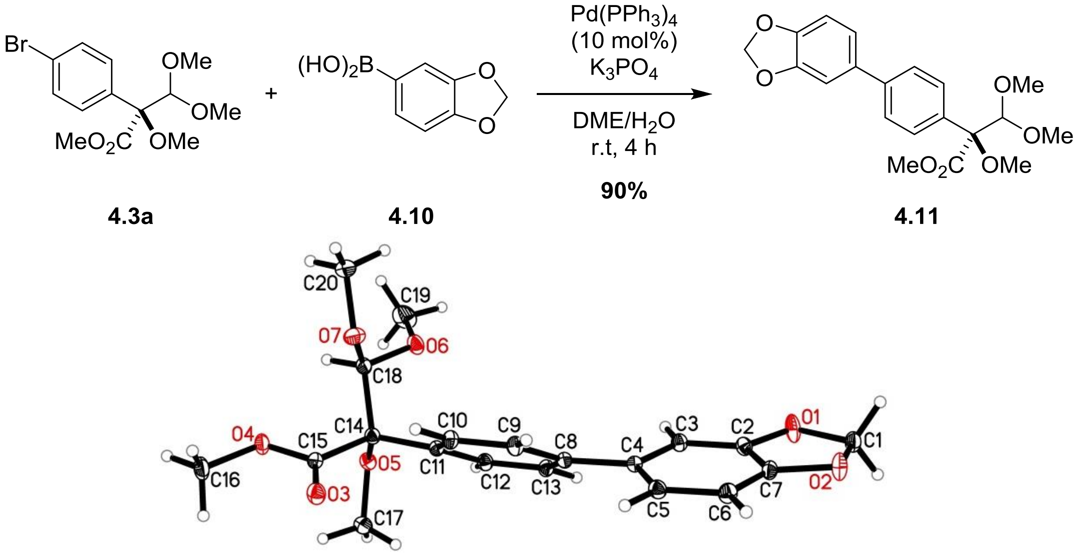
Scheme 4.22. Potential for further functionalization of the aldehyde 4.7.

The ester functionality of **4.3a** could be efficiently reduced with $LiAlH_4$ in THF at 0 °C. The reaction was complete within 30 min and the corresponding alcohol (**4.8a**) was isolated in 90% yield (Scheme 4.23, (a)). Saponification of the methyl ester at elevated temperature resulted the formation of carboxylic acid **4.9a** in quantitative yield after aqueous work-up (Scheme 4.23, (b)).



Scheme 4.23. (a) Reduction of methyl 2-(4-bromophenyl)-2,3,3-trimethoxypropanoate (4.3a) with $LiAlH_4$; (b) saponification with LiOH in THF/H_2O.

Derivatization of the phenyl moiety of **4.3a** can be conveniently achieved under Suzuki-Miyaura cross-coupling conditions. When bromo arene **4.3a** was reacted with benzo[*d*][1,3]dioxol-5-ylboronic acid (**4.10**) in the presence of tetrakistriphenylphosphine palladium(II) the corresponding cross-coupling product methyl 2-(4-(benzo[*d*][1,3]dioxol-5-yl)phenyl)-2,3,3-trimethoxypropanoate (**4.11**) was isolated in 90% yield (Scheme 4.24). Recrystallization of **4.11** afforded crystals in a quality suitable for x-ray crystallography.



Scheme 4.24. Suzuki-Miyaura cross-coupling of 4.3a and 4.10 and crystal structure of the reaction product.

4.4.4 Mechanistic considerations

As mentioned in the Project outline at the beginning of this chapter, we initially attempted to pursue a similar C−H insertion pathway (Figure 4.6, (1)) for the introduction of trimethyl orthoformate as an alternative C1-building block similar to the reaction described with 1,3,5-trioxane (Chapter 2). Though, trimethyl orthoformate could indeed be implemented into phenyl and vinyl actetate scaffolds *via* C−C bond formation, the pathway was divergent from the postulated C−H bond insertion mechanism (Figure 4.6, (2)).

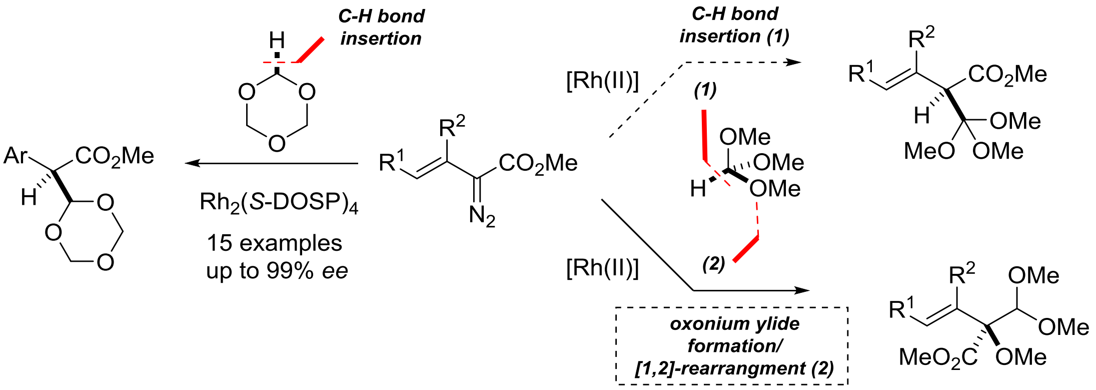


Figure 4.6. Schematic overview for the activation mode of 1,3,5-trioxane versus trimethyl orthoformate.

A comparison of the physicochemical of trimethyl orthoformate **4.3** and 1,3,5-trioxane (**2.2**) aids to rationalize the opposed reactivity. *Berthelot* and co-workers compared the hydrogen bond basicity pK_{HB} of various cyclic ethers using 4-fluorophenol as a reference hydrogen-bond donor.[46a] Equilibrium constants, K_f, for the formation of 1:1 hydrogen bonded complexes have been derived from FTIR spectroscopic data. According to their results, 1,3,5-trioxane possesses a medium hydrogen bond basicity of 0.5 (0.02)[134] (Figure 4.7). The oxygen lone-pairs in trimethyl orthoformate impart a significantly higher hydrogen bond basicity of 1.02 (0.55). This feature significantly contributes to the affinity for ylide formation.

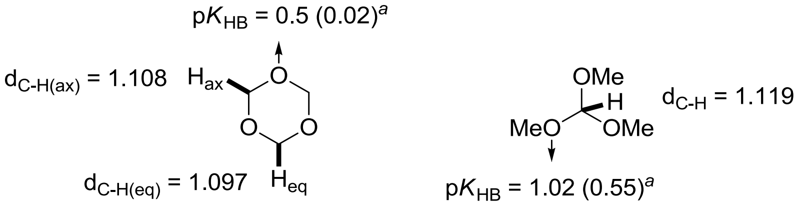
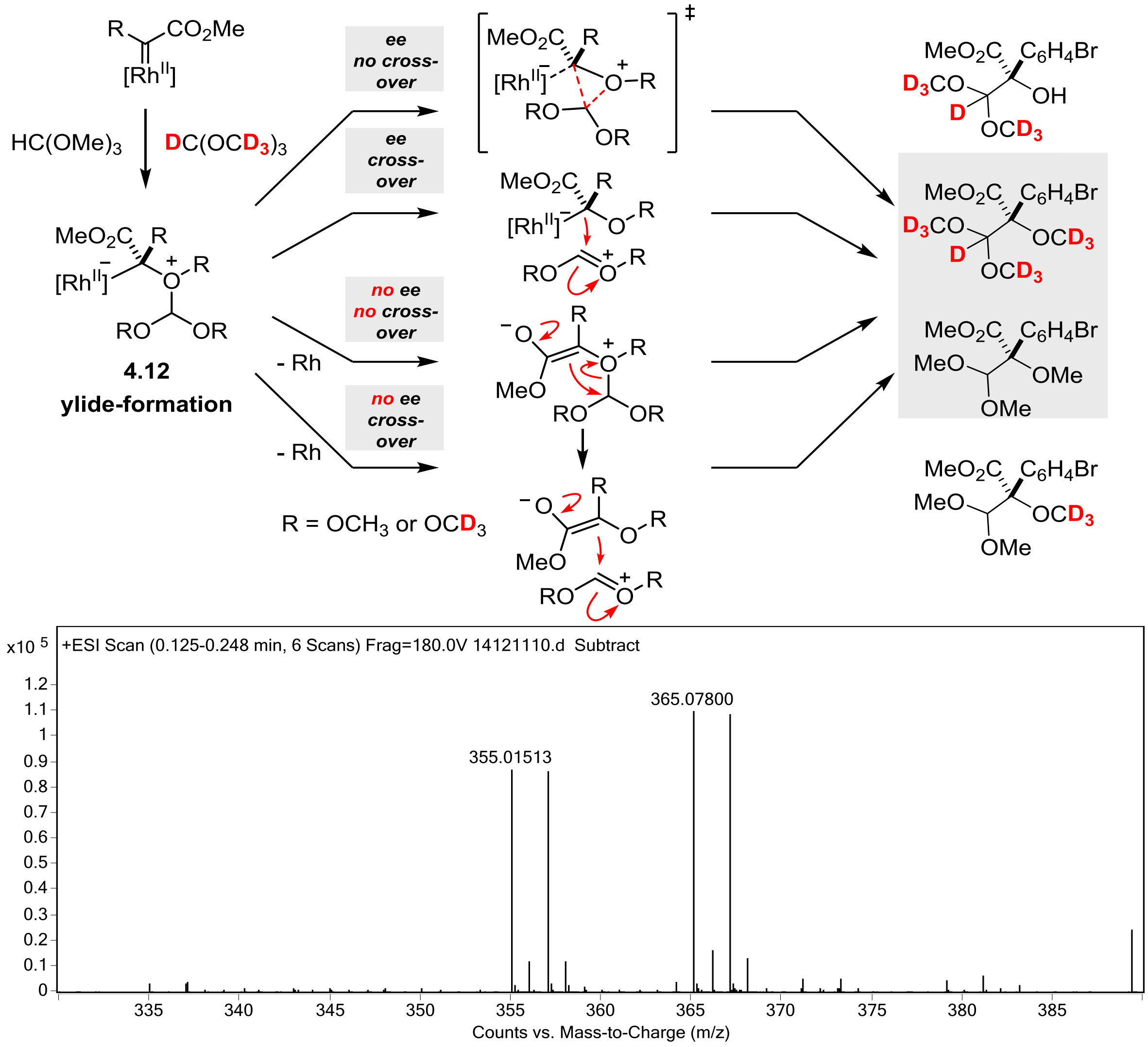


Figure 4.7. C−H bond length and *O*-basicity in 1,3,5-trioxane and trimethyl orthoformate. ^{a} Hydrogen bond basicity, statistically corrected value is shown in parenthesis.

However, the ylide formation represents only one step of a sequence that accounts to the product formation and different reaction pathways are conceivable for the alkoxylation/acetalization of donor-acceptor substituted carbenes triggered by rhodium(II) complexes (Scheme 4.25.). Pending the initial formation of the reactive rhodium(II) carbenoid species *via* rhodium(II) carboxylate catalyzed decomposition of the diazo compound, the electrophilic attack of the carbenoid on the oxygen electron lone pairs forms the oxonium species **4.12** which then undergoes a formal 1,2-shift to form product **4.3**. A direct 1,2-Stevens rearrangement from a chiral catalyst-bound intermediate (**A**), ought lead to product with some enantioselection. In addition, breakdown of the ylide and subsequent stereospecific attack of the metal bound tight ion pair (pathway **B**) would also lead to stereochemical induction. As no enantiomeric excess is observed using the chiral Rh catalyst, pathways **A** and **B** can be disregarded.

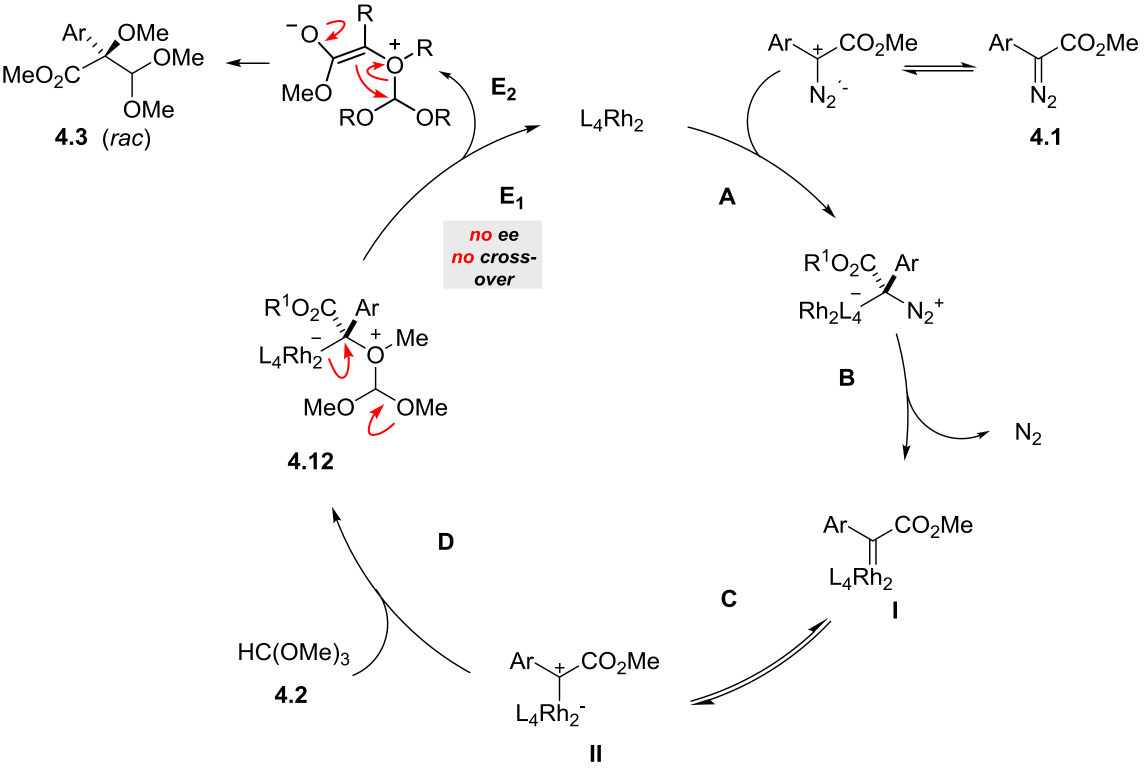
Pathways **C** and **D** involve reversible formation of a planar enolate, thereby losing all stereochemical information.[120] C–C bond formation can either occur through a [1,2]-Stevens rearrangement[135] or a stepwise process involving formation of an ion pair.[136] We initially favoured separation of the intermediate, as three component couplings, involving interception of the ylide by external electrophiles, are well established and thermodynamically feasible considering the high stability of dialkylcarbonium ions.[137]



Scheme 4.25. Migration of the oxonium ylide and abstraction of the rhodium catalyst.

We reasoned that a simple cross-over experiment, employing a 1:1 mixture of undeuterated (**[^{2}H]$_0$-2**) and fully deuterated (**[^{2}H]$_{10}$-2**) trimethyl ortho ester, could elucidate this difference as observation of mixed products, such as D$_3$-methoxy/dimethylacetal (**[^{2}H]$_3$-3a**) and methoxy/D$_7$-dimethylacetal (**[^{2}H]$_7$-3a**), would indicate a separation of the catalytic intermediate into an ion pair. We tested the reaction in four different solvents of varying polarity, which would affect the tightness of the ion pair and thus the degree of cross-over, and found (ESI-MS) no evidence of any mixed products. Therefore, this strongly indicates that the concerted pathway **C** is operational.

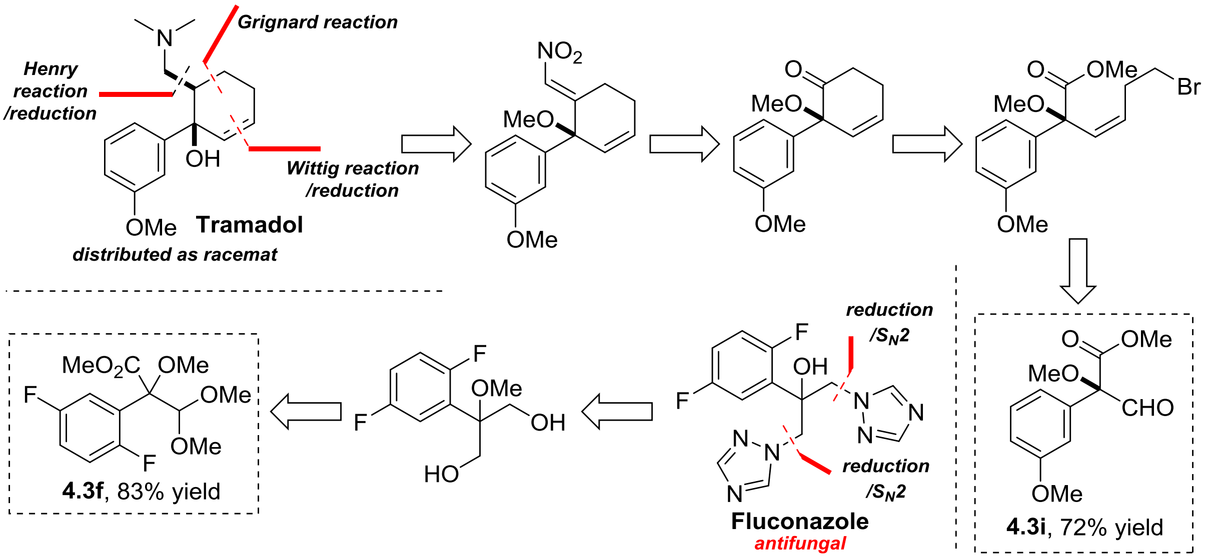
Scheme 4.26 depicts a plausible catalytic cycle for the rhodium(II)-catalyzed methoxylation/acetalization of donor/acceptor substituted diazo compounds. At the outset of the catalytic cycle the vacant axial site of the rhodium(II) catalyst coordinates to the zwitterionic form of diazo compound **4.1** (**A**). Nitrogen extrusion (**B**) results in the formation of carbenoid species **I** and **II** (**C**) which exist in equilibrium. In step **D**, the Lewis-basic oxygen atom attacks the electron-deficient carbenium of complex **II** and forms oxonium species **4.12**. Eventually, liberation of the rhodium catalyst closes the catalytic cycle (**E$_1$**). The final C–C bond formation (**E$_2$**) proceeds in an off cycle process *via* a zwitterionic enolate species that can rearrange to racemic product **4.3** through a an intramolecular 1,2-shift.



Scheme 4.26. Proposed catalytic cycle.

4.5 Conclusion and outlook

The developed methodology allows for the rapid creation of highly value-added molecular architectures from inexpensive chemical commodities. Academically the intermolecular C−O/C−C bond formation of trimethyl formate reveals a novel reactivity of this vastly used compound. In the net reaction almost full atom-economy is achieved. The only expelled waste product is nitrogen gas. From an industrial point of view, the created scaffolds offer new opportunities for revised syntheses of important pharmaceuticals and their derivatives. Tramadol, a sever pain-relieving agent often used in cancer therapy and anti-fungal fluconazole that was listed among the essential drugs by the world health organization (WHO) represent only two examples for potential applications (Scheme 4.27). As a future endeavor, it is desirable to develop a chiral version of the presented transformation.



Scheme 4.27. Proposed retrosynthetic analysis for the synthesis of *O*-methyl tramadol from 4.3i and *O*-methyl fluconazole from 4.3f.

5 Summary

In times of growing environmental awareness and shortage of resources, sustainable synthesis of chemical commodities constitutes a primary goal. In the past decades, transition metal catalysis undoubtedly largely contributed to streamline the synthesis of organic molecules, especially in the field of direct C−C coupling chemistry, thus often supplying a more sustainable approach than traditional coupling reactions

This thesis summarizes the development of new transformations for the transition metal-catalyzed introduction of carbon monoxide and alternative C1-building blocks into molecular scaffolds *via* the direct functionalization of C−H and C−O bonds. The developed methodologies provide with novel opportunities for the implementation of functional groups and expand the molecular space of organic buildings block synthesis. The presented strategies are characterized by their (i) high over-all atom-economy, (ii) minimal waste generation and (iii) capability to supply rapid access value-added molecular architectures.

The first chapter described the development of carbonylative arylations of (hetero)arenes through direct sp^2-C−H bond activation, initiated by an inexpensive ruthenium catalyst precursor. This facile three component synthesis of complex aryl-heteroaryl ketones proceeded *via* successive twofold $C(sp^2)-C(sp^2)$ bond formation in an aqueous reaction medium and describes a conceptually new path for the construction of benzophenone derivatives. Starting with simple phenylpyridine derivatives, this chemistry was later extended to the preparation of aryl-heteroaryl ketones including examples with cleavable directing groups. The synthetic applicability of the developed methodology has been demonstrated in the streamlined synthesis of an unprecedented analog of the top-selling selective estrogen receptor modulator Raloxifene (Evista®) and the gram-scale synthesis of a key intermediate of marinopyrroles and pyoluteorin.

In the next part, a conceptually different approach for the implementation of a formal C1-building block in an aldehyde oxidation state by means of sp^3-C−H bond activation has been investigated. The rhodium(II)-catalyzed insertion of donor-acceptor substituted carbenoids into one of the six chemically equivalent C−H bonds of 1,3,5-trioxane provided access to a novel substance class of chiral alkyl 2-phenyl-2-(1,3,5-trioxan-2-yl)acetates. Because of its structural relation to naturally occurring arylpropionates such as atropine and artificial methylphenidates, this substance class holds great promise as valuable building blocks for medicinal chemistry.

In a subsequent work, the rhodium(II)-catalyzed decomposition of methyl-sulfonyl-1,4-triazoles in the presence of 1,3,5-trioxane was studied. In this reaction, ylide formation of the oxygen-heterocycle with the rhodium-carbenoid species outcompetes the C−H bond functionalization pathway. Successful optimization of the reaction condition allowed for the one-pot preparation of unprecedented nine-membered 1,3,5,7-trioxazonine rings.

Finally, a conceptually new approach for the concomitant alkoxylation/formylation of diazo compounds, mediated by rhodium(II) catalysts has been developed. There are basically no straightforward procedures known that supply direct synthetic access to α-carbonyl-α-methoxy arylpropionic acids. Hence, the developed methodology for the one step synthesis of quaternary carbon centers bearing an aryl or alkenyl, alkoxy, masked aldehyde and ester functionality from inexpensive chemical commodities, constitutes a conceptual advancement compared to existing procedures.

Noteworthy, besides the relatively high costs of rhodium, the reactions described in Chapter 2, 3 and 4 proceed with almost full atom-economy, generating nitrogen as the sole by-product.

The presented results are expected to stimulate further research interest for the development of powerful methodologies for the straightforward functionalization of organic molecules.

6 Experimental section

6.1 General remarks

All reactions involving moisture- or air-sensitive reagents or products were performed under an atmosphere of dry argon using standard Schlenk techniques and predried glassware. Syringes for handling of dry solvents or liquid reagents were flushed with dry argon prior to use. Analytical data of substances that are known in literature (marked by corresponding references) were compared with those described in the literature.

Solvents

All solvents for reactions containing moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (argon or nitrogen) according to following standard procedures.

***N*,*N*-Dimethylacetamide** was dried over KH and distilled under ambient pressure.

***N*,*N*-Dimethylformamide** was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.

Methanol was dried over Mg and refluxed prior to distillation.

***N*-Methyl-2-pyrrolidone** was stirred at 150 °C for 4 h and subsequently distilled under reduced pressure.

Tetrahydrofuran using a SPS solvent purification system by MBRAUN.

Toluene was pre-dried over KH and distilled over sodium/benzophenone.

Water was degassed for 2 h and ultrasonicated.

1,2-Dichloroethane was pre-dried over molecular sieves 4Å, distilled and stored over molecular sieves.

Commercially available dry solvents were purchased from SIGMA-ALDRICH and ACROS ORGANICS.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under ultraviolet light (254 nm) and developed by treatment with the $KMnO_4$ solution or Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.063-0.200 mm, 70–230 mesh ASTM).

Vacuum

Following pressures were measured on the used vaccuum pump and are not corrected: membrane pump vacuum (MPV): 3.1 mbar, oil pump vacuum (OPV): 0.05 mbar.

Analytical Data

Analytical data of substances that are known in literature (marked by corresponding references) were compared with those described in the literature.

Infrared Spectroscopy

Infrared spectra were recorded using a BRUKER ALPHA-P spectrometer. Liquid probes were measured as film, solid probes were measured neat. Absorption is given in wave numbers (cm-1). Spectra were recorded in the range of 4000–400 cm-1. Following abbreviations were used for characterization: s (strong), m (medium), w (weak).

Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectra were recorded at 300 or 600 MHz (1H-NMR) and 75 or 125 MHz (13C-NMR, APT (Attached Proton Test) on BRUCKER AM 250, VARIAN Unity-300 and Inova 500 instruments. Chemical shifts are reported as *δ*-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively.

	^{1}H-NMR	^{13}C-NMR
d_1-Chloroform	7.26 ppm,	77.0 ppm
d_6-DMSO	2.49 ppm 7	7.0 ppm

For characterization of the observed signal multiplicities the following abbreviations were applied: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants *J* are reported in Hertz (Hz).

Mass spectroscopy

Mass spectra were measured on FINNIGAN MAT 95 (200 eV, EI-MS) or LCQ (70 eV, ESI-MS). The ratio of mass to charge are indicated, intensities relative to the base peak (I = 100) are written in parentheses. High resolution mass spectras (HRMS) were recorded on BRUKER APEX IV (7 T, Transform Ion Cyclotron Resonance (FTICR) mass spectrometer).

Melting Points

Melting points were measured using a BÜCHI melting point apparatus. Reported values are uncorrected.

Crystallographic data

Crystallographic data were collected on a BRUKER KAPPA APEX II DUO diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares procedures on F^2 with the SHELXTL software package (Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112.). XP (BRUKER

AXS) was used for graphical representation. Displacement ellipsoids are drawn at the 30% probability level.

High-pressure reactions

High-pressure reactions were carried out in WEATHON screw capped glass vials (5 mL) with silicone/PTFE septum, equipped with a magnetic stirring bar and a needle. The reaction mixtures were placed in a PARR 300 mL stainless steel autoclave and pressurized with carbon monoxide (LINDE).

6.2 General procedures

General procedure A: Ruthenium-catalyzed carbonylative direct arylation

A glass vial (4 mL) was charged with [RuCl$_2$(cod)] polymer (5.0 mmol%), $NaHCO_3$ (2.0 equiv.) and KOAc (20 mol%) and a stirring bar. The vial was placed into an alloy plate, equipped with a septum and an inlet needle, evacuated and backfilled with argon before 2-(aryl)pyridine (2.0 equiv.), iodoarene **1.2** (1.0 equiv.) and degassed H_2O (1.0 mL) were added. The alloy plate with six vials was then placed in an autoclave (300 mL, Parr Instruments 4560 series). At room temperature, the autoclave was flushed with CO (3 x 5 bar) and finally pressurized with CO (30 bar). The autoclave was heated to 120 °C for 16 , cooled to room temperature, and the remaining CO was released slowly. The apparatus was flushed with nitrogen with vigorous stirring. The reaction mixture was further diluted with EtOAc (5 mL) and H_2O (5 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layer were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash-chromatography (*n*-heptane/EtOAc).

General procedure B: Ruthenium-catalyzed carbonylative direct arylation of heteroarenes

A glass vial (4 mL) was charged with [RuCl$_2$(cod)] polymer (5.0 mmol%), $NaHCO_3$ (2.0 equiv.) and KOAc (20 mol%) and a stirring bar. The vial was placed into an alloy plate, equipped with a septum and an inlet needle, evacuated and backfilled with argon before 2-(heteroaryl)pyridine (1.0 equiv.), iodoarene **1.2** (2.0 equiv.) and degassed H_2O (1.0 mL) were added. The following procedures is analogues to general procedure **A**.

General Procedure C: Synthesis of 2-(aryl)-2-diazoacetates

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 equiv.) was added dropwise to a stirring solution methyl phenyl acetate (1.0 equiv.) and TsN_3 (1.2 equiv.) in MeCN (0.3 M) at 0°C under inert atmosphere. The reaction was allowed to warm to ambient temperature and stirred over night. All volatiles were removed under reduced pressure and the crude product was purified by flash chromatography (*n*-pentane:EtOAc). All diazo compounds were stored at -18°C.

General Procedure D: Rhodium-catalyzed synthesis of alkyl 2-aryl-2-(1,3,5-trioxan-2-yl)acetates

A solution of methyl 2-aryl-2-diazoacetate **2.1** (1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (1.0 mol%) and 1,3,5-trioxane (10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc) yielded the desired product **2.3**.

A racemic sample was prepared using $Rh_2(esp)_2$ (1.0 mol%) at 40°C under otherwise identical reaction conditions.

General procedure E: Rhodium-catalyzed synthesis of 6,7-dihydro-1,3,5,7-trioxazonines

To a solution of triazole **3.1** (1.0 equiv.) in $CHCl_3$ (0.5 M) was added 1,3,5-trioxane **3.2** (5.0 equiv.). The mixture was stirred for 2 min at ambient temperature before $Rh_2(Opiv)_4$ (0.5 mol%) was added. The reaction mixture was stirred at 40 °C for 16 hours. The crude mixture was concentrated under reduced and purified by column chromatography on silica gel (*n*-pentane/EtOAc), concentrated and dried under reduced pressure.

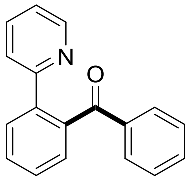
General Procedure F: Rhodium-catalyzed synthesis of methyl 2-(aryl)-2,3,3-trimethoxypropanoates

Over the course of one hour, 2 mL of a 0.2 M solution of alkyl 2-(aryl)-2-diazoacetate **4.1** (1.0 equiv.) and trimethyl orthoformate **4.2** (2.5 equiv.) in dichloromethane was added dropwise to a stirring solution of Rh_2(*S*-pttl)$_4$ (1.0 mol%) and trimethyl orthoformate **4.2** (2.5 equiv.) in dichloromethane (0.3 mL) at room temperature. The crude mixture was concentrated and purified by flash chromatography (*n*-pentane/EtOAc = 20:1). The desired product **4.3** was concentrated and dried under reduced pressure.

6.2.1 Experimental part to Chapter 1

This project has been done in collaboration with *Dr. Anis Tlili*.

Synthesis of (2-phenyl(2-(pyridin-2'-yl)phenyl)methanone (1.3a)



1.3a

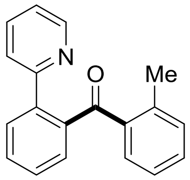
Following general procedure **A**, **1.3a** was isolated as white solid (80 mg, 0.30 mmol, 62%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.36 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, CH), 7.79–7.74 (m, 1H, CH), 7.71–7.65 (m, 2H, CH), 7.64–7.46 (m, 5H, CH), 7.38 (ddt, *J* = 8.2, 6.7, 1.4 Hz, 1H, CH), 7.30–7.22 (m, 2H, CH), 7.01 (ddd, *J* = 7.3, 4.9, 1.3 Hz, 1H, CH).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 198.3 (CO), 156.8 (C_q), 149.1 (CH), 139.7 (C_q), 139.5 (C_q), 137.9 (C_q), 136.3 (CH), 132.4 (CH), 130.2 (CH), 129.5 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 122.7 (CH), 122.0 (CH).

HR-MS (EI) *m*/z calcd. for $C_{18}H_{14}NO$ $[M+H]^+$: 260.1069; found: 260.1074.

Synthesis of (2-(pyridin-2'-yl)phenyl)(o-tolyl)methanone (1.3b)



1.3b

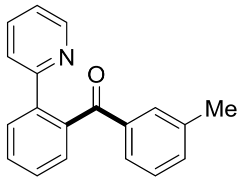
Following general procedure **A**, **1.3b** was isolated as yellow oil (101 mg, 0.37 mmol, 74%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8,43 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.68–7.51 (m, 5H), 7.41 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.11–7.06 (m, 1H), 7.01 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 6.97–6.90 (m, 1H), 2.58 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 199.2 (CO), 157.5 (C_q), 148.8 (CH), 140.7 (C_q), 140.2 (C_q), 139.2 (C_q), 138.1 (C_q), 136.2 (CH), 131.2 (CH), 131.0 (CH), 130.5 (CH), 130.5 (CH), 129.8 (CH), 129.1 (CH), 128.5 (CH), 124.8 (CH), 122.6 (CH), 121.8 (CH), 21.1 (CH_3).

HR-MS (EI) *m*/z calcd. for $C_{19}H_{16}NO$ $[M+H]^+$: 274.1226; found: 274.1226.

Synthesis of (2-(pyridin-2'-yl)phenyl)(m-tolyl)methanone (1.3c)



1.3c

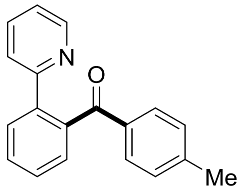
Following general procedure **A**, **1.3c** was isolated as yellow oil (71 mg, 0.26 mmol, 52%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.39 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.79–7.73 (m, 1H), 7.63–7.43 (m, 8H), 7.23–7.10 (m, 2H), 7.02 (ddd, *J* = 7.4, 4.9, 1.3 Hz, 1H), 2.27 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 197.3 (CO), 155.9 (C_q), 147.9 (CH), 138.6 (C_q), 138.5 (C_q), 136.7 (C_q), 136.7 (C_q), 135.3 (CH), 132.2 (CH), 129.1 (CH), 128.9 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 126.9 (CH), 125.9 (CH), 121.8 (CH), 120.9 (CH), 20.2 (CH_3).

HR-MS (EI) *m*/z calcd. for $C_{19}H_{16}NO$ $[M+H]^+$: 274.1226; found: 274.1223.

Synthesis of (2-(pyridin-2'-yl)phenyl)(p-tolyl)methanone (1.3d)



1.3d

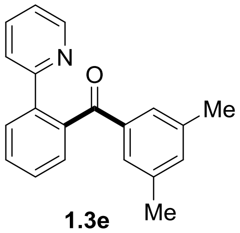
Following general procedure **A**, **1.3d** was isolated as yellow oil (73 mg, 0.27 mmol, 54%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.40 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H, CH), 7.77 (dt, *J* = 7.6, 1.0 Hz, 1H, CH), 7.63–7.54 (m, 4H, CH), 7.53–7.46 (m, 3H, CH), 7.10–7.01 (m, 3H, CH), 2.32 (s, 3H, CH_3).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 197.9 (CO), 156.9 (C_q), 149.1 (CH), 143.1 (C_q), 136.3 (CH), 135.3 (C_q), 130.1 (C_q), 130.1 (CH), 129.8 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 122.9 (CH), 122.0 (CH), 21.6 (CH_3).

HR-MS (EI) *m*/z calcd. for $C_{19}H_{16}NO$ $[M+H]^+$: 274.1226; found: 274.1225.

Synthesis of (3,5-dimethylphenyl)(2-(pyridin-2’-yl)phenyl)methanone (1.3e)



1.3e

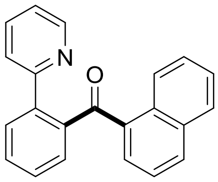
Following general procedure **A**, **1.3e** was isolated as yellow oil (79 mg, 0.27 mmol, 55%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.43 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, CH), 7.76 (dt, *J* = 7.6, 1.0 Hz, 1H, CH), 7.72–7.49 (m, 5H, CH), 7.45 (dt, *J* = 7.9, 1.1 Hz, 1H, CH), 7.36–7.28 (m, 2H, CH), 7.08–7.00 (m, 2H, CH), 2.23 (q, *J* = 0.7 Hz, 6H, CH_3).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 198.5 (CO), 157.1 (C_q), 149.0 , 139.8 (C_q), 139.7 (C_q), 137.7 (C_q), 136.3 (CH), 134.3 (CH), 130.2 (CH), 129.1 (CH), 129.1 (CH), 128.4 (CH), 127.6 (CH), 123.0 (CH), 122.0 (CH), 21.1(CH_3).

HRMS (EI, m/z) calcd. For $C_{20}H_{18}NO$ $[M+H]^+$: 288.1382; found: 288.1382.

Synthesis of (2-naphthalen-1-yl(2-(pyridin-2-yl)phenyl)methanone (1.3f)



1.3f

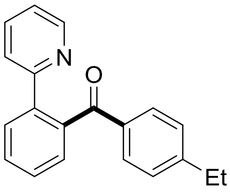
Following general procedure **A**, **1.3f** was isolated as white solid (86 mg, 0.28 mmol, 56%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.90 (dq, *J* = 8.7, 0.9 Hz, 1H, CH), 8.20–8.12 (m, 1H, CH), 7.80–7.68 (m, 4H, CH), 7.66–7.60 (m, 2H, CH), 7.59–7.50 (m, 2H, CH), 7.43–7.32 (m, 3H, CH), 7.16 (dd, *J* = 8.2, 7.2 Hz, 1H, CH), 6.77 (ddd, *J* = 6.8, 4.9, 1.9 Hz, 1H, CH).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 199.6 (CO), 157.0 (C_q), 148.9 (CH), 140.3 (C_q), 136.3 (C_q), 136.2 (CH), 133.6 (C_q), 132.4 (CH), 131.0 (CH), 130.7 (CH), 130.2 (CH), 129.7 (CH), 129.0 (CH), 128.6 (CH), 128.1 (CH), 127.7 (CH), 126.5 (CH), 126.3 (CH), 123.8 (CH), 122.4 (CH), 121.5 (CH).

HR-MS (EI) *m*/z calcd. for $C_{22}H_{15}NO$ $[M+H]^+$: 309.1148; found: 309.1139.

Synthesis of (4-ethylphenyl)(2-(pyridin-2'-yl)phenyl)methanone (1.3g)



1.3g

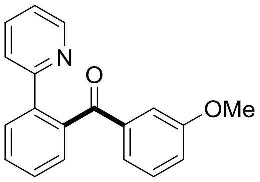
Following general procedure **A**, **1.3g** was isolated as yellow oil (87 mg, 0.30 mmol, 61%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.40 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H, CH), 7.77 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.66–7.45 (m, 7H, CH), 7.13–7.07 (m, 2H, CH), 7.03 (ddd, *J* = 7.4, 4.9, 1.3 Hz, 1H, CH), 2.61 (q, *J* = 7.6 Hz, 2H, CH_2), 1.18 (t, *J* = 7.6 Hz, 3H, CH_3).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 197.7 (CO), 157.0 (C_q), 149.3 (C_q), 149.1 (CH), 139.7 (C_q), 139.7 (C_q), 136.3 (CH), 135.5 (C_q), 130.1 (CH), 129.9 (CH), 129.0 (CH), 128.4 (CH), 127.6 (CH), 122.9 (CH), 121.9 (CH), 28.9 (CH_2), 15.2 (CH_3).

HR-MS (EI) *m*/z calcd. for $C_{20}H_{17}NO$ $[M+H]^+$: 288.1382; found: 288.1381.

Synthesis of (2-(3-methoxyphenyl)(2-(pyridin-2'-yl)phenyl)methanone (1.3i)



1.3i

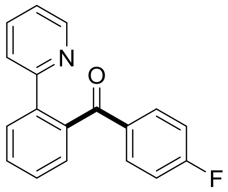
Following general procedure **A**, **1.3i** was isolated as yellow oil (59 mg, 0.20 mmol, 41%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.37 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, CH), 7.82–7.72 (m, 1H, CH), 7.63–7.47 (m, 5H, CH), 7.33 (ddd, *J* = 2.7, 1.4, 0.6 Hz, 1H, CH), 7.20–7.09 (m, 2H, CH), 7.02 (ddd, *J* = 7.4, 4.9, 1.3 Hz, 1H, CH), 6.94 (ddd, *J* = 7.3, 2.7, 1.8 Hz, 1H, CH), 3.77 (s, 3H, CH_3).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 198.0 (CO), 159.4 (C_q), 156.8 (C_q), 149.1 (CH), 139.6 (C_q), 139.5 (C_q), 139.3 (C_q), 136.4 (CH), 130.2 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 122.7 (CH), 122.6 (CH), 122.0 (CH), 119.2 (CH), 113.1 (CH), 55.4 (CH_3).

HR-MS (EI) *m*/z calcd. for $C_{19}H_{15}NO_2$ $[M+H]^+$: 289.1097; found: 289.1096.

Synthesis of (4-fluorophenyl)(2-(pyridin-2-yl)phenyl)methanone (1.3j)



1.3j

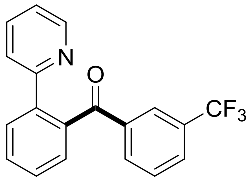
1 Following general procedure **A**, **1.3j** was isolated as yellow oil (55 mg, 0.20 mmol, 40%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.35 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, CH), 7.76 (dt, *J* = 7.7, 1.0 Hz, 1H, CH), 7.76–7.63 (m, 2H, CH), 7.68–7.52 (m, 2H, CH), 7.57–7.44 (m, 3H, CH), 7.03 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H, CH), 7.00–6.84 (m, 2H, CH).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 196.8 (CO), 165.1 (d, $^1J_{C-F}$ = 253.5 Hz, C_q), 156.6 (C_q), 149.1 (CH), 139.4 (d, $^2J_{C-F}$ = 23.0 Hz, C_q), 136.4 (CH), 134.4 (d, $^4J_{C-F}$ = 3.0 Hz, C_q), 132.0 (d, $^3J_{C-F}$ = 9.2 Hz, CH), 130.35 (CH), 129.01 (CH), 128.78 (CH), 128.64 (CH), 125.0 (C_q), 122.4 (d, JC-F = 41.7 Hz, CH), 115.3 (CH), 115.0 (CH).

HR-MS (EI) *m*/z calcd. for $C_{18}H_{12}NOF$ [M+H]$^+$: 277.0897; found: 277.0896.

Synthesis of (2-(pyridin-2'-yl)phenyl)(3-(trifluoromethyl)phenyl)methanone (1.3k)



1.3k

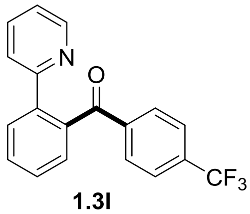
Following general procedure A, **1.3**k was isolated as yellow oil (88 mg, 0.27 mmol, 54%).

^{1}H-NMR (300 MHz, Chloroform-*d*) δ = 8.27 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H, CH), 7.92 (tt, *J* = 1.7, 0.8 Hz, 1H, CH), 7.82 (dddd, *J* = 7.9, 1.9, 1.3, 0.7 Hz, 1H, CH, CH), 7.78 (dt, *J* = 7.7, 1.0 Hz, 1H, CH), 7.66–7.52 (m, 6H, CH), 7.37 (ddt, *J* = 8.5, 7.0, 0.7 Hz, 1H), 6.99 (ddd, *J* = 6.7, 4.9, 1.9 Hz, 1H, CH).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 196.7 (CO), 156.3 (C_q), 148.9 (CH), 139.6 (C_q), 138.8 (C_q), 138.6 (C_q), 136.6 (CH), 132.3 (CH), 130.7 (CH), 130.5 (q, $^2J_{C-F}$ = 32.7 Hz, C_q), 130.3 (C_q), 129.3 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.4 (q, $^4J_{C-F}$ = 3.5 Hz, CH), 125.83 (q, $^4J_{C-F}$ = 3.9 Hz, CH), 122.3 (CH), 122.2 (CH).

HR-MS (EI) *m*/z calcd. for $C_{19}H_{15}NOF_3$ [M+H]$^+$: 327.0863; found: 327.0865.

Synthesis of (2-(pyridin-2'-yl)phenyl)(4-(trifluoromethyl)phenyl)methanone (1.3l)



1.3l

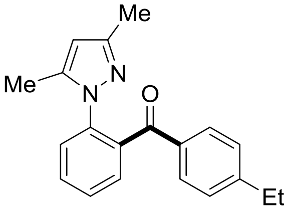
Following general procedure **A**, **1.3l** was isolated as yellow oil (75 mg, 0.23 mmol, 46%).

^{1}**H NMR** (300 MHz, Chloroform-*d*) δ = 8.28 (ddd, *J* = 4.9, 1.7, 1.1 Hz, 1H), 7.78 (dddd, *J* = 6.8, 5.9, 1.8, 0.9 Hz, 3H), 7.67–7.56 (m, 3H), 7.56–7.48 (m, 4H), 7.01 (ddd, *J* = 6.7, 4.9, 1.9 Hz, 1H).

^{13}**C NMR** (75 MHz, Chloroform-*d*) δ = 197.0 (CO), 156.1 (C_q), 148.9 (CH), 141.1 (C_q), 139.4 (C_q), 138.9 (C_q), 136.7 (CH), 133.3 (d, *J* = 32.5 Hz, CH), 130.6 (CH), 129.4 (CH), 129.2 (CH), 128.8 (CH), 128.4 (CH), 125.0 (q, JC-F = 3.5 Hz, C_q), 122.2 (CH), 122.2 (CH).

HR-MS (EI) *m*/z calcd. for $C_{18}H_{12}NOF_3$ $[M+H]^+$: 327.0865; found: 327.0862.

Synthesis of 2-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)(4-ethylphenyl)-methanone (1.5a)



1.5a

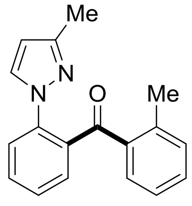
Following general procedure **A**, **1.5a** was isolated as a colorless oil (64 mg, 0.21 mmol, 42%).

^{1}**H NMR** (300 MHz, Chloroform-*d*) *δ* = 7.65–7.57 (m, 1H), 7.54–7.46 (m, 2H), 7.43 (ddd, *J* = 7.7, 1.3, 0.6 Hz, 1H), 7.13–7.07 (m, 1H), 5.6 –5.59 (m, 1H), 2.62 (q, *J* = 7.6 Hz, 1H), 2.13 (d, *J* = 0.8 Hz, 2H), 2.00 (s, 1H), 1.19 (t, *J* = 7.6 Hz, 1H).

^{13}**C NMR** (75 MHz, Chloroform-*d*) δ = 195.5 (CO), 149.6 (Cq), 149.2 (Cq), 140.5 (Cq), 138.1 (Cq), 136.9 (Cq), 134.5 (Cq), 131.1 (CH), 129.9 (CH), 129.4 (CH), 128.1 (CH), 127.3 (CH), 126.9 (CH), 106.4 (CH), 29.0 (CH2) , 15.4 (CH3), 13.2 (CH3), 11.8 (CH3).

HR-MS (EI) *m*/z calcd. for $C_{20}H_{19}ON_2$ $[M+H]^+$: 303.14919; found: 303.1494.

Synthesis of (2-(3‘-Methylpyrazol-1‘-yl)phenyl)(o-tolyl)methanone (1.6a)



1.6a

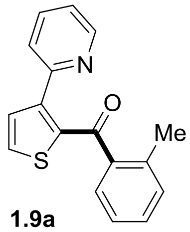
Following general procedure **A**, **1.6a** was isolated as a colorless oil (55 mg, 0.20 mmol, 40%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.68 (ddd, *J* = 7.5, 1.6, 0.6 Hz, 1H), 7.59 (td, *J* = 7.7, 1.6 Hz, 1H), 7.50–7.41 (m, 2H), 7.41–7.38 (m, 1H), 7.19 (ddd, *J* = 7.5, 6.9, 1.6 Hz, 1H), 7.14–7.09 (m, 1H), 6.99 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.92 (dddd, *J* = 8.4, 6.9, 1.5, 0.6 Hz, 1H), 5.89–5.81 (m, 1H), 2.60 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 197.2 (CO), 150.4 (Cq), 139.3 (Cq), 139.1 (Cq), 137.0 (Cq), 135.1 (Cq), 131.5 (CH), 131.2 (CH), 131.1 (CH), 130.6 (CH), 129.7 (CH), 129.5 (CH), 127.4 (CH), 124.6 (CH), 123.0 (CH), 107.5 (CH), 21.1 (CH3), 13.2 (CH3); HRMS

HR-MS (EI) *m*/z calcd. for $C_{19}H_{15}ON_2$ $[M+H]^+$: 275.1180; found: 275.1180.

Synthesis of (3-(pyridin-2-yl)thiophen-2-yl)(o-tolyl)methanone (1.9a)



1.9a

m.p.: 76-77 °C

^{1}H NMR (500 MHz, Chloroform-*d*) *δ* = 8.40 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.64 (d, *J* = 5.0 Hz, 1H), 7.40 (ddd, *J* = 7.7, 7.7,1.8 Hz, 1H), 7.39 (d, *J* = 5.0 Hz, 1H), 7.20 (ddd, *J* = 7.8, 1.1, 1.0 Hz, 2H), 7.12 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H), 7.06 (ddt, *J* = 7.7, 1.4, 0.7 Hz, 1H), 6.99 (ddd, *J* = 7.6, 4.9, 1.1 Hz, 1H), 6.88 (ddd, *J* = 7.8, 7.7,1.7 Hz, 1H), 2.45 (s, 3H).

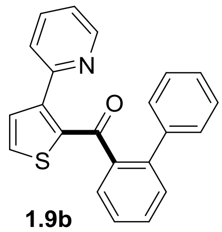
^{13}C NMR (126 MHz, Chloroform-*d*) *δ* = 191.3 (C_q), 153.4 (C_q), 149.0 (CH), 146.1 (C_q), 140.7 (C_q), 138.6 (C_q), 137.5 (C_q), 135.4 (CH), 131.2 (CH), 130.7 (CH), 130.6 (CH), 130.5 (CH), 129.2 (CH), 124.7 (CH), 124.2 (CH), 122.0 (CH), 20.1 (CH_3).

MS (GC-MS) m/z (relative intensity) = 279 (18, $[M^+]$), 250 (69), 236 (100), 217 (11), 188 (20), 160 (15), 116 (10), 91 (31).

HR-MS (EI) m/z calcd for $C_{17}H_{13}NOS^+$ $[M+H]^+$ 279.0712, found 279.0711.

IR (ATR, neat, cm^{-1}): 1632 (m), 1578 (m), 1465 (w), 1402 (m), 1377 (m), 1279 (m), 1255 (m), 863 (m), 791 (m), 749 (s), 737 (s), 646 (s).

Synthesis of [1,1'-biphenyl]-2-yl(3-(pyridin-2-yl)thiophen-2-yl)methanone (1.9b)



1.9b

1.9b was synthesized according to representative procedure **B**, using 2-iodo-1,1'-biphenyl (132 mg, 0.47 mmol) and 2-(thiophen-3-yl)pyridine (1.3 µL, 1.0 mmol). Purification by flash chromatography (PhMe:EtOAc = 20:1 → 15:1) yielded **1.9b** (116 mg, 0.34 mmol, 72%) as a white solid.

m.p.: 128-129 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.30 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.48 – 7.38 (m, 3H), 7.30 – 7.07 (m, 10H), 6.96 (ddd, *J* = 7.6, 4.9, 1.1 Hz, 1H).

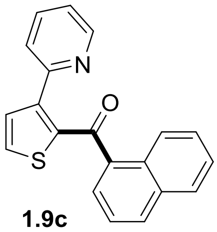
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 191.1 (CO), 153.2 (C_q), 148.9 (CH), 145.8 (C_q), 140.8 (C_q), 140.6 (C_q), 140.0 (C_q), 139.1 (C_q), 135.5 (CH), 131.6 (CH), 130.7 (CH), 130.5 (CH), 130.0 (CH), 129.6 (CH), 129.1 (CH), 128.1 (CH), 127.4 (CH), 126.6 (CH), 124.2 (CH), 122.1 (CH).

MS (GC-MS) *m/z* (relative intensity) = 341 (25) [M^{+}], 312 (29), 280 (100), 236 (65), 188 (30), 160 (17), 152 (65), 89 (15).

HR-MS (ESI-TOF) *m/z* calcd for $C_{22}H_{15}NOS^{+}$ [M+H]$^{+}$ 341.0869, found 341.0868.

IR (ATR, neat, cm^{-1}): 1626 (m), 1469 (w); 1429 (w); 1397 (m), 1296 (w), 1268 (w), 1255 (w), 1246 (w), 861 (m), 743 (s), 737 (s), 704 (m), 646 (m).

Synthesis of naphthalen-1-yl(3-(pyridin-2-yl)thiophen-2-yl)methanone (1.9c)



1.9c

1.9c was synthesized according to representative procedure **B**, using 1-iodonaphthalene (128 mg, 0.50 mmol) and 2-(thiophen-3-yl)pyridine (1.3 µL, 1.0 mmol). Purification by flash chromatography (*n*-pentane:Et_2O = 10:1 → 1:1) yielded **1.9c** (93 mg, 0.30 mmol, 59%) as a pale yellow oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.4 (ddd, *J* = 8.5, 1.4, 0.7 Hz, 1H), 8.1 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H), 7.8 – 7.7 (m, 2H), 7.7 (d, *J* = 5.1 Hz, 1H), 7.6 – 7.4 (m, 3H), 7.4 (d, *J* = 5.1 Hz, 1H), 7.2 – 7.0 (m, 3H), 6.8 (ddd, *J* = 6.8, 4.9, 1.7 Hz, 1H).

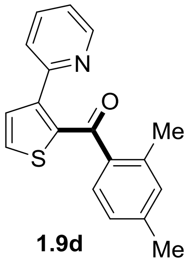
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 190.8 (CO), 153.4 (C_q), 148.9 (CH), 146.4 (C_q), 141.3 (C_q), 136.5 (C_q), 135.3 (CH), 133.4 (C_q), 131.7 (CH), 131.5 (CH), 130.9 (C_q), 130.5 (CH), 128.5 (CH), 128.2 (CH), 127.5 (CH), 126.3 (CH), 125.7 (CH), 123.9 (CH), 1239 (CH), 121.9 (CH).

MS (GC-MS) *m/z* (relative intensity) = 315 (23) [M^+], 286 (100), 254 (8), 237 (18), 188 (9), 127 (15).

HR-MS (ESI-TOF) *m/z* calcd for $C_{20}H_{13}NOS^+$ $[M+H]^+$ 315.0712, found 315.0715.

IR (ATR, neat, cm^{-1}): 1630 (m), 1586 (m), 1507 (w), 1431 (w), 1401 (w), 1284 (m), 1239 (m), 1195 (m), 1148 (w), 884 (m), 781 (s), 768 (s), 741 (s), 613 (m).

Synthesis of (2,4-dimethylphenyl)(3-(pyridin-2-yl)thiophen-2-yl)methanone (1.9d)



1.9d

1.9d was synthesized according to representative procedure **B**, using 1-iodo-2,4-dimethylbenzene (120 mg, 0.52 mmol) and 2-(thiophen-3-yl)pyridine (1.3 µL, 1.0 mmol). Purification by flash chromatography (PhMe/Et_2O = 10:1 → 5:1) yielded **1.9d** (61 mg, 0.21 mmol, 41%) as a yellowish oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.42 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.60 (d, *J* = 5.0 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.18 (ddd, *J* = 7.9, 7.9, 1.0 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.00 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 6.67 (ddd, *J* = 7.8, 1.7, 0.9 Hz, 1H), 2.42 (s, 3H), 2.20 (s, 3H).

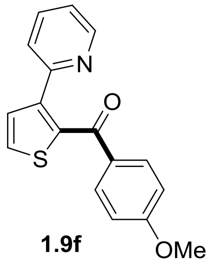
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 191.2 (CO), 153.6 (C_q), 149.1 (CH), 145.8 (C_q), 141.1 (C_q), 140.9 (C_q), 138.0 (C_q), 135.8 (CH), 135.5 (C_q), 131.7 (CH), 130.8 (CH), 130.6 (CH), 130.0 (CH), 125.5 (CH), 124.3 (CH), 121.9 (CH), 21.3 (CH_3), 20.2 (CH_3).

MS (GC-MS) m/z (relative intensity) = 293 (24, [M^+]), 264 (63), 250 (100), 188 (20), 160 (15), 116 (10), 103 (16), 77 (25).

HR-MS (EI) m/z calcd for $C_{18}H_{15}NOS$+ [M+H]+ 293.0869, found 293.0865.

IR (ATR, neat, cm^{-1}): 1632 (s), 1610 (m), 1587 (m), 1432 (m), 1401 (m), 1376 (m), 1278 (s), 1231 (s), 1150 (w), 858 (w), 813 (m), 759 (s), 743 (s), 606 (s).

Synthesis of (4-methoxyphenyl)(3-(pyridin-2-yl)thiophen-2-yl)methanone (1.9f)



1.9f

1.9f was synthesized according to representative procedure **B**, using 4-iodoanisole (117 mg, 0.50 mmol) and 3-(thiophen-2-yl)pyridine (164 mg, 1.0 mmol). Purification by flash chromatography (*n*-hexane/EtOAc = 7:1 → 2:1) yielded **1.9f** (83 mg, 0.28 mmol, 56%) as a off-white solid.

m.p.: 121 °C

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.44 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.67 (d, *J* = 8.9 Hz, 2H), 7.56 (d, *J* = 5.1 Hz, 1H), 7.47 (d, *J* = 5.1 Hz, 1H), 7.42 (ddd, *J* = 7.8, 1.8, 1.8 Hz, 1H), 7.23 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.01 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 6.69 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H).

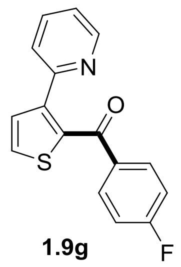
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 188.9 (CO), 163.2 (C_q), 153.5 (C_q), 149.3 (CH), 144.2 (C_q), 138.9 (C_q), 135.8 (CH), 132.1 (CH), 130.6 (C_q), 129.4 (CH), 129.0 (CH), 124.1 (CH), 122.0 (CH), 113.3 (CH), 55.4 (OCH_3).

MS (EI) *m/z* (relative intensity) = 295 (32) [M^+], 266 (100), 223 (13), 188 (14), 92 (8).

HR-MS (EI) *m/z* calcd for $C_{17}H_{13}NO_2S^+$ [M+H]$^+$ 296.0740, found 296.0740.

IR (ATR, neat, cm^{-1}): 1634 (m), 1593 (s), 1573 (m), 1463 (m), 1421 (m), 1288 (m), 1265 (m), 1250 (s), 1173 (s), 1017 (m), 923 (w), 888 (m), 848 (m), 763 (s), 742 (s), 646 (m), 612 (m).

Synthesis of (4-methoxyphenyl)(3-(pyridin-2-yl)thiophen-2-yl)methanone (1.9g)



1.9g

1.9g was synthesized according to representative procedure **B**, using 1-fluoro-4-iodobenzene (117 mg, 0.50 mmol) and 3-(thiophen-2-yl)pyridine (164 mg, 1.0 mmol). Purification by flash chromatography (*n*-hexane/EtOAc = 7:1 → 2:1) yielded **1.9g** (83 mg, 0.28 mmol, 55%) as a pale yellow oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.38 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.67 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.62 (d, *J* = 5.0 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.23 (ddd, *J* = 7.9, 1.0, 1.0 Hz, 1H), 7.02 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.7 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ = 189.1 (CO), 165.5 (d, *J* = 254.2 Hz, C_q), 153.6 (C_q), 149.7 (CH), 145.5 (C_q), 139.0 (C_q), 136.3 (CH), 134.6 (d, *J* = 2.9 Hz, C_q), 132.4 (d, *J* = 9.2 Hz, CH), 130.2 (CH), 129.8 (CH), 124.3 (CH), 122.5 (CH), 115.4 (d, *J* = 22.0 Hz, CH).

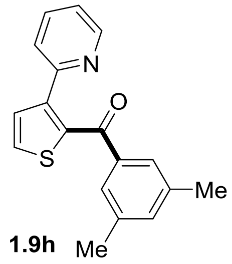
^{19}F{^{1}H} NMR (282 MHz, Chloroform-*d*) δ = -105.94 (s).

MS (EI) *m/z* (relative intensity) = 283 (17) [M$^+$], 254 (100), 188 (16), 116 (5), 95 (15).

HR-MS (EI) *m/z* calcd for $C_{16}H_{10}FNOS^+$ [M+H]$^+$ 284.0540, found 284.0544.

IR (ATR, neat, cm^{-1}): 1634 (m), 1594 (s), 1504 (m), 1411 (m), 1282 (m), 1232 (s), 1153 (s), 907 (m), 907 (m), 878 (m), 725 (s), 602 (s).

Synthesis of (2,4-dimethylphenyl)(3-(pyridin-2-yl)thiophen-2-yl)methanone (1.9h)



1.9h

1.9h was synthesized according to representative procedure **B**, using 1-iodo-3,5-dimethylbenzene (110 mg, 0.47 mmol) and 2-(thiophen-3-yl)pyridine (1.3 µL, 1.0 mmol). Purification by flash chromatography (*n*-pentane:EtOAc = 10:1 → 5:1) yielded **1.9h** (65 mg, 0.22 mmol, 47%) as a brownish oil.

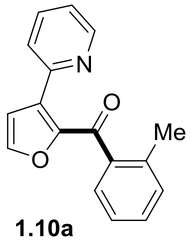
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.37 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.55 (d, *J* = 5.0 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.32 (ddd, *J* = 7.7, 1.8, 1.8 Hz, 1H), 7.18 (q, *J* = 1.2 Hz, 2H), 7.10 (ddd, *J* = 7.9, 7.9, 1.0 Hz, 1H), 6.94 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 6.89 (dd, *J* = 2.4, 0.9 Hz, 1H), 2.09 (s, 6H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 190.3 (CO), 153.8 (C_q), 149.2 (CH), 145.2 (C_q), 139.3 (C_q), 137.7 (C_q), 137.6 (C_q), 135.7 (CH), 134.1 (CH), 130.0 (CH), 129.9 (CH), 127.6 (CH), 124.3 (CH), 122.1 (CH), 21.0 (CH_3).

MS (GC-MS) m/z (relative intensity) = 293 (16, [M^+]), 264 (100), 250 (18), 188 (26), 160 (9), 116 (8), 103 (8), 77 (15).

HR-MS (EI) m/z calcd for $C_{18}H_{15}NOS+$ $[M+H]^+$ 293.0869, found 293.0873.

Synthesis of (3-(pyridin-2-yl)furan-2-yl)(o-tolyl)methanone (1.10a)



1.10a

1.10a was synthesized according to representative procedure **B**, using 2-iodotoluene (109 mg, 0.5 mmol) and 3-(furan-2-yl)pyridine (145 mg, 0.5 mmol). Purification by flash chromatography (*n*-heptane/EtOAc = 20:1 → 5:1) yielded **1.10a** (71 mg, 0.27 mmol, 54%) as a colorless oil.

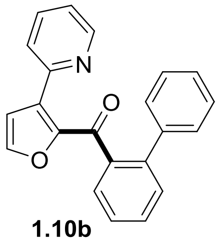
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.61 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.97 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.41 – 7.27 (m, 2H), 7.24 – 7.08 (m, 4H), 2.37 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 187.0 (CO), 150.7 (C_q), 149.4 (CH), 148.2 (C_q), 145.5 (CH), 138.5 (C_q), 137.1 (C_q), 136.1 (CH), 134.9 (C_q), 130.9 (CH), 130.7 (CH), 128.8 (CH), 125.3 (CH), 125.1 (CH), 123.0 (CH), 114.8 (CH), 19.8 (CH_3).

MS (GC-MS) m/z (relative intensity) = 263 (26, [M^+]), 234 (100), 220 (58), 206 (44), 191 (8), 116 (13), 91 (35).

HR-MS (ESI-TOF) m/z calcd for $C_{17}H_{13}NO_2^+$ $[M+H]^+$ 264.1019, found 264.1018.

Synthesis of (3-(pyridin-2-yl)furan-2-yl)(o-tolyl)methanone (1.10b)



1.10b

1.10b was synthesized according to representative procedure **B**, using 2-iodo-1,1'-biphenyl (88 µL, 0.5 mmol) and 3-(furan-2-yl)pyridine (144 mg, 1.0 mmol). Purification by flash chromatography (*n*-heptane/EtOAc = 20:1 → 5:1) yielded **1.10b** (106 mg, 0.33 mmol, 65%) as a yellow oil.

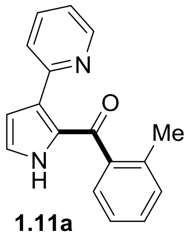
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.55 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.92 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.37 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 7.29 – 7.13 (m, 7H), 6.80 (d, *J* = 1.8 Hz, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 187.5 (CO), 150.4 (C_q), 149.2 (CH), 147.9 (C_q), 145.0 (CH), 141.5 (C_q), 140.1 (C_q), 138.9 (C_q), 136.1 (CH), 133.9 (C_q), 130.9 (CH), 129.9 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 127.5 (CH), 127.2 (CH), 124.7 (CH), 122.9 (CH), 114.3 (CH).

MS (GC-MS) m/z (relative intensity) = 324 (1, [M$^+$]), 296 (100), 268 (11), 220 (5), 152 (17), 104 (8).

HR-MS (EI) m/z calcd for $C_{22}H_{14}NO_2^+$ [M+H]$^+$ 324.1019, found 324.1015.

Synthesis of ((3-(pyridin-2-yl)-1H-pyrrol-2-yl)(o-tolyl)methanone (1.11a)



1.11a

1.11a was synthesized according to representative procedure **B**, using 2-iodotulene (112 mg, 0.51 mmol) and 2-(1*H*-pyrrol-3-yl)pyridine (144 mg, 1.00 mmol). Purification by flash chromatography (cyclohexane/EtOAc = 1:1) yielded **1.11a** (63 mg, 0.24 mmol, 47%) as a colorless solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 9.90 (s, 1H), 8.36 (ddd, *J* = 4.1, 1.7 Hz, 1H), 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 7.13 – 6.99 (m, 4H), 6.90 (m, 2H), 6.82 – 6.73 (m, 1H), 6.59 (dd, *J* = 2.7,2.7 Hz, 1H), 2.36 (s, 3H).

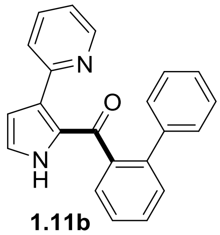
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 188.2 (CO), 153.8 (C_q), 149.0 (CH), 138.9 (C_q), 136.6 (C_q), 134.9 (CH), 133.3 (C_q), 130.4 (CH), 129.9 (CH), 129.1 (C_q), 128.8 (CH), 124.9 (CH), 124.7 (CH), 124.1 (CH), 121.2 (CH), 113.1 (CH), 19.7 (CH_3).

MS (GC-MS) m/z (relative intensity) = 262 (33, [M$^+$]), 247 (24), 233 (100), 219 (57), 204 (6), 167 (10), 116 (15), 91 (14).

HR-MS (EI) m/z calcd for $C_{17}H_{14}N_2O^+$ [M+H]$^+$ 262.1100, found 262.1099.

IR (ATR, neat, cm^{-1}): 1734 (w), 1617 (m), 1588 (s), 1488 (m), 1390 (s), 1329 (w), 1230 (w), 1282 (w), 1240 (w), 1175 (w), 1045 (w), 913 (m), 886 (m), 742 8s), 660 (m).

Synthesis of [1,1'-biphenyl]-2-yl(3-(pyridin-2-yl)-1H-pyrrol-2-yl)methanone (1.11b)



1.11b

1.11b was synthesized according to representative procedure **B**, using 2-iodo-1,1'-biphenyl (146 mg, 0.52 mmol) and 2-(1*H*-pyrrol-3-yl)pyridine (144 mg, 1.00 mmol). Purification by flash chromatography (cyclohexane/EtOAc = 1:1) yielded **1.11b** (107 mg, 0.33 mmol, 63%) as a colorless solid.

m.p.: 168-169 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 9.87 (s, 1H), 8.25 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.40 – 7.20 (m, 8H), 7.17 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.13 – 6.99 (m, 2H), 6.92 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 6.87 (dd, *J* = 2.7 Hz, 1H), 6.41 (dd, *J* = 2.7 Hz, 1H).

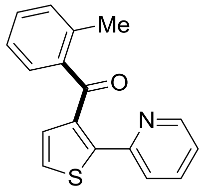
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 188.3 (CO), 153.7 (C_q), 148.7 (CH), 140.7 (C_q), 140.3 (C_q), 139.0 (C_q), 135.2 (CH), 132.7 (C_q), 130.0 (CH), 130.0 (CH), 129.3 (CH), 129.1 (C_q), 129.0 (CH), 128.2 (CH), 127.3 (CH), 126.5 (CH), 124.1 (CH), 123.9 (CH), 121.1 (CH), 112.6 (CH).

MS (GC-MS) m/z (relative intensity) = 324 (42, [M$^+$]), 295 (100), 280 (17), 247 (13), 219 (36), 152 (24), 116 (11).

HR-MS (EI) m/z calcd for $C_{22}H_{16}N_2O^+$ [M+H]$^+$ 324.1257, found 324.1252.

IR (ATR, neat, cm^{-1}): 1618 (m), 1498 (w), 1391 (m), 1334 (m), 1180 (w), 1010 (w), 916 (w), 883 (w), 771 (m), 740 (s), 699 (s), 666 (m), 620 (m).

Synthesis of (2-(pyridin-2-yl)thiophen-3-yl)(o-tolyl)methanone (1.12a)



1.12a

1.12a was synthesized according to representative procedure **B**, using 2-iodotoluene (108 mg, 0.49 mmol) and 2-(thiophen-2-yl)pyridine (164 mg, 1.0 mmol). Purification by flash chromatography (*n*-hexane:EtOAc = 10:1 → 7:1) yielded **1.12a** (79 mg, 0.0.28 mmol, 57%) as a pale yellow solid.

m.p.: 60-63 °C

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.46 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.48 (ddd, J = 8.0, 7.4, 1.8 Hz, 1H), 7.43 (dt, J = 8.0, 1.3 Hz, 1H), 7.36 (d, J = 5.2 Hz, 1H),), 7.35 (m, 1H), 7.23 (m, 1H), 7.23 (d, J = 5.2 Hz, 1H), 7.17 (ddd, J = 7.7, 1.5, 0.7 Hz, 1H), 7.06 (ddd, J = 7.4, 4.9, 1.3 Hz, 1H), 7.02 (ddd, J = 7.4, 7.4, 0.8 Hz, 1H), 2.54 (s, 3H).

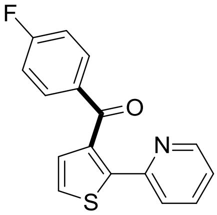
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 194.7 (CO), 151.5 (C_q), 149.3 (CH), 147.5 (C_q), 139.3 (C_q), 138.7 (C_q), 138.4 (C_q), 136.1 (CH), 131.4 (CH), 131.3 (CH), 130.6 (CH), 130.5 (CH), 126.2 (CH), 125.3 (CH), 123.0 (CH), 122.6 (CH), 20.8 (CH_3).

MS (GC-MS) m/z (relative intensity) = 279 (15, [M^+]), 250 (80), 236 (100), 218 (24), 188 (25), 116 (13), 91 (22).

HR-MS (EI) *m/z* calcd for $C_{17}H_{14}NOS^+$ $[M+H]^+$ 280.0790, found 280.0789.

IR (ATR, neat, cm^{-1}): 1654 (s), 1582 (m), 1421 (m), 1293 (m), 1273 (s), 1246 (m), 1012 (w), 1003 (w), 861 (m), 775 (s), 727 (s), 702 (s), 667 (m).

Synthesis of (4-fluorophenyl)(2-(pyridin-2-yl)thiophen-3-yl)methanone (1.12b)



1.12b

1.12b was synthesized according to representative procedure **B**, using K_2CO_3 (2.0 equiv.) as base, 1-fluoro-4-iodobenzene (117 mg, 0.53 mmol) and 2-(thiophen-2-yl)pyridine (164 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane:Et_2O = 15:1 → 2:1) yielded **1.12b** (67 mg, 0.24 mmol, 45%) as a pale yellow oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.46 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.84 (dd, *J* = 9.0, 5.5 Hz, 1H), 7.49 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.34 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.22 (d, *J* = 5.2 Hz, 1H), 7.08 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.01 (dd, *J* = 9.0, 8.4 Hz, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 192.8 (CO), 166.2 (d, *J* = 255.2 Hz, C_q), 151.7 (C_q), 150.0 (CH), 146.1 (C_q), 138.2 (CH), 136.9 (CH), 134.6 (d, *J* = 3.0 Hz, C_q), 133.0 (CH), 132.9 (CH), 130.3 (CH), 127.3 (CH), 123.0 (d, *J* = 1.9 Hz, C_q), 116.1 (d, *J* = 22.0 Hz, CH).

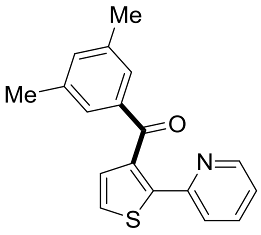
^{19}F NMR (282 MHz, Chloroform-*d*) δ = -104.46 (m).

MS (EI) *m/z* (relative intensity) = 283 (13) [M^+], 254 (100), 188 (20), 116 (5), 95 (15).

HR-MS (EI) *m/z* calcd for $C_{16}H_{11}FNOS^+$ $[M+H]^+$ 284.0540, found 284.0544.

IR (ATR, neat, cm^{-1}): 1658 (m), 1594 (s), 1465 (m), 1279 (s), 1230 (s), 1151 (s), 907 (m), 865 (m), 851 (m), 726 (s), 604 (s).

Synthesis of (3,5-dimethylphenyl)(2-(pyridin-2-yl)thiophen-3-yl)methanone (1.12c)



1.12c

1.12c was synthesized according to representative procedure **B**, using 1-iodo-3,5-dimethylbenzene (117 mg, 0.50 mmol) and 2-(thiophen-2-yl)pyridine (170 mg, 1.1 mmol). Purification by flash chromatography (*n*-pentane:Et_2O = 15:1 → 2:1) yielded **1.12c** (100 mg, 0.34 mmol, 68%) as a pale yellow oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.51 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.47 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.37 (ddd, *J* = 8.0, 1.1, 1.0 Hz, 1H), 7.20 (d, *J* = 5.2 Hz, 1H), 7.13 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.08 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H), 2.27 (s, 6H).

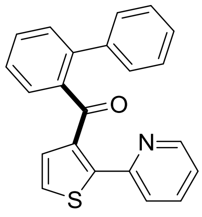
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 194.2 (CO), 151.6 (C_q), 149.5 (CH), 145.9 (C_q), 138.2 (C_q), 138.2 (C_q), 137.7 (C_q), 136.4 (CH), 135.1 (CH), 130.1 (CH), 127.9 (CH), 126.5 (CH), 122.6, (CH), 122.5 (CH), 21.2 (CH_3).

MS (EI) *m/z* (relative intensity) = 293 (16) [M^+], 264 (100), 188 (25), 116 (6), 89 (6).

HR-MS (EI) *m/z* calcd for $C_{18}H_{15}NOS^+$ $[M+H]^+$ 294.0947, found 294.0950.

IR (ATR, neat, cm^{-1}): 1654 (m), 1582 (m), 1465 (m), 1304 (s), 1145 (m), 906 (m), 773 (m), 723 (s), 706 (s).

Synthesis of [1,1'-biphenyl]-2-yl(2-(pyridin-2-yl)thiophen-3-yl)methanone (1.12d)



1.12d

1.12d was synthesized according to representative procedure **B**, using 2-iodo-1,1'-biphenyl (142 mg, 0.52 mmol) and 2-(thiophen-2-yl)pyridine (174 mg, 1.1 mmol). Purification by flash chromatography (*n*-pentane:EtOAc = 5:1 → 1:1) yielded **1.12d** (102 mg, 0.30 mmol, 57%) as a colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.51 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.68 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.64 – 7.52 (m, 2H), 7.46 (ddd, *J* = 7.7, 7.5, 1.5 Hz, 1H), 7.38 (ddd, *J* = 7.6, 7.5, , 1.3 Hz, 1H), 7.33 – 7.18 (m, 7H), 7.16 – 7.10 (m, 2H), 7.06 (dd, *J* = 5.3, 0.6 Hz, 1H).

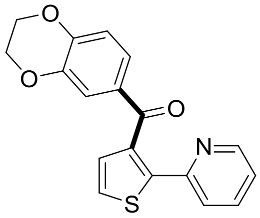
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 194.0 (CO), 151.3 (C_q), 149.1 (CH), 148.7 (C_q), 141.7 (C_q), 140.3 (C_q), 139.8 (C_q), 138.4 (C_q), 136.0 (CH), 131.3 (CH), 130.9 (CH), 130.3 (CH), 129.9 (CH), 129.0 (CH), 128.1 (CH), 127.4 (CH), 127.0 (CH), 125.6 (CH), 123.4 (CH), 122.6 (CH).

MS (EI) *m/z* (relative intensity) = 341 (24) [M$^+$], 312 (100), 280 (30), 236 (74), 188 (30), 152 (36), 116 (12).

HR-MS (EI) *m/z* calcd for $C_{22}H_{15}NOS^+$ [M+H]$^+$ 341.0869, found 341.0868.

IR (ATR, neat, cm^{-1}): 1654 (m), 1581 (w), 1464 (m), 1421 (m), 1279 (s), 858 (m), 777 (m), 742 (m), 696 (s).

Synthesis of (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(2-(pyridin-2-yl)thiophen-3-yl)methanone (1.12e)



1.12e

1.12e was synthesized according to representative procedure **B**, using 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine (148 mg, 0.54 mmol) and 2-(thiophen-2-yl)pyridine (161 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane:EtOAc = 5:1 → 1:1) yielded **1.12e** (90 mg, 0.28 mmol, 57%) as a colorless solid.

m.p.: 137-138 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.49 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.49 (ddd, *J* = 7.9, 7.4, 1.8 Hz, 1H), 7.44 – 7.31 (m, 4H), 7.15 (d, *J* = 5.1 Hz, 1H), 7.07 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 4.29 – 4.24 (m, 2H), 4.23 – 4.19 (m, 2H).

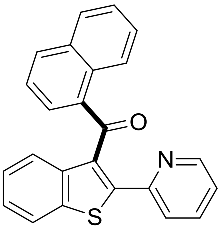
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 192.7 (CO), 151.4 (C_q), 149.5 (CH), 148.4 (C_q), 145.0 (C_q), 143.4 (C_q), 138.0 (C_q), 136.5 (CH), 131.2 (C_q), 129.7 (CH), 126.6 (CH), 124.5 (CH), 122.4 (CH), 122.1 (CH), 119.2 (CH), 117.2 (CH), 64.7 (CH_2), 64.1 (CH_2).

MS (GC-MS) *m/z* (relative intensity) = 323 (31) [M^+], 294 (100), 238 (9), 210 (9), 188 (20), 107 (8).

HR-MS (ESI-TOF) *m/z* calcd for $C_{18}H_{13}NOS^+$ $[M+H]^+$ 324.0689, found 324.0686.

IR (ATR, neat, cm^{-1}): 1641 (m), 1574 (m), 1501 (w), 1464 (m), 1421 (m), 1231 (s), 1279 (s), 1194 (m), 1118 (m), 1061 (m), 885 (s), 778 (s), 735 (s).

Synthesis of naphthalen-1-yl(2-(pyridin-2-yl)benzo[*b*]thiophen-3-yl)methanone (1.14a)



1.14a

1.14a was synthesized according to the described procedure **B**, using 1-iodonaphthalene (120 mg, 0.48 mmol) and 2-(benzothiophen-2-yl)pyridine (211 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane:Et_2O = 20:1 → 5:1) yielded **1.14a** (116 mg, 0.32 mmol, 66%) as a colorless solid.

m.p.: 119 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 9.14 (ddd, *J* = 8.6, 1.0, 1.0 Hz, 1H), 8.26 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.97 – 7.90 (m, 1H), 7.86 (ddt, *J* = 9.2, 7.6, 0.9 Hz, 3H), 7.74 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.49 – 7.29 (m, 4H), 7.19 (dd, *J* = 8.2, 7.2 Hz, 1H), 6.92 (ddd, *J* = 7.4, 4.8, 1.0 Hz, 1H).

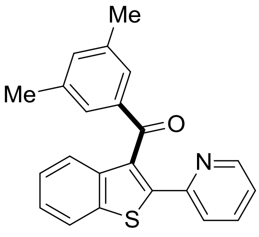
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 195.8 (CO), 151.3 (C_q), 149.3 (CH), 144.9 (C_q), 140.0 (C_q), 139.4 (C_q), 136.3 (CH), 135.9 (C_q), 135.5 (C_q), 133.9 (C_q), 133.5 (CH), 131.3 (C_q), 131.1 (CH), 128.5 (2xCH), 126.7 (CH), 126.3 (CH), 125.9 (CH), 125.5 (CH), 124.4 (CH), 124.1 (CH), 122.8 (CH), 122.7 (CH), 122.4 (CH).

MS (GC-MS) *m/z* (relative intensity) = 365 (29) [M^+], 336 (100), 304 (19), 287 (24), 238 (14), 209 (8), 127 (23).

HR-MS (ESI-TOF) *m/z* calcd for $C_{24}H_{16}NOS^+$ $[M+H]^+$ 366.0947, found 366.0947.

IR (ATR, neat, cm^{-1}): 1654 (s), 1581 (m), 1523 (w), 1507 (w), 1226 (m), 1891 (m), 1113 (m), 959 (w), 881 (m), 735 (s), 746 8s), 723 (s).

Synthesis of (3,5-dimethylphenyl)(2-(pyridin-2-yl)benzo[*b*]thiophen-3-yl)methanone (1.14b)



1.14b

1.14b was synthesized according to representative procedure **B**, using 1-iodo-3,5-dimethylbenzene (120 mg, 0.52 mmol) and 2-(benzothiophen-2-yl)pyridine (211 mg, 1.0 mmol). Purification by flash chromatography (*n*-heptane:EtOAc = 20:1 → 10:1) yielded **1.14b** (113 mg, 0.33 mmol, 64%) as a pale yellow foam.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.52 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.91 (dt, J = 8.2, 0.9 Hz, 1H), 7.60 (ddd, J = 8.2, 8.0, 1.4 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.45 – 7.28 (m, 3H), 7.13 (dq, J = 1.8, 0.9 Hz, 1H), 7.09 (ddd, J = 7.4, 4.8, 1.3 Hz, 1H), 2.24 (s, 6H).

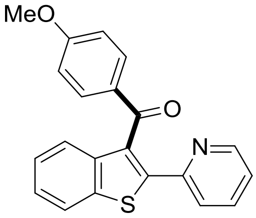
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 195.4 (CO), 151.4 (C_q), 149.6 (CH), 143.8 (C_q), 139.8 (C_q), 139.6 (C_q), 138.4 (C_q), 137.5 (C_q), 136.5 (CH), 135.5 (CH), 133.5 (C_q), 127.6 (CH), 125.7 (CH), 125.1 (CH), 123.8 (CH), 122.9 (CH), 122.7 (CH), 122.4 (CH), 21.2 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 343 (32) [M$^+$], 314 (100), 300 (25), 282 (16), 238 (36), 209 (11), 139 (11).

HR-MS (EI) *m/z* calcd for $C_{22}H_{18}NOS^+$ [M+H]$^+$ 344.1104, found 344.1106.

IR (ATR, neat, cm^{-1}): 1657 (s), 1583 (s), 1429 (m), 1294 (s), 1176 (s), 1160 (m), 846 (m), 767 (s), 722 (s).

Synthesis of (4-methoxyphenyl)(2-(pyridin-2-yl)benzo[b]thiophen-3-yl)methanone (1.14c)



1.14c

1.14c was synthesized according to the described procedure **B**, using 4-iodoanisole (118 mg, 0.50 mmol) and 2-(benzothiophen-2-yl)pyridine (220 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane:Et_2O = 10:1 → 2:1) yielded **1.14c** (84 mg, 0.24 mmol, 49%) as a yellow oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.52 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.95 – 7.79 (m, 3H), 7.58 (ddd, *J* = 7.8, 1.4, 0.8 Hz, 1H), 7.54 – 7.27 (m, 4H), 7.09 (ddd, *J* = 7.1, 4.8, 1.4 Hz, 1H), 6.86 – 6.74 (m, 2H), 3.79 (s, 3H).

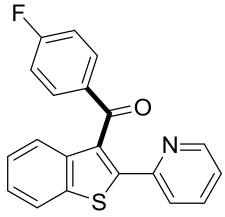
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 193.6 (CO), 164.1 (C_q), 151.4 (C_q), 149.7 (CH), 143.3 (C_q), 139.8 (C_q), 139.6 (C_q), 136.6 (CH), 133.4 (C_q), 132.3 (CH), 130.4 (C_q), 125.7 (CH), 125.1 (CH), 123.7 (CH), 122.9 (CH), 122.6 (CH), 122.4 (CH), 114.0 (CH), 55.6 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 345 (32) [M^+], 316 (100), 273 (12), 273 (16), 209 (7), 135 (6), 77 (7).

HR-MS (ESI-TOF) *m/z* calcd for $C_{21}H_{15}NO_2S^+$ $[M+H]^+$ 345.0818, found 345.0815.

IR (ATR, neat, cm^{-1}): 1649 (m), 1592 (s), 1571 (m), 1507 (m), 1458 (m), 1430 (m), 1420 (m), 1342 (w), 1251 (m), 1236 (s), 1023 (m), 965 (w), 848 (m), 821 (m), 766 (m), 729 (s), 606 (s).

Synthesis of (4-fluorophenyl)(2-(pyridin-2-yl)benzothiophen-3-yl)methanone (1.14d)



1.14d

1.14d was synthesized according to the described procedure **B**, using 1-fluoro-4-iodobenzene (112 mg, 0.50 mmol) and 2-(benzothiophen-2-yl)pyridine (210 mg, 1.0 mmol). Purification by flash chromatography (*n*-heptane:EtOAc = 20:1 → 15:1) yielded **1.14d** (88 mg, 0.26 mmol, 53%) as a colorless solid.

m.p.: 109-110 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.47 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.95 – 7.84 (m, 3H), 7.63 (ddd, *J* = 7.9, 1.7, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 7.43 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 3H), 7.39 (dd, *J* = 2.8, 1.6 Hz, 1H), 7.10 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.00 (dd, *J* = 8.9, 8.3 Hz, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 193.1 (CO), 165.9 (d, *J* = 255.8 Hz, C_q), 151.1 (C_q), 149.5 (CH), 143.7 (C_q), 139.5 (C_q), 139.4 (C_q), 136.5 (CH), 134.0 (d, *J* = 2.9 Hz, C_q), 132.8 (C_q), 132.3 (d, *J* = 9.5 Hz, CH), 125.8 (CH), 125.2 (CH), 123.6 (CH), 122.9 (CH), 122.6 (CH), 122.4 (CH), 115.7 (d, *J* = 22.0 Hz, CH).

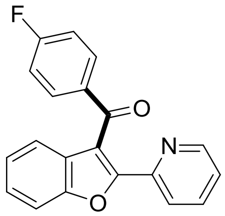
^{19}F NMR (282 MHz, Chloroform-*d*) δ = -103.88 (m).

MS (GC-MS) *m/z* (relative intensity) = 333 (26) [M^+], 304 (100), 238 (23), 209 (8), 95 (16).

HR-MS (ESI-TOF) *m/z* calcd for $C_{20}H_{12}FNOS^+$ $[M+H]^+$ 334.0696, found 334.0699.

IR (ATR, neat, cm^{-1}): 1664 (s), 1583 (m), 1227 (s), 1157 (s), 856 (m), 823 (m), 757 (m), 729 (s), 606 (s).

Synthesis of (4-fluorophenyl)(2-(pyridin-2-yl)benzofuran-3-yl)methanone (1.15a)



1.15a

1.15a was synthesized according to the described procedure **B**, using 1-fluoro-4-iodobenzene (78 mg, 0.35 mmol) and 2-(benzofuran-2-yl)pyridine (137 mg, 1.0 mmol) and [RuCl$_2$(cod)]$_n$ (5.6 mg, 5.7 mol%). Purification by flash chromatography (*n*-heptane:EtOAc = 30:1) yielded **1.15a** (44 mg, 0.14 mmol, 40%) as a colorless solid.

m.p.: 161-162 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.36 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.90 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.82 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.66 (dd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.60 (ddd, *J* = 8.3, 0.9, 0.8 Hz, 1H), 7.52 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H), 7.38 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.11 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 6.99 (dd, *J* = 8.7 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ = 190.9 (C$_q$), 165.7 (d, *J* = 254.7 Hz, C$_q$), 154.3 (C$_q$), 153.6 (C$_q$), 149.7 (C$_q$), 148.1 (CH), 136.5 (CH), 134.6 (d, *J* = 2.9 Hz, C$_q$), 132.1 (d, *J* = 9.2 Hz, CH), 128.2 (C$_q$), 126.2 (CH), 124.1 (CH), 123.5 (CH), 121.8 (CH), 121.2 (CH), 118.1 (C$_q$), 115.5 (d, *J* = 21.9 Hz, CH), 111.7 (CH).

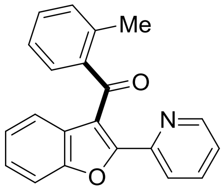
^{19}F NMR (282 MHz, Chloroform-*d*) δ = -104.78 (p, *J* = 8.7 Hz).

MS (EI) *m/z* (relative intensity) = 317 (34) [M$^+$], 288 (100), 222 (16), 140 (5), 95 (15).

HR-MS (ESI-TOF) *m/z* calcd for $C_{20}H_{12}FNO_2^+$ [M+H]$^+$ 318.0925, found 318.0925.

IR (ATR, neat, cm^{-1}): 1655 (m), 1593 (m), 1558 (m), 1234 (s), 1211 (m), 1126 (m), 891 (m), 738 (s), 603 (s).

Synthesis of (2-(pyridin-2-yl)benzofuran-3-yl)(o-tolyl)methanone (1.15b)



1.15b

1.15b was synthesized according to the described procedure **B**, using 2-iodotoluene (110 mg, 0.50 mmol) and 2-(benzofuran-2-yl)pyridine (195 mg, 1.0 mmol). Purification by flash chromatography (PhMe:EtOAc = 20:1) yielded **1.15b** (111 mg, 0.354 mmol, 71%) as colorless oil.

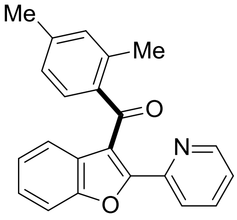
^{1}**H NMR** (300 MHz, Chloroform-*d*) δ = 8.32 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.64 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.60 – 7.47 (m, 3H), 7.34 – 7.12 (m, 5H), 7.01 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.91 – 6.82 (m, 1H), 2.57 (s, 3H).

^{13}**C NMR** (75 MHz, Chloroform-*d*) δ = 194.3 (CO), 155.3 (C_q), 154.0 (C_q), 149.1 (CH), 148.1 (C_q), 139.1 (C_q), 138.7 (C_q), 136.1 (CH), 131.2 (CH), 131.1 (CH), 129.9 (CH), 129.0 (CH), 126.0 (C_q), 125.2 (CH), 124.2 (CH), 123.4 (CH), 122.6 (CH), 121.7 (CH), 119.9 (CH), 111.6 (C_q), 20.7 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 313 (79) [M^+], 296 (45), 284 (100), 268 (45), 222 (26), 166 (16), 140 (23), 91 (37).

HR-MS (ESI-TOF) *m/z* calcd for $C_{21}H_{15}FO_2^+$ $[M+H]^+$ 313.1097, found 313.1095.

Synthesis of (2,4-dimethylphenyl)(2-(pyridin-2-yl)benzofuran-3-yl)methanone (1.15c)



1.15c

1.15c was synthesized according to the described procedure **B**, using 1-iodo-2,4-dimethylbenzene (115 mg, 0.50 mmol) and 2-(benzofuran-2-yl)pyridine (198 mg, 1.0 mmol). Purification by flash chromatography (PhMe:EtOAc = 20:1 → 15:1) yielded **1.15c** (108 mg, 0.33 mmol, 66%) as a colorless oil.

^{1}**H NMR** (300 MHz, Chloroform-*d*) δ = 8.46 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.76 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.39 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.11 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 6.06 (d, *J* = 1.8 Hz, 1H), 6.78 (dd, *J* = 8.0, 2.2, 1.2 Hz, 1H), 2.67 (s, 3H), 2.27 (s, 3H).

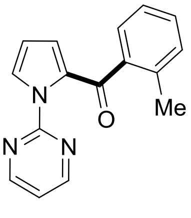
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 194.0 (CO), 154.6 (C_q), 154.2 (C_q), 149.6 (CH), 148.2 (C_q), 141.9 (C_q), 139.2 (C_q), 136.2 (CH), 136.1 (C_q), 132.4 (CH), 130.8 (CH), 128.2 (C_q), 126.0 (CH), 126.0 (CH), 124.1 (CH), 123.4 (CH), 122.5 (CH), 121.6 (CH), 120.3 (C_q), 111.7 (CH), 21.5 (CH_3) 21.0 $(CH)_3$.

MS (GC-MS) m/z (relative intensity) = 327 (100, [M^+]), 310 (75), 298 (98), 284 (70), 254 (9), 222 (29), 166 (16), 140 (25), 103 (22).

HR-MS (EI) m/z calcd for $C_{22}H_{17}NO_2^+$ $[M+H]^+$ 327.1254, found 327.1252.

IR (ATR, neat, cm^{-1}): 1653 (m), 1608 (m), 1557 (m), 1450 (m), 1424 (m), 1370 (m), 1278 (m), 1123 (m), 941 (m), 867 (s), 742 (s)611 (w).

Synthesis of (2-methylphenyl)(1-(pyrimidin-2-yl)-1H-pyrrol-2-yl)methanone (1.16a)



1.16a

1.16a was synthesized according to the described procedure **B**, using 2-iodo-toluene (64 µL, 0.5 mmol) and 2-(1*H*-pyrrol-1-yl)pyrimidine (145 mg, 1.0 mmol). Purification by flash chromatography (*n*-hexane:EtOAc = 10:1 → 2:1) yielded **1.16a** (95 mg, 0.36 mmol, 72%) as a colorless solid.

m.p: 99-100 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.55 (d, J = 4.8 Hz, 2H), 7.58 (dd, J = 2.9, 1.7 Hz, 1H), 7.52 – 7.42 (m, 1H), 7.24 (td, J = 7.5, 1.5 Hz, 1H), 7.11 (m, 2H), 7.05 (d, J = 4.8 Hz, 1H), 6.65 (dd, J = 3.6, 1.7 Hz, 1H), 6.26 (dd, J = 3.6, 2.9 Hz, 1H), 2.42 (s, 3H).

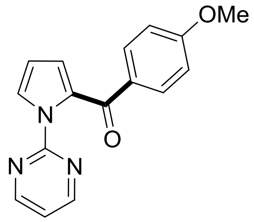
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 187.7 (CO), 158.3 (CH), 157.1 (C_q), 138.7 (C_q), 138.5 (C_q), 134.0 (C_q), 131.2 (CH), 130.8 (CH), 129.8 (CH), 128.5 (CH), 125.1 (CH), 123.2 (CH), 118.7 (CH), 110.6 (CH), 20.4 (CH_3).

MS (GC-MS) m/z (relative intensity) = 263 (100, [M^+]), 234 (19), 172 (35), 168 (15), 118 (59), 90 (34).

HR-MS (EI) m/z calcd for $C_{16}H_{13}N_3O$+ [M+H]+ 263.1053, found 263.1055.

IR (ATR, neat, cm^{-1}): 1643 (w), 1570 (m), 1437 (m), 1408 (m), 1284 (w), 1254 (w), 1167 (w), 900 (m), 761 (m), 739 (s), 666 (m), 636 (m).

Synthesis of (4-methoxyphenyl)(1-(pyrimidin-2-yl)-1H-pyrrol-2-yl)methanone (1.16b)



1.16b

1.16b was synthesized according to the described procedure **B**, using 4-iodo-anisole (117 mg, 0.5 mmol) and 2-(1*H*-pyrrol-1-yl)pyrimidine (145 mg, 1.0 mmol). Purification by flash chromatography (*n*-hexane:EtOAc = 10:1 → 1:1) yielded **1.16b** (70 mg, 0.25 mmol, 50%) as a colorless solid.

m.p.: 156-157 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.61 (d, *J* = 4.8 Hz, 2H), 7.95 (d, *J* = 9.0 Hz, 2H), 7.70 (dd, *J* = 3.0, 1.6 Hz, 1H), 7.11 (dd, *J* = 4.8, 4.8 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.78 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.35 (dd, *J* = 3.6, 3.0 Hz, 1H), 3.87 (s, 3H).

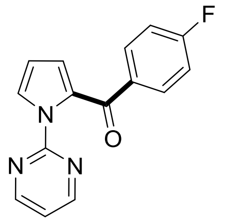
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 185.0 (CO), 163.2 (C_q), 158.2 (CH), 156.9 (C_q), 132.3 (C_q), 131.9 (CH), 131.1 (C_q), 127.3 (CH), 121.8 (CH), 118.3 (CH), 113.5 (CH), 110.3 (CH), 55.5 (OMe).

MS (GC-MS) m/z (relative intensity) = 279 (98, [M$^+$]), 250 (28), 236 (13), 172 (100), 135 (19), 117 (18).

HR-MS (EI) m/z calcd for $C_{16}H_{13}N_3O_2^+$ [M+H]$^+$ 279.1002, found 279.1009.

IR (ATR, neat, cm^{-1}): 1636 (m), 1598 (m), 1567 (s), 1436 (s), 1404 (s), 1293 (m), 1257 (s), 1027 (w), 1018 (w), 897 (w), 852 (w), 811 (w), 752 (s), 635 (m).

Synthesis of (4-fluorophenyl)(1-(pyrimidin-2-yl)-1H-pyrrol-2-yl)methanone (1.16c)



1.16c

1.16c was synthesized according to the described procedure **B**, using 1-fluoro-4-iodobenzene (58 µL, 0.5 mmol) and 2-(1*H*-pyrrol-1-yl)pyrimidine (145 mg, 1.0 mmol). Purification by flash chromatography (*n*-hexane:EtOAc = 10:1 → 2:1) yielded **1.16c** (60 mg, 0.22 mmol, 45%) as a colorless solid.

m.p.: 155-156 °C

^{1}H NMR (300 MHz, Chloroform-*d*) *δ* = 8.61 (d, *J* = 4.8 Hz, 2H), 7.97 (dd, *J* = 9.0, 5.5 Hz, 2H), 7.73 (dd, *J* = 3.0, 1.6 Hz, 1H), 7.16 – 7.08 (m, 3H), 6.81 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.37 (dd, *J* = 3.6, 3.0 Hz, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*) *δ* = 184.5 (CO), 165.4 (d, *J* = 253.6 Hz, C_q), 158.3 (CH), 134.7 (CH), 132.1 (d, *J* = 9.2 Hz, CH), 131.9 (C_q), 128.0 (CH), 122.5 (CH), 118.5 (CH), 115.4 (d, *J* = 21.7 Hz, CH), 110.5 (CH).

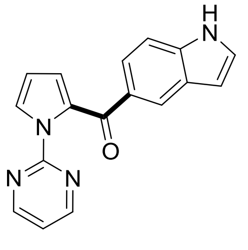
^{19}F NMR (282 MHz, Chloroform-*d*) *δ* = –(104.6–107.1) (m).

MS (GC-MS) m/z (relative intensity) = 267 (79, [M^+]), 238 (32), 172 (100), 117 (17), 95 (22), 75 (10).

HR-MS (EI) m/z calcd for $C_{15}H_{10}N_3F^+$ $[M+H]^+$ 267.0802, found 267.0809.

IR (ATR, neat, cm^{-1}): 1644 (m), 1571 (m), 1435 (m), 1409 (m), 1302 (m), 1148 (m), 901 8m), 757 (s).

Synthesis of (1*H*-indol-5-yl)(1-(pyrimidin-2-yl)-1H-pyrrol-2-yl)methanone (1.16d)



1.16d

1.16d was synthesized according to the described procedure **B**, using 5-iodoindole (121 mg, 0.5 mmol) and 2-(1*H*-pyrrol-1-yl)pyrimidine (145 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane:EtOAc = 4:1 → 1:1) yielded **1.16d** (99 mg, 0.34 mmol, 69%) as a colorless solid.

m.p.: 195 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H, N*H*), 8.56 (d, *J* = 4.8 Hz, 2H), 8.34 (ddd, *J* = 1.8, 0.8 Hz, 1H), 7.86 (ddd, *J* = 8.6, 1.8 Hz, 1H), 7.73 (dd, *J* = 3.0, 1.7 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 3.2, 2.4 Hz, 1H), 7.04 (dd, *J* = 4.8 Hz, 1H), 6.82 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.61 (m, 1H), 6.37 (dd, *J* = 3.6, 3.0 Hz, 1H).

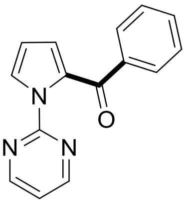
^{13}C NMR (75 MHz, Chloroform-*d*) δ 187.0 (CO), 158.3 (CH), 157.1 (C_q), 138.5 (C_q), 132.9 (C_q), 130.6 (C_q), 127.4 (C_q), 127.3 (CH), 125.7 (CH), 124.8 (CH), 123.8 (CH), 122.1 (CH), 118.3 (CH), 111.1 (CH), 110.4 (CH), 104.3 (CH).

MS (GC-MS) m/z (relative intensity) = 288 (100, [M^+]), 259 (75), 172 (66), 144 (23), 116 (38), 89 (25).

HR-MS (EI) m/z calcd for $C_{17}H_{12}N_4$ $[M]^+$ 288.1006, found 288.1003.

IR (ATR, neat, cm^{-1}): 1598 (m), 1568 (s), 1426 (s), 1399 (s), 1341 (m), 1302 (m), 1094 (w), 854 (m), 749 (s).

Synthesis of (phenyl)(1-(pyrimidin-2-yl)-1H-pyrrol-2-yl)methanone (1.16e)



1.16e

1.16e was synthesized according to the described procedure **B**, using iodobenzene (1.28 g, 6.25 mmol) and 2-(1*H*-pyrrol-1-yl)pyrimidine (1.81 g, 13.0 mmol, 1.0 equiv.). Purification by flash chromatography (*n*-hexane:EtOAc = 10:1 → 2:1) yielded **1.16e** (1.2 g, 4.81 mmol, 77%) as a colorless solid.

m.p.: 120-121 °C

^{1}H NMR (300 MHz, Chloroform-d) δ 8.60 (d, J = 4.8 Hz, 2H, 2‘-H, 4‘-H), 7.97 – 7.91 (m, 2H, 7-H, 12-H), 7.72 (dd, J = 2.9, 1.6 Hz, 1H, 2-H), 7.54 (m, 1H),, 7.43 (m, 2H, 9-H, 11-H), 7.11 (t, J = 4.8 Hz, 1H, 4‘-H), 6.83 (dd, J = 3.6, 1.6 Hz, 1H, 4-H), 6.37 (dd, J = 3.6, 2.9 Hz, 1H, 3-H).

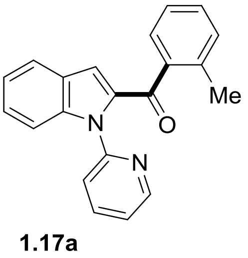
^{13}C NMR (75 MHz, Chloroform-d) δ 186.0 (CO), 158.3 (CH), 157.0 (C$_q$), 138.4 (C$_q$), 132.5 (CH), 132.4 (C$_q$), 129.8 (CH), 128.3 (CH), 128.0 (CH), 122.7 (CH), 118.6 (CH), 110.6 (CH).

MS (GC-MS) *m/z* (relative intensity) = 249 (63) [M$^+$], 220 (28), 172 (100), 117 (16), 77 (17).

HRMS (EI, m/z) calcd. for $C_{15}H_{11}ON_3$ [M]$^+$: 249.0897; found: 249.0893.

IR (ATR, neat, cm^{-1}): 3133 (w), 3096 (w), 1644 (m); 1571 (s), 1436 (s), 1406 (m), 1288 (m), 1256 (m), 1160 (m), 897 (w), 811 (w), 756 (m), 716 (s), 689 (m), 674 (m).

Synthesisi of (1-(pyridin-2-yl)-indol-2-yl)(*o*-tolyl)methanone (1.17a)



1.17a

1.17a was synthesized according to the described procedure **A**, using 2-iodotoluene (107 mg, 0.50 mmol) and 1-(pyridin-2-yl)-indol (194 mg, 1.0 mmol). Purification by flash chromatography (*n*-heptane:EtOAc = 20:1 → 10:1) yielded **1.17a** (115 mg, 0.37 mmol, 75%) as a colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) *δ* = 8.63 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.88 (ddd, *J* = 8.4, 7.8, 1.9 Hz, 1H), 7.71 (ddd, *J* = 8.4, 7.8, 1.0 Hz, 2H), 7.53 (ddd, *J* = 8.5, 1.8, 0.9 Hz, 1H), 7.45 (ddd,

J = 8.0, 1.0, 1.0 Hz, 1H), 7.40 (m, 2H), 7.34 (ddd, J = 7.5, 2.6, 1.1 Hz, 1H), 7.29 (d, J = 7.4 Hz, 2H), 7.23 (ddd, J = 8.4, 7.0, 1.0 Hz, 1H), 7.05 (d, J = 0.9 Hz, 1H), 2.47 (s, 3H).

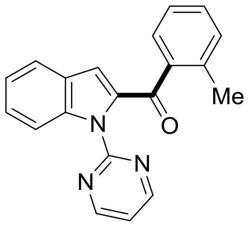
^{13}C NMR (101 MHz, Chloroform-*d*) δ = 189.0 (C_q), 151.7 (C_q), 149.3 (CH), 140.2 (C_q), 138.5 (C_q), 138.1 (CH), 137.9 (C_q), 137.3 (C_q), 131.2 (CH), 130.8 (CH), 129.7 (CH), 126.9 (CH), 126.8 (C_q), 125.1 (CH), 123.1 (CH), 122.5 (CH), 122.0 (CH), 121.4 (CH), 117.0 (CH), 111.7 (CH), 20.2 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 312 (100) [M^+], 283 (43), 221 (21), 118 (17), 91 (18).

HR-MS (ESI-TOF) *m/z* calcd for $C_{21}H_{16}N_2O^+$ $[M+H]^+$ 313.1335, found 313.1337.

IR (ATR, neat, cm^{-1}): 1642 (m), 1588 (m), 1516 (m), 1466 (s), 1438 (s), 1387 (m), 1217 (m), 905 (s), 725 (s).

Synthesisi of (1-(pyrimidin-2-yl)-indol-2-yl)(*o*-tolyl)methanone (1.18b)



1.18b

1.18b was synthesized according to the described procedure **B**, using 2-iodotoluene (107 mg, 0.50 mmol) and 1-(pyridin-2-yl)-indole (194 mg, 1.0 mmol). Purification by flash chromatography (*n*-heptane:EtOAc = 20:1 → 10:1) yielded **1.18b** (83 mg, 0.27 mmol, 54%) as a colorless viscous oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.67 (d, J = 4.9 Hz, 2H), 8.31 (dd, J = 8.5, 0.9 Hz, 1H), 7.69 (ddd, J = 7.9, 1.3, 0.8 Hz, 1H), 7.58 (dd, J = 7.6, 1.3 Hz, 1H), 7.44 (ddd, J = 8.5, 7.1, 1.3 Hz, 1H), 7.35 (td, J = 7.5, 1.5 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.17 (dddd, J = 8.2, 7.2, 1.5, 0.7 Hz, 1H), 7.08 (d, J = 0.8 Hz, 1H), 7.07 (dd, J = 4.8, 4.9 Hz, 1H), 2.58 (s, 3H).

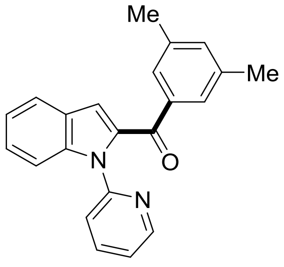
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 189.3 (CO), 158.0 (CH), 157.5 (C_q), 138.8 (C_q), 138.1 (C_q), 131.3 (CH), 131.2 (CH), 130.0 (CH), 127.9 (C_q), 126.8 (CH), 125.2 (CH), 125.0 (C_q), 122.9 (CH), 122.7 (CH), 117.7 (CH), 116.3 (CH), 114.1 (CH), 20.5 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 313 (100) [M^+], 295 (29), 284 (26), 233 (15), 222 (40), 193 (22), 118 (28), 91 (37).

HR-MS (EI) *m/z* calcd for $C_{20}H_{15}N_2O^+$ $[M]^+$ 313.1210, found 313.1204.

IR (ATR, neat, cm^{-1}): 1642 (m), 1588 (m), 1516 (m), 1466 (s), 1438 (s), 1387 (m), 1217 (m), 905 (s), 725 (s).

Synthesis of (3,5-dimethylphenyl)(1-(pyridin-2-yl)-1H-indol-2-yl)methanone (1.17b)



1.17b

1.17b was synthesized according to the described procedure **B**, using 5-iodo-*m*-xylene (113 mg, 0.50 mmol) and 1-(pyridin-2-yl)-indol (195 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane:Et_2O = 30:1 → 15:1) yielded **1.17b** (101 mg, 0.31 mmol, 62%) as a colorless solid.

m.p.: 165-167 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.56 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.9 Hz, 1H), 7.77 – 7.72 (m, 1H), 7.63 (d, *J* = 1.9 Hz, 2H), 7.56 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.45 – 7.33 (m, 2H), 7.32 – 7.17 (m, 4H), 2.39 (s, 6H).

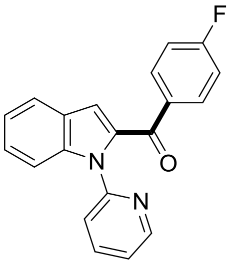
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 187.3 (CO), 151.6 (C_q), 149.4 (CH), 139.6 (C_q), 138.3 (C_q), 138.1 (C_q), 138.1 (CH), 136.4 (C_q), 134.5 (CH), 127.8 (CH), 127.0 (C_q), 126.5 (CH), 123.1 (CH), 122.2 (CH), 122.0 (CH), 121.1 (CH), 115.9 (CH), 111.6 (CH), 21.4 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 326 (77) [M^+], 297 (58), 221 (100), 192 (21), 105 (10), 78 (13).

HR-MS (ESI-TOF) *m/z* calcd for $C_{22}H_{19}N_2O^+$ $[M+H]^+$ 327.1492, found 327.1495.

IR (ATR, neat, cm^{-1}): 1650 (m), 1466 (m), 1444 (m), 1301 (m), 1175 (m), 1145 (m), 964 (w), 750 (s), 740 (s).

Synthesis of (4-fluorophenyl)(1-(pyridin-2-yl)-indol-2-yl)methanone (1.17d)



1.17d

1.17d was synthesized according to the described procedure **A**, using 1-fluoro-4-iodotoluene (112 mg, 0.50 mmol) and 1-(pyridin-2-yl)-indol (200 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane:Et_2O = 10:1 → 5:1) yielded **1.17d** ($NaHCO_3$ (2.0 equiv.): 95 mg, 0.30 mmol, 60%; K_2CO_3 (2.0 equiv.): 87 mg, 0.28 mmol, 55%) as a colorless solid.

m.p.: 107-108 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.45 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.94 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.79 – 7.76 (dd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.64 (ddd, *J* = 7.9, 1.0, 0.9 Hz, 1H), 7.44 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.33 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.28 (ddd, *J* = 8.4, 7.1, 1.0 Hz, 1H), 7.23 – 7.02 (m, 5H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ = 185.5 (CO), 165.6 (d, *J* = 254.2 Hz, C_q), 151.4 (C_q), 149.4 (CH), 139.6 (C_q), 138.2 (CH), 135.9 (C_q), 134.5 (d, *J* = 3.0 Hz, C_q), 132.5 (CH), 132.4 (CH), 126.9 (C_q), 126.7 (CH), 123.1 (CH), 122.4 (CH), 122.1 (CH), 121.0 (CH), 115.9 (CH), 115.5 (d, *J* = 21.9 Hz, CH), 111.5 (CH).

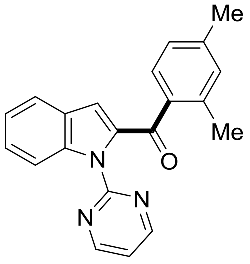
^{19}F NMR (282 MHz, Chloroform-*d*) δ = -105.32 (td, *J* = 9.3, 4.4 Hz).

MS (GC-MS) *m/z* (relative intensity) = 316 (100) [M$^+$], 287 (73), 192 (27), 123 (14), 95 (32).

HR-MS (ESI-TOF) *m/z* calcd for $C_{20}H_{13}FN_2O^+$ [M+H]$^+$ 317.1085, found 317.1086.

IR (ATR, neat, cm^{-1}): 1665 (m), 1594 (m), 1584 (m), 1532 (w), 1503 (w), 1470 (w), 1411 (w), 1340 (w), 1228 (s), 1158 (s), 857 (m), 823 (m), 757 (m), 729 (s), 607 (s).

Synthesis of (2,4-dimethylphenyl)(1-(pyrimidin-2-yl)-1H-indol-2-yl)methanone (1.18b)



1.18b

1.18b was synthesized according to the described procedure **A**, using 1-iodo-2,4-dimethylbenzene (113 mg, 0.49 mmol) and 1-(pyrimidin-2-yl)-indol (195 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane:EtOAc = 30:1 → 15:1) yielded **1.18b** (101 mg, 0.31 mmol, 62%) as a yellowish oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.67 (dd, *J* = 4.8, 0.7 Hz, 2H), 8.34 (dq, *J* = 8.4, 0.8 Hz, 1H), 7.69 (ddd, *J* = 7.9, 1.3, 0.7 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.45 (ddt, *J* = 8.4, 7.1, 1.0 Hz, 1H), 7.35 – 7.23 (m, 1H), 7.10 – 7.05 (m, 3H), 6.98 (ddt, *J* = 7.9, 1.5, 0.8 Hz, 1H), 2.57 (s, 3H), 2.35 (s, 3H).

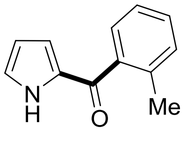
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 189.2 (CO), 158.0 (CH), 157.6 (C_q), 141.7 (C_q), 139.0 (C_q), 139.0 (C_q), 138.6 (C_q), 135.4 (C_q), 132.3 (CH), 130.6 (CH), 128.0 (C_q), 126.6 (CH), 125.8 (CH), 122.8 (CH), 122.6 (CH), 117.6 (CH), 115.8 (CH), 114.1 (CH), 21.5 (CH_3), 20.6 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 327 (100) [M$^+$], 309 (28), 247 (13), 222 (33), 193 (20), 132 (28), 103 (24), 79 (33).

HR-MS (EI) m/z calcd for $C_{21}H_{17}N_3^+$ [M+H]$^+$ 327.1366, found 327.1358.

IR (ATR, neat, cm^{-1}): 1648 (m), 1563 (m), 1419 (s), 1344 (m), 1210 (m), 1140 (w), 1042 (w), 958 (m), 801 (w), 765 (s), 745 (s), 705 (w), 599 (m).

Synthesis of (1*H*-Pyrrol-2-yl)(o-tolyl)methanone (1.19)



1.19

NaOEt (41 mg, 0.60 mmol, 3 equiv.) was added to a stirring solution of (1-(pyrimidin-2-yl)-1H-pyrrol-2-yl)(o-tolyl)methanone (**1.16a**) (50 mg, 0.19 mmol, 1.0 equiv.) in DMSO (2 mL) under argon atmosphere and the reaction mixture was stirred at 100 °C for 5 h. The reaction was quenched by addition of EtOAc (5 mL) and the reaction mixture was portioned between EtOAc and H2O (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layer were washed with H2O (5 mL) and Brine (5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (n-pentane/Et_2O = 5:1). **1.19** (32 mg, 0.17 mmol, 91%) was obtained as colorless solid.

m.p.: 64-65 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 10.36 (s, 1H, NH), 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.39 (ddd, *J* = 7.5, 1.5 Hz, 1H), 7.32 – 7.21 (m, 2H), 7.16 (ddd, *J* = 2.8, 1.4 Hz, 1H), 6.63 (ddd, *J* = 3.8, 2.4, 1.4 Hz, 1H), 6.29 (ddd, *J* = 3.8, 2.4 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 187.4 (CO), 138.5 (C_q), 136.8 (C_q), 132.5 (C_q), 131.1 (CH), 130.1 (CH), 128.6 (CH), 126.1 (CH), 125.2 (CH), 120.6 (CH), 111.1 (CH), 19.9 (CH_3).

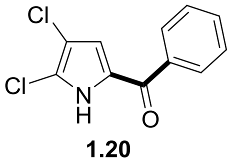
MS (GC-MS) *m/z* (relative intensity) = 185 (100) [M$^+$], 168 (27), 156 (15), 128 (11), 94 (20), 91 (22), 66 (15).

HR-MS (ESI-TOF) *m/z* calcd for $C_{12}H_{11}NO^+$ [M]$^+$ 186.0913, found 186.0916.

IR (ATR, neat, cm^{-1}): 3244 (w), 1617 (m), 1605 (m), 1593 (m), 1538 (w), 1391 (m), 1132 (m), 1089 (w), 1039 (m), 892 (m), 748 (s), 734 (s), 666 (m), 602 (m).

The analytical data are in accordance with those described in literature.

Synthesis of (4,5-dichloro-1H-pyrrol-2-yl)(phenyl)methanone (1.20)



1.20

m.p.: 190-191°C

^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.40 (s, 1H), 7.93 – 7.83 (m, 2H), 7.61 (ddt, *J* = 8.3, 6.6, 1.3 Hz, 1H), 7.51 (ddt, *J* = 8.3, 6.6, 1.3 Hz, 2H), 6.83 (d, *J* = 2.4 Hz, 1H).

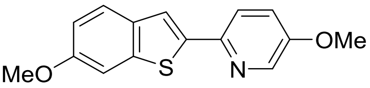
^{13}C NMR (75 MHz, Chloroform-*d*) δ 183.6 (CO), 137.1 (C_q), 132.8 (CH), 129.1 (CH), 128.7 (CH), 128.3 (C_q), 121.7 (C_q), 118.8 (CH) , 112.2 (C_q).

MS (GC-MS) *m/z* (relative intensity) = 239 (100) [M^+], 204 (26), 162 (38), 105 (61), 77 (80).

HRMS (EI, m/z) calcd. for $C_{11}H_7Cl_2ON$ $[M]^+$: 240.9870; found: 240.9873.

IR (ATR, neat, cm^{-1}): 3185 (m), 3134 (w), 3068 (w), 1621 (m), 1572 (w), 1467 (m), 1413 (m), 1391 (m), 1261 (m), 1019 (m), 891 (m), 826 8m), 721 (s), 692 (s), 625 8m), 595 (m).

Synthesis of 5-methoxy-2-(6-methoxybenzo[b]thiophen-2-yl)pyridine (1.27)



1.27

1.27 was synthesized following representative procedure **A**, using 2-bromo-5-methoxypyridine (526 mg, 2.80 mmol, 1.0 equiv.) and (6-methoxybenzo[*b*]thiophen-2-yl)boronic acid/(4-methoxybenzo[*b*]thiophen-2-yl)boronic acid (5.2:1, 700 mg, 3.36 mmol, 1.2 equiv.). Purification by flash chromatography (*n*-pentane/Et_2O = 7:1 → 5:1) yielded the title compound **1.27** (555 mg, 2.05 mmol, 61%) as a colorless solid.

m.p.: 155-156 °C

^{1}H NMR (500 MHz, Chloroform-*d*) *δ* = 8.31 (dd, *J* = 2.8, 0.7 Hz, 1H), 7.68 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.60 (s, 1H), 7.32 (d, *J* = 2.3 Hz, 1H), 7.24 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.97 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H).

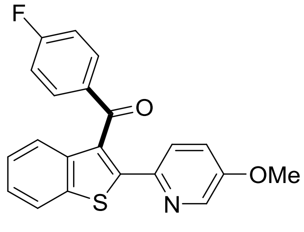
^{13}C NMR (126 MHz, Chloroform-*d*) *δ* = 157.8 (C_q), 154.8 (C_q), 145.7 (C_q), 141.9 (C_q), 136.6 (CH), 134.7 (C_q), 124.5 (CH), 121.6 (CH), 119.8 (CH), 119.3 (CH), 114.6 (CH), 104.9 (CH), 55.8 (CH_3), 55.6 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 271 (100) [M^+], 256 (81), 228 (15), 201 (21), 186 (13), 158 (20), 136 (7).

HR-MS (EI) *m/z* calcd for $C_{15}H_{14}NO_2S^+$ $[M+H]^+$ 272.0740, found 272.00738.

IR (ATR, neat, cm^{-1}): 1598 (w), 1528 (w), 1477 (m), 1436 (m), 1260 (m), 1220 (m), 1022 (s), 1008 (s), 844 (m), 833 (s).

Synthesis of (4-fluorophenyl)(6-methoxy-2-(5-methoxypyridin-2-yl)benzo[b]thiophen-3-yl)methanone (1.29)



1.29

1.29 was synthesized according to representative procedure **B**, using 1-fluoro-4-iodobenzene (111 mg, 0.5 mmol) and 2-(benzo[b]thiophen-2-yl)-5-methoxypyridine (**5c**) (241 mg, 1.0 mmol). Purification by flash chromatography (*n*-heptane:EtOAc = 20:1 → 10:1) yielded **1.29** (92 mg, 0.27 mmol, 53%) as a pale yellow foam. Crystals were obtained by recrystallization from EtOH.

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.17 (dd, *J* = 3.0, 0.7 Hz, 1H), 7.93 – 7.85 (m, 3H), 7.60 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.42 – 7.29 (m, 3H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.06 – 6.96 (m, 2H), 7.01 (d, *J* = 8.7 Hz, 2H)3.79 (s, 1H).

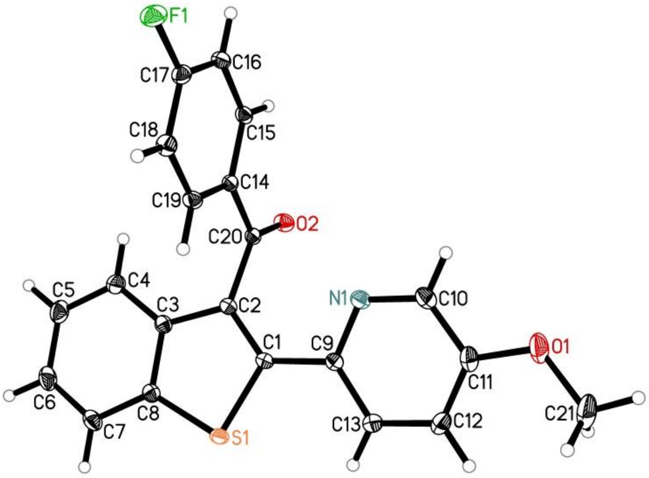
^{13}C NMR (75 MHz, Chloroform-*d*) δ = 193.4 (CO), 166.0 (d, *J* = 255.5 Hz, C_q), 155.3 (C_q), 144.1 (C_q), 143.7 (C_q), 139.7 (C_q), 139.3 (C_q), 137.5 (CH), 134.2 (d, *J* = 2.9 Hz, C_q), 132.4 (d, *J* = 9.5 Hz, CH), 131.4 (C_q), 125.3 (CH), 125.2 (CH), 123.4(CH), 123.4 (CH), 122.4 (CH), 120.6 (CH), 115.8 (d, *J* = 21.9 Hz, CH), 55.8 (CH_3).

^{19}F NMR (282 MHz, Chloroform-*d*) δ = -102.6 – -105.1 (m).

MS (GC-MS) *m/z* (relative intensity) = 363 (47) [M^+], 334 (100), 291 (14), 268 (22), 225 (10), 181 (33), 145 (25), 95 (12).

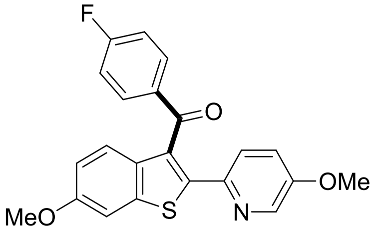
HR-MS (EI) *m/z* calcd for $C_{21}H_{14}FNO_2S^+$ $[M+H]^+$ 363.0724, found 363.0719.

IR (ATR, neat, cm^{-1}): 1665 (s), 1593 /m), 1578 (m), 1477 (m),1231 (s), 1218 (s), 1159 (m), 751 (s), 823 (s) 722 (s), 605 (s).



Empirical formula	$C_{12}H_{12}F_2O_5$	
Formula weight	274.22	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.9463(7) Å	α= 104.074(2)°.
	b = 8.7658(8) Å	β= 104.446(2)°.
	c = 10.3812(10) Å	γ = 112.083(2)°.
Volume	601.39(10) Å^3	
Z	2	
Density (calculated)	1.514 Mg/m^3	
Absorption coefficient	0.137 mm^{-1}	
F(000)	284	
Crystal size	0.50 x 0.36 x 0.14 mm^3	
Theta range for data collection	2.19 to 28.00°.	
Index ranges	-10<=h<=10, -11<=k<=11, -13<=l<=13	
Reflections collected	16835	
Independent reflections	2911 [R(int) = 0.0389]	
Completeness to theta = 28.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.855	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2911 / 0 / 173	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2sigma(I)]	R1 = 0.0412, wR2 = 0.1225	
R indices (all data)	R1 = 0.0527, wR2 = 0.1358	
Largest diff. peak and hole	0.374 and -0.271 e.Å^{-3}	

Synthesis of (4-fluorophenyl)(6-methoxy-2-(5-methoxypyridin-2-yl)benzo[b]thiophen-3-yl)methanone (1.30)



1.30

1.30 was synthesized according to representative procedure **B**, using 1-fluoro-4-iodobenzene (111 mg, 0.5 mmol) and 5-methoxy-2-(6-methoxybenzo[b]thiophen-2-yl)pyridine (**1.27**) (270 mg, 1.0 mmol). Purification by flash chromatography (*n*-heptane:EtOAc = 20:1 → 10:1) yielded **1.30** (107 mg, 0.27 mmol, 55%) as a pale yellow foam.

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.16 (dd, *J* = 3.0, 0.7 Hz, 1H, 2’-C), 7.88 (dd, *J* = 8.9, 5.4 Hz, 2H, A/B), 7.48 (d, *J* = 8.9 Hz, 1H, 4-C), 7.34 (d, *J* = 2.4 Hz, 1H, 7-C), 7.30 (dd, *J* = 8.8, 0.7 Hz, 1H, 5’-C), 7.00 (d, *J* = 8.8 Hz, 1H, 6’-C), 6.99 (dd, *J* = 8.9, 6.4 Hz, 2H, AB), 6.96 (dd, *J* = 8.9, 2.4 Hz, 1H, 5-C), 3.88 (s, 3H, OMe), 3.79 (s, 3H, OMe).

^{13}C NMR (126 MHz, Chloroform-*d*) δ = 193.4 (CO), 166.0 (d, *J* = 255.4 Hz, C$_q$), 158.4 (C$_q$), 155.0 (C$_q$), 144.0 (C$_q$), 141.7 (C$_q$), 140.9 (C$_q$), 137.4 (CH), 134.2 (d, *J* = 2.8 Hz, C$_q$), 133.8 (C$_q$), 132.4 (d, *J* = 9.4 Hz, CH), 131.1 (C$_q$), 124.2 (CH), 123.1 (CH), 120.7 (CH), 115.8 (d, *J* = 22.0 Hz, CH), 115.3 (CH), 104.8 (CH), 55.8 (2xCH$_3$).

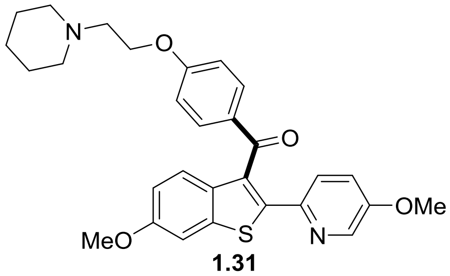
^{19}F{^{1}H} NMR (282 MHz, Chloroform-*d*) δ = -104.5 (s).

MS (GC-MS) *m/z* (relative intensity) = 393 (75) [M$^+$], 364 (100), 298 (20), 283 (6), 240 (6), 197 (6), 123 (12), 95 (17).

HR-MS (ESI-TOF) *m/z* calcd for $C_{22}H_{16}FNO_3S^+$ [M+H]$^+$ 393.0829, found 393.0829.

IR (ATR, neat, cm^{-1}): 3068 (w), 3005 (w), 2961 (w), 2936 (w), 2836 (w), 1734 (w), 1660 (m), 1594 (m), 1573 (m), 1469 (m), 1436 (m), 1261 (s), 1222 (s), 1150 (m), 1044 (m), 1025 (m), 824 (s), 609 (m).

Synthesis of (6-methoxy-2-(5’-methoxypyridin-2’-yl)benzo[*b*]thiophen-3-yl)(4-(2-(piperidin-1-yl)ethoxy) phenyl)methanone (1.31)



1.31

1.31 was synthesized according to a procedure described by Schmid[12]. A solution of (4-fluorophenyl)(6-methoxy-2-(5-methoxypyridin-2-yl)benzo[b]thiophen-3-yl)methanone (**1.30**) (24 mg, 63 mmol, 1.0 equiv.) in DMF (0.5 mL) was added dropwise to astirring suspension of NaH (60% in mineral oil, 6 mg, 0.14 mmol, 2.2 equiv.) and 2-(piperidin-1-yl)ethanol (17 µL, 0.13 mmol, 2.0 equiv.) in DMF (1.0 mL) at ambient temperature. The reaction mixture was continuously stirred at ambient temperature for 1 h. After complete conversion of the starting material (1h) the reaction was quenched by addition of Et_2O (1 mL) and sat. aq. NH_4Cl (1 mL). The phases were separated via a phase-separating filter. The supernatant was washed with additional Et_2O (5 mL) and DCM (5 mL). The organic solvent was removed under reduced pressure and the crude product was purified by flash chromatography (*n*-heptane/EtOAc = 1: 0 → 2:1 → EtOAc/DCM/MeOH = 3:1:0.2). **1.31** (26 mg, 0.052 mmol, 81%) was obtained as a yellow oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.22 (dd, *J* = 3.0, 0.5 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.9 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 8.8, 0.5 Hz, 2H), 6.99 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.92 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 4.12 (t, *J* = 5.9 Hz, 2H), 3.88 (s, 4H), 3.80 (s, 3H), 2.76 (t, *J* = 5.9 Hz, 2H), 2.59 – 2.43 (m, 4H), 1.60 (ddt, *J* = 5.7 Hz, 4H), 1.44 (ddt, *J* = 11.8, 8.3, 4.8 Hz, 2H).

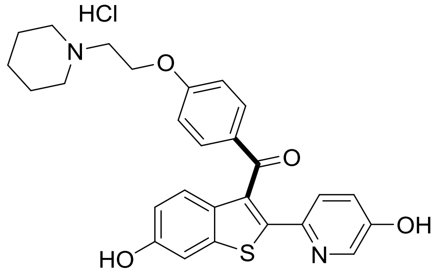
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 193.8 (CO), 163.3 (C_q), 158.2 (C_q), 155.0 (C_q), 144.3 (C_q), 141.1 (C_q), 141.0 (C_q), 137.4 (CH), 134.1 (C_q), 132.4 (CH), 131.6 (C_q), 130.6 (C_q), 124.3 (CH), 123.0 (CH), 120.8 (CH), 115.1 (CH), 114.6 (CH), 104.7 (CH), 66.3 (CH_2), 57.8 (CH_2), 55.8 (OCH_3), 55.2 (OCH_3), 25.9 (CH_2), 24.2 (CH_2).

MS (GC-MS) *m/z* (relative intensity) = 502 (13) [M^+], 404 (6), 374 (4), 281 (10), 253 (9), 98 (100).

HR-MS (ESI-TOF) *m/z* calcd for $C_{29}H_{30}O_4N_2S^+$ $[M+H]^+$ 502.1921, found 502.1922.

IR (ATR, neat, cm^{-1}): 2931 (w), 2834 (w), 2781 (w), 1651 (w), 1594 (m), 1570 (m), 1466 (m), 1259 (m), 1222 (s), 1162 (m), 1026 (m), 825 (m).

Synthesis of (6-hydroxy-2-(5-hydroxypyridin-2-yl)benzo[b]thiophen-3-yl)(4-(2-(piperidin -1-yl)ethoxy)-phenyl)methanone hydrochloride (1.32)



1.32

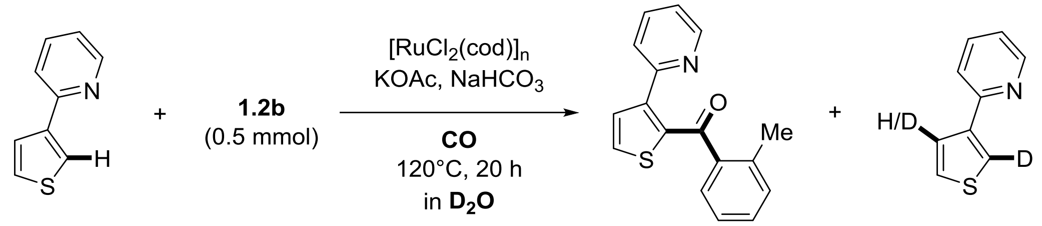
(6-methoxy-2-(5-methoxypyridin-2-yl)benzo[b]thiophen-3-yl) (4-(2-(piperidin-1-yl) ethoxy) phenyl)methanone hydrochloride (**1.31HCl**) (13 mg, 24.1 µmol, 1.0 equiv.) was dissolved in DCM (2.0 mL). At 0 °C, BBr_3 (1 M in DCM, 100 µL, 4.0 equiv.) was added dropwise over 30 min. The reaction mixture was slowly warmed to ambient temperature and heated to 35 °C for 2 h. The mixture was cooled to 0 °C and MeOH (1 mL) was added dropwise over 10 min. The sluggish, red reaction mixture turned into a clear, yellow solution that was refluxed at 40 °C for 45 min. The volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (washed with *n*-pentane, product was eluted with MeOH), yielding the title compound **1.32** (12 mg, 24 µL, 99%) as a pale yellow solid.

^{1}H NMR (300 MHz, Methanol-d_4) δ = 8.08 (t, *J* = 3.3 Hz, 1H), 7.80 – 7.70 (m, 2H), 7.53 – 7.26 (m, 3H), 7.18 (ddd, *J* = 8.8, 2.7, 2.6 Hz, 1H), 7.01 – 6.79 (m, 3H), 4.14 (t, *J* = 5.5 Hz, 2H), 3.88 (s, 1H, OH), 3.79 (m, 3H), 2.79 (t, *J* = 5.5 Hz, 2H), 2.55 (m, 4H), 1.62 (p, *J* = 5.5 Hz, 4H), 1.47 (p, *J* = 5.5 Hz, 2H).

^{13}C NMR (75 MHz, Methanol-d_4) δ = 194.6 (CO), 163.6 (C_q), 156.5 (C_q), 155.6 (C_q), 144.1 (C_q), 142.9 (C_q), 141.1 (C_q), 139.9 (C_q), 137.3 (CH), 133.0 (C_q), 132.2 (CH), 130.8 (C_q), 124.0 (CH), 123.3 (CH), 120.8 (CH), 115.4 (CH), 114.5 (CH), 107.0 (CH), 104.7 (CH), 100.0 (CH), 65.5 $(CH)_2$, 57.5 (CH_2), 55.3 (CH_2), 54.8 (CH_2), 25.3 (CH_2), 23.8 (CH_2).

IR (ATR, neat, cm^{-1}): 3356 (w), 2935 (w), 2650 (w), 1642 (w), 1594 (m), 1548 (m), 1308 (w), 1224 (s), 1168 (s), 1007 (m), 840 (m), 795 (m).

H/D-Exchange Experiments



1.8 (1.0 mmol)

1.9a **Yield of 3ab**

***d*-1.8** **H/D exchange at C-2**

	Yield of 3ab	H/D exchange at C-2
after 3 h:	28% (NMR)	65%
after 20 h:	91% (isol.)	95%

General procedure **B** was followed, using 2-(thiophen-3-yl)pyridine **1.8** (160 mg, 1.0 mmol, 2.0 equiv.) and 2-iodotoluene **1.2b** (115 mg, 0.53 mmol) in D_2O (1.0 mL). The reaction mixture was stirred for the indicated time at 120 °C under 30 bar of carbon monoxide pressure. Purification by flash chromatography (*n*-pentane/Et_2O = 10:1 → 4:1) yielded **1.9a** (134 mg, 0.48 mmol, 91%) as yellow oil and ***d*-1.8** (71 mg, 0.44 mmol, 83% based on **A**) as colorless oil.

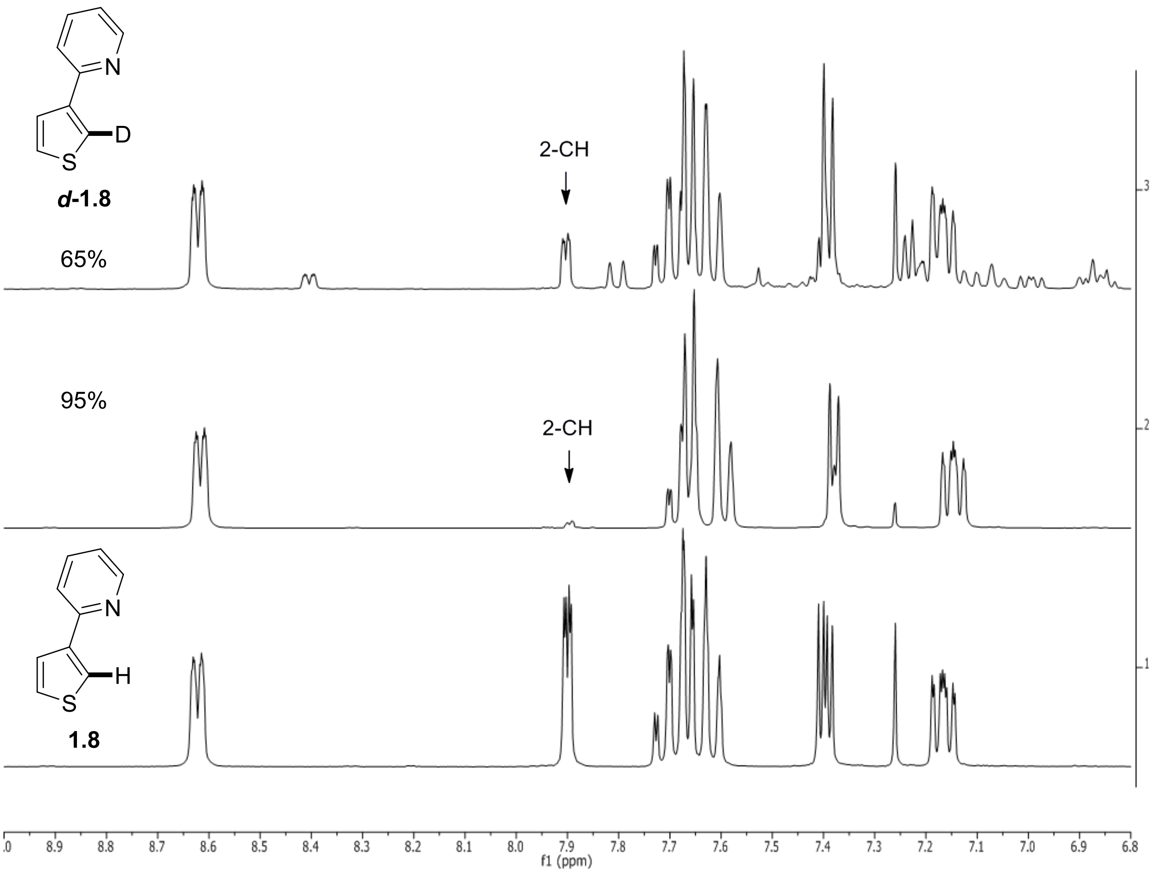
According to ^{1}H-NMR spectroscopy the deuterium incorporation at C-2 amounted 65% after 3 hours and 95% after 20 hours, respectively. After 20 hours 15% H/D-exchange was found at C-4 and <7% in **3ba**.

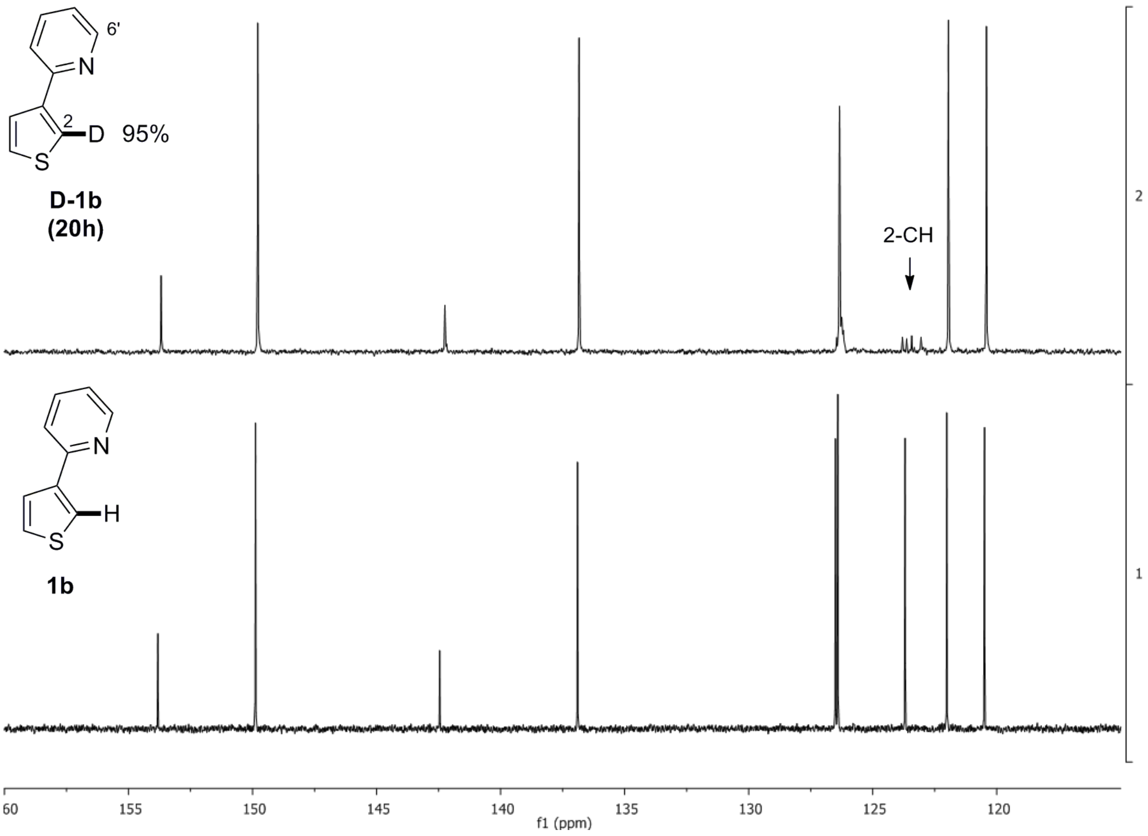
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.52 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.50 (dq, J = 8.0, 1.0 Hz, 1H), 7.29 (dd, J = 5.0, 2.5 Hz, 1H), 7.05 (ddd, J = 7.1, 4.8, 1.0 Hz, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 153.6 (C_q), 149.7 (CH), 142.2 (C_q), 136.8 (CH), 126.3 (CH), 126.2 (CH), 123.4 (t, J = 28 Hz, CD), 121.9 (CH), 120.3 (CH).

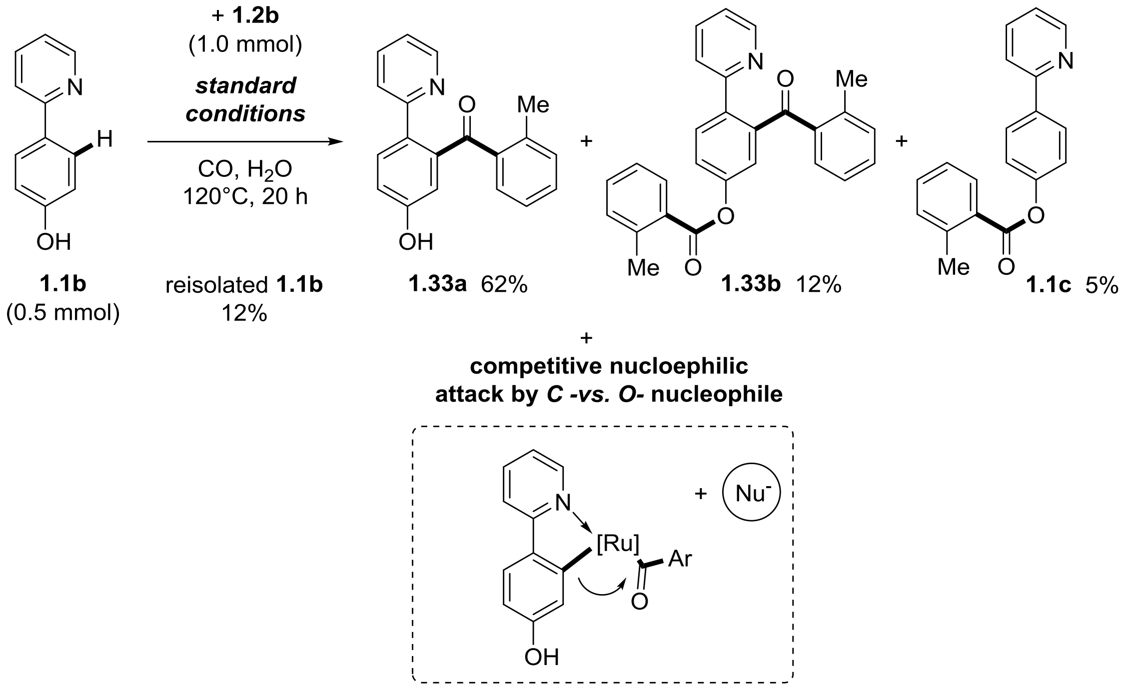
MS (GC-MS) m/z (relative intensity) = 162 (100) [M+], 136 (11), 118 (20), 105 (6), 91 (6), 81 (5).

HR-MS (ESI-TOF) m/z calcd for $C_9H_6DNS^+$ [M+H]+ 163.0435, found 163.0434.

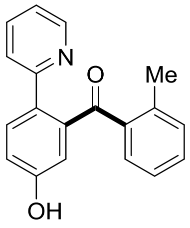




Evidence for Competitive Attack of the Ru-Acyl species



Following a modified representative procedure **B**, 4-(pyridin-2-yl)phenol (86 mg, 0.5 mmol, 1.0 equiv.) and 2-iodophenol (218 mg, 1.0 mmol, 2.0 equiv.) were reacted. The crude products were purified by flash chromatography (*n*-heptane/EtOAc = 10:1 → 5:1), yielding **1.33a** (90 mg, 0.31 mmol, 62%), **1.33b** (24 mg, 0.06 mmol, 12%) and **1.1c** (7 mg, 0.03 mmol, 5%) besides re-isolated **1.1b** (10 mg, 0.06 mmol, 12%).



1.33a

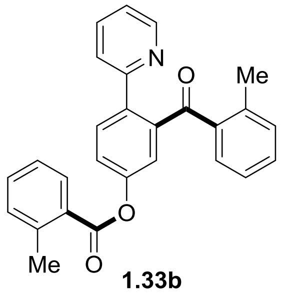
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 9.58 (s, 1H), 8.46 (ddd, J = 5.1, 1.7, 0.9 Hz, 1H), 7.61 (dd, J = 7.7, 1.7 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.24 (dd, J = 9.8, 7.4 Hz, 2H), 7.16 – 7.05 (m, 3H), 7.05 – 6.97 (m, 1H), 6.95 (dd, J = 8.4, 2.5 Hz, 1H), 2.60 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-d) δ = 200.1 (CO), 157.7 (C_q), 157.6 (C_q), 148.2 (CH), 141.5 (C_q), 139.2 (C_q), 137.7 (C_q), 136.7 (CH), 131.3 (CH), 131.2 (CH), 131.1 (C_q), 130.9 (CH), 130.9 (CH), 125.0 (CH), 123.4 (CH), 121.7 (CH), 118.3 (CH), 117.5 (CH), 21.1 (CH_3).

MS (GC-MS) m/z (relative intensity) = 289 (41) [M$^+$], 260 (100), 246 (97), 198 (63), 115 (30), 91 (42), 65 (32).

HR-MS (EI) m/z calcd for $C_{19}H_{15}NO_2^+$ [M]$^+$ 288.1019, found 288.1016.

IR (ATR, neat, cm^{-1}): 1660 (m), 1560 (w), 1467 (w), 1312 (w), 1216 (w), 862 (m), 780 8m), 742 (s).

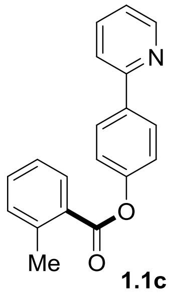

1.33b

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.42 (dt, *J* = 4.7, 1.2 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.77 – 7.69 (m, 1H), 7.60 – 7.39 (m, 5H), 7.34 (m, 2H), 7.24 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.18 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.12 – 7.06 (m, 1H), 7.04 – 6.92 (m, 2H), 2.69 (s, 3H), 2.60 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 198.5 (CO), 165.4 (C$_q$), 156.7 (C$_q$), 151.0 (C$_q$), 148.8 (CH), 142.0 (C$_q$), 141.5 (C$_q$), 139.4 (C$_q$), 137.7 (C$_q$), 137.6 (C$_q$), 136.3 (CH), 133.0 (CH), 132.0 (CH), 131.3 (CH), 131.1 (CH), 130.5 (CH), 130.2 (CH), 128.1 (C$_q$), 126.0 (CH), 124.9 (CH), 123.9 (CH), 123.1 (CH), 122.5 (CH), 121.8 (CH), 22.0 (CH$_3$), 21.1 (CH$_3$).

MS (GC-MS) m/z (relative intensity) = 407 (4) [M$^+$], 364 (8), 288 (15), 272 (15), 119 (100), 91 (54).

HR-MS (ESI-TOF) m/z calcd for $C_{27}H_{22}NO_3^+$ [M+H]$^+$ 408.1594, found 408.1596.


1.1c

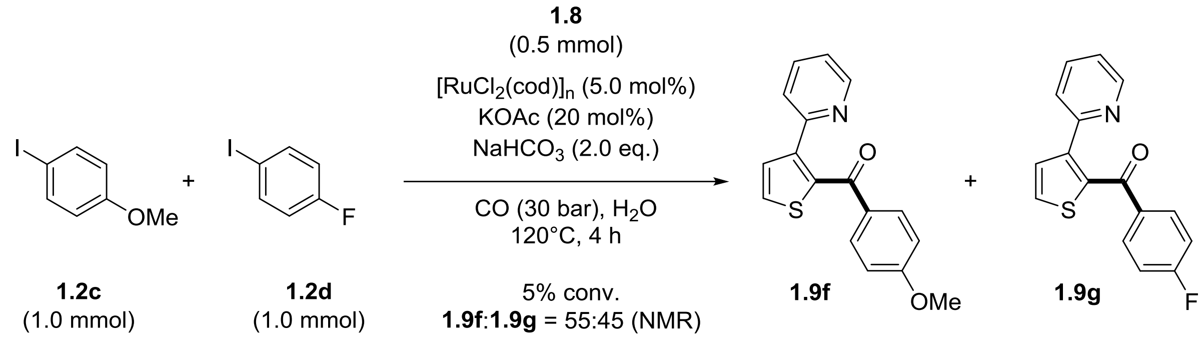
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.73 – 8.67 (m, 1H), 8.23 – 8.16 (m, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.82 – 7.71 (m, 2H), 7.49 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.33 (dd, *J* = 6.8, 6.8 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.25 – 7.21 (m, 1H), 2.70 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ = 165.8 (CO$_2$), 156.8 (C$_q$), 151.8 (C$_q$), 149.8 (CH), 141.5 (C$_q$), 137.2 (C$_q$), 137.0 (CH), 132.9 (CH), 132.1 (CH), 131.4 (CH), 128.6 (C$_q$), 128.2 (CH), 126.1 (CH), 122.3 (CH), 122.3 (CH), 120.6 (CH), 22.1 (CH$_3$).

MS (GC-MS) m/z (relative intensity) = 289 (4) [M+], 170 (3), 141 (12), 119 (100), 91 (38).

HR-MS (ESI-TOF) m/z calcd for $C_{19}H_{16}NO_2^+$ [M+H]+ 290.1176, found 290.1175.

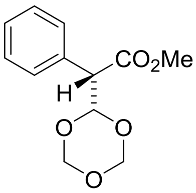
Intermolecular Competition Experiment



The intermolecular competition experiment was conducted using 2-(thiophen-3-yl)pyridine (**1.8**) (80 mg, 0.5 mmol, 1 equiv.), 1-iodo-4-methoxybenzene (**1.2c**) (234 mg, 1.0 mmol, 2.0 equiv.), 1-fluoro-4-iodobenzene (**1.2d**) (222 mg, 1.0 mmol, 2.0 equiv.), $[RuCl_2(cod)]_n$ (7 mg, 0.025 mmol, 5 mol%), $NaHCO_3$ (84 mg, 1.0 mmol), KOAc (10 mg, 20 mol%) in H_2O (1 mL). The reaction mixture was pressurized with CO (30 bar) and stirred for 4 h at 120 °C. After cooling to 0 °C, the pressure was released and the autoclave was purged with N_2 (2 x 10 bar). The reaction mixture was quenched with DCM. The phases were separated using a silicon impregnated filter paper. The supernatant was washed with DCM and the organic phase was removed under reduced pressure. A ^{1}H-NMR spectrum was recorded after thorough drying. Integration of relevant peaks revealed the formation of the desired reaction products **3bf** and **3bg** in a 1.2 to 1.0 ratio after 7% conversion.

6.2.2 Experimental part to Chapter 2

Synthesis of (*S*)-methyl 2-phenyl-2-(1,3,5-trioxan-2-yl)acetate (2.3a):



2.3a

A solution of methyl 2-phenyl-2-diazoacetate (**2.1a**) (89 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 30:1 → 20:1) yielded the title compound (*S*)-**2.3a** (43 mg, 0.18 mmol, 36%)as translucent oil.

A racemic sample was prepared using $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3a** (44 mg, 0.18 mmol, 37%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 7.29 (m, 5H), 5.47 (d, *J* = 8.3 Hz, 1H), 5.24 (dd, *J* = 6.3, 1.2 Hz, 1H), 5.16 (d, *J* = 6.3 Hz, 1H), 5.13 (dd, *J* = 6.3, 1.2 Hz, 1H), 5.00 (d, *J* = 6.3 Hz, 1H), 3.95 (d, *J* = 8.3 Hz, 1H), 3.70 (s, 3H).

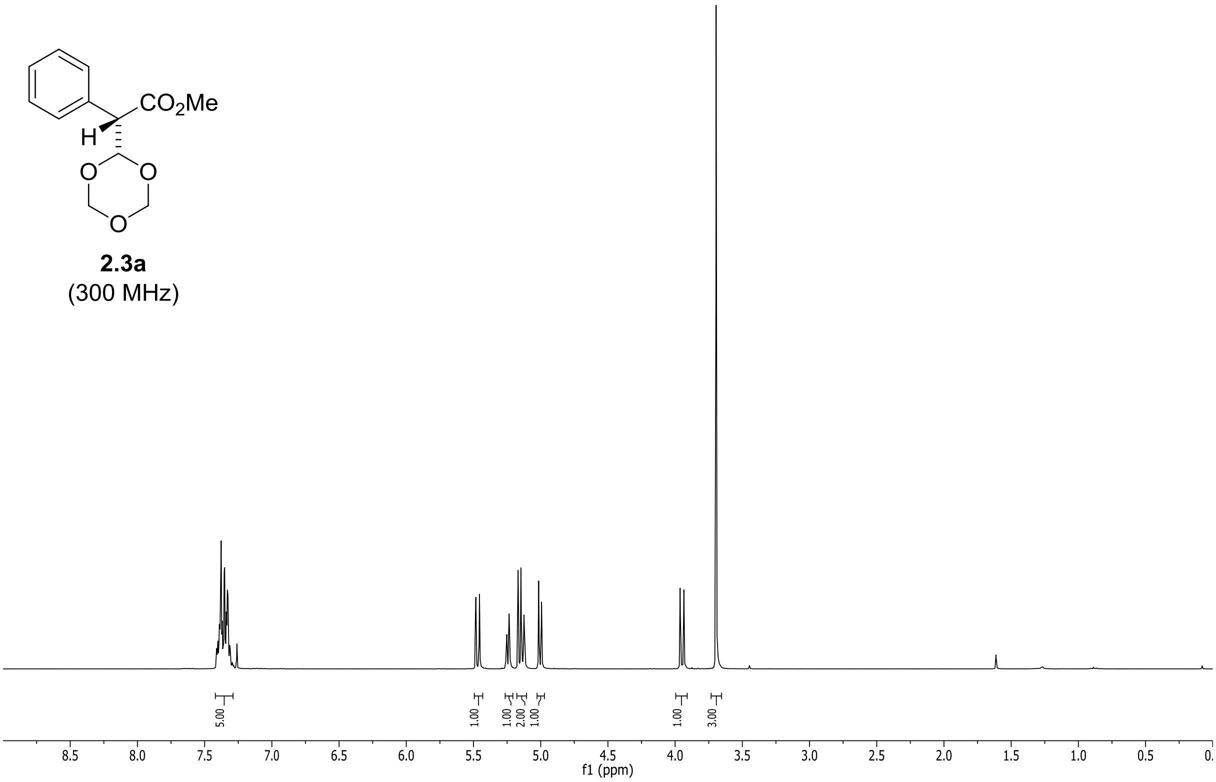
^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.8 (CO_2R), 133.1 (C_q), 128.9 (CH), 128.8 (CH), 128.3 (CH), 101.8 (CH), 93.5 (CH_2), 93.4 (CH_2), 56.3 (CH), 52.5 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 316 (1) [M^+], 230 (14), 196 (14), 134 (11), 89 (100).

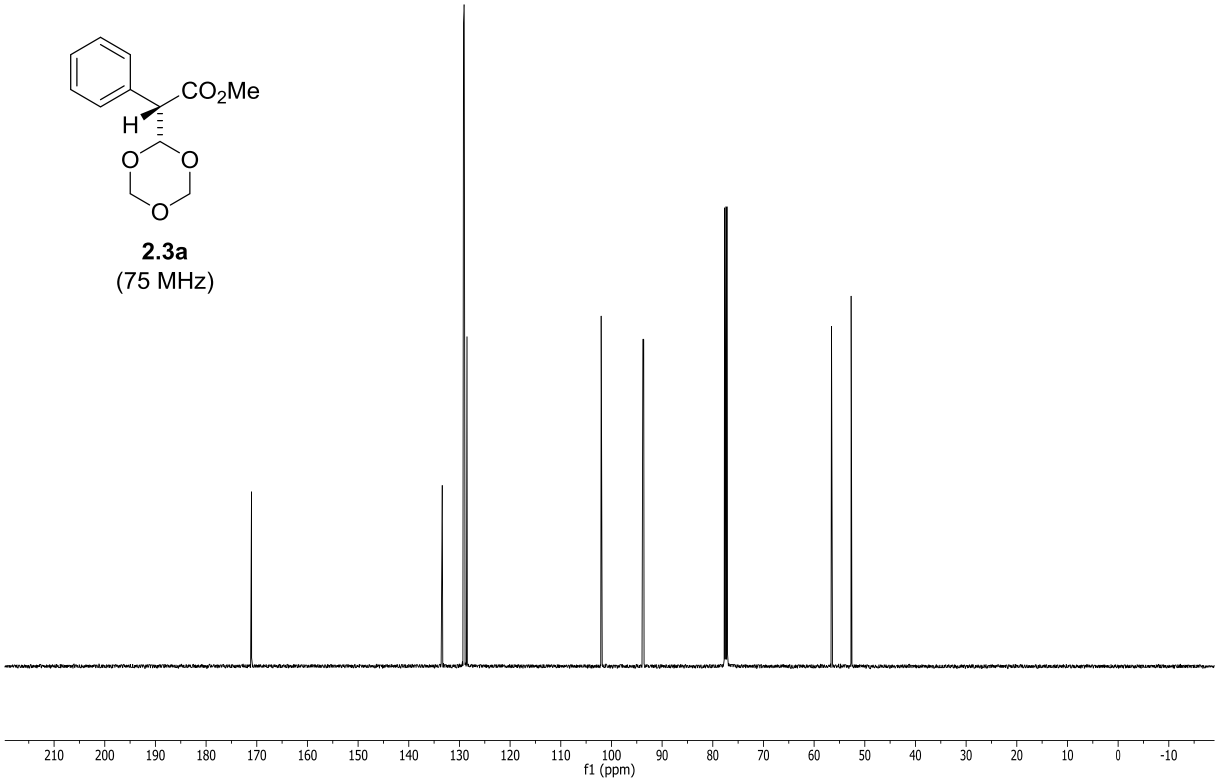
HRMS (EI, m/z) calcd. For $C_{12}H_{14}O_5$ $[M]^+$: 238.0836; found: 238.0830.

IR (ATR, neat, cm^{-1}): 2953 (w), 2862 (w), 1734 (s), 1434 (m), 1316 (m), 1215 (m), 1161 (s), 1136 (s), 1060 (s), 990 (m), 971 (m), 953 (m), 735 (m), 700 (m), 529 (m).

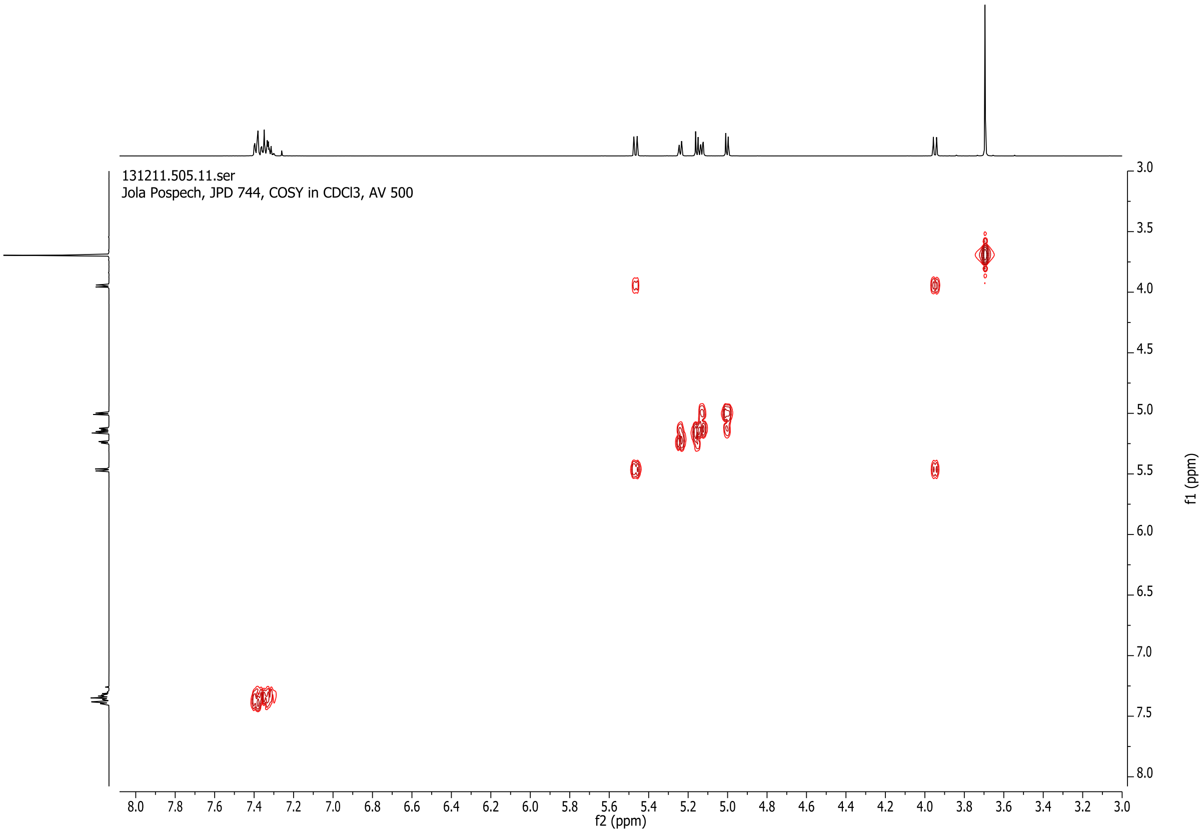
HPLC: Chiracel OD-H, *n*-heptane/*i*-PrOH = 99.7:0.3, 1.0 mL/min, 220 nm, 92% *ee* (t_R (minor) = 15.6 min, t_R (major) = 18.0 min).

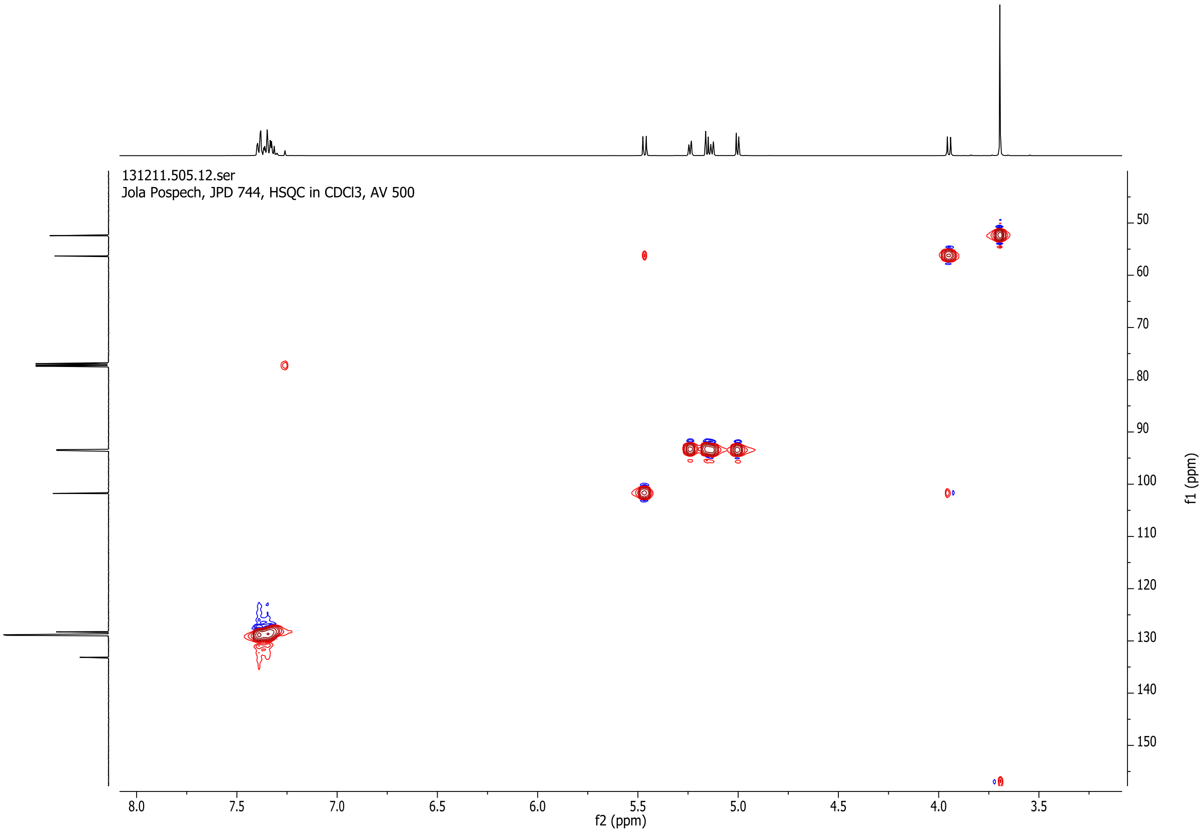


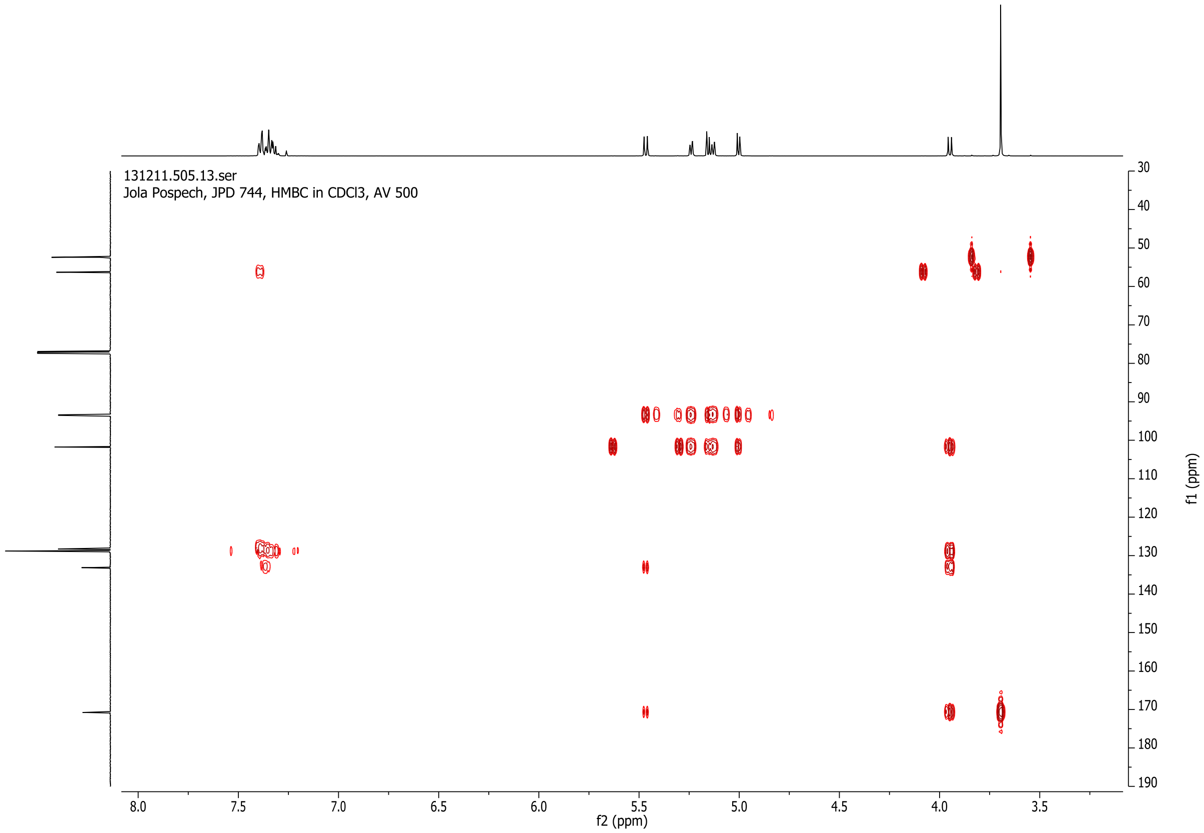
2.3a
(300 MHz)

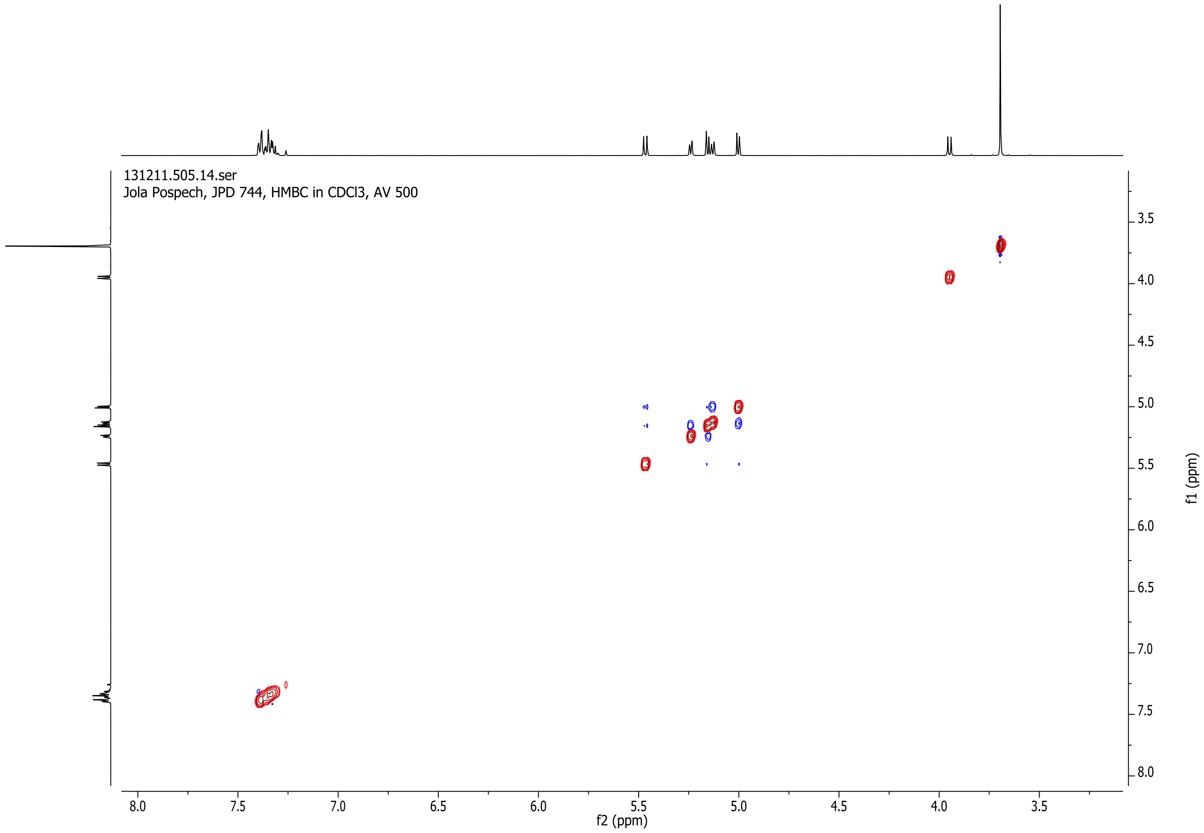


2.3a
(75 MHz)

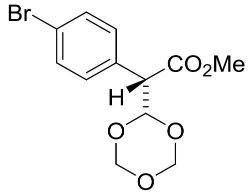

131211.505.11.ser
Jola Pospech, JPD 744, COSY in CDCl3, AV 500
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
f2 (ppm)
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


131211.505.12.ser
Jola Pospech, JPD 744, HSQC in CDCl3, AV 500
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f2 (ppm)
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)


131211.505.13.ser
Jola Pospech, JPD 744, HMBC in CDCl3, AV 500
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f2 (ppm)


131211.505.14.ser
Jola Pospech, JPD 744, HMBC in CDCl3, AV 500
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f2 (ppm)

Synthesis of (*S*)- and (*R*)-methyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3b)



2.3b

A solution of methyl 2-(4-bromophenyl)-2-diazoacetate (**2.1b**) (126 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 30:1 → 20:1) yielded the title compound (*S*)-**2.3b** (67 mg, 0.21 mmol, 42%) as translucent oil. Recrystallization from MeOH afforded an analytically pure sample.

A racemic sample was prepared using $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3b** (86 mg, 0.27 mmol).

m.p.: 114 °C (recrystallized from MeOH)

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 5.42 (d, J = 8.0 Hz, 1H), 5.23 (dd, J = 6.3, 1.2 Hz, 1H), 5.16 – 5.11 (m, 2H), 5.00 (d, J = 6.3 Hz, 1H), 3.90 (d, J = 8.0 Hz, 1H), 3.70 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.4 (CO_2R), 132.1 (C_q), 132.0 (CH), 130.7 (CH), 122.5 (C_q), 101.4 (CH), 93.5 (CH_2), 93.4 (CH_2), 55.7 (CH), 52.6 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 316 (1) [M^+], 228 (14), 196 (14), 169 (9), 134 (11), 89 (100).

HRMS (EI, m/z) calcd. For $C_{12}H_{13}O_5Br$ $[M]^+$: 315.9941; found: 315.9948.

IR (ATR, neat, cm^{-1}): 3013 (w), 2958 (w), 2884 (w), 1736 (s), 1488 (m), 1210 (m), 1136 (s), 1054 (s), 1009 (s), 988 (s), 956 (m), 943 (s), 828 (m), 767 (m), 542 (s).

(*S*)-2.3b:

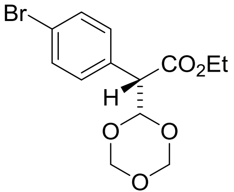
HPLC: Chiracel OD-H, *n*-heptane/*i*-PrOH = 99:1, 0.5 mL/min, 220 nm, 95% *ee* (t_R (minor) = 20.5 min, t_R (major) = 26.0 min).

[*α*]^{28} = -41.28° (*c* = 1.00, $CHCl_3$)

(*R*)-**2.3b**:

HPLC: Chiracel OD-H, *n*-heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 220 nm, 99% *ee* (t_R (major) = 8.83 min).

Synthesis of (*S*)-ethyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3c)



2.3c

A solution of ethyl 2-(4-bromophenyl)-2-diazoacetate (**2.1c**) (135 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*R*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at ambient temperature within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 μL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 30:1 → 20:1) yielded the title compound (*R*)-**2.3c** (63 mg, 0.19 mmol, 38%) as translucent oil. Recrystallization from MeOH afforded a colorless solid.

A racemic sample was prepared using Rh_2(esp)$_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3c** (53 mg, 0.16 mmol, 32%).

m.p.: 148-149 °C (recrystallized from MeOH)

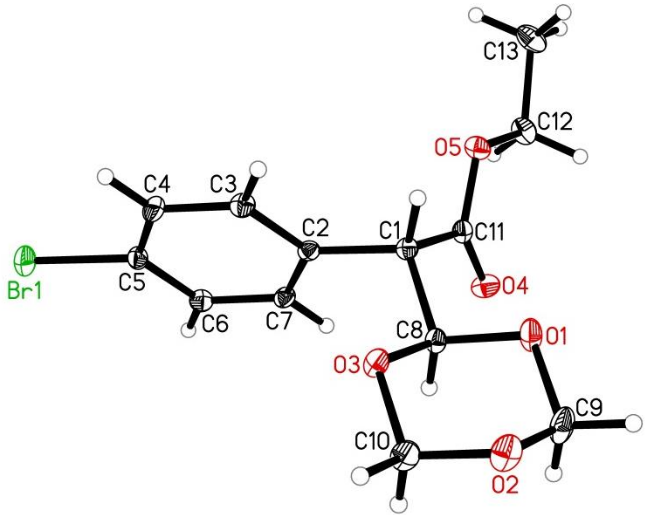
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 5.41 (d, *J* = 8.0 Hz, 1H), 5.23 (dd, *J* = 6.3, 1.2 Hz, 1H), 5.16 – 5.11 (m, 2H), 5.00 (d, *J* = 6.3 Hz, 1H), 4.25 – 4.15 (m, 2H), 3.87 (d, *J* = 8.1 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 169.8 (-CO_2R), 132.1 (C_q), 131.8 (CH), 130.6 (CH), 122.3 (C_q), 101.4 (CH), 93.4 (CH_2), 93.2 (CH_2), 61.5 (CH_2), 55.7 (CH), 14.0 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 332 (2) [M^+], 256 (4), 244 (12), 198 (14), 169 (13), 89 (100).

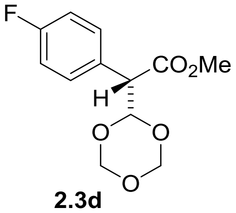
HRMS (EI, m/z) calcd. For $C_{12}H_{13}O_5Br$ $[M]^+$: 315.9941; found: 315.9948.

HPLC: Chiracel OD-H, *n*-heptane/*i*-PrOH = 99:1, 0.5 mL/min, 220 nm, 95% *ee* (t_R (minor) = 20.5 min, t_R (major) = 25.9 min).



Empirical formula	$C_{13}H_{15}BrO_5$	
Formula weight	331.16	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.7276(3) Å	α= 90°.
	b = 7.9566(3) Å	β= 90°.
	c = 30.6039(13) Å	γ = 90°.
Volume	1394.69(11) $Å^3$	
Z	4	
Density (calculated)	1.577 Mg/m^3	
Absorption coefficient	2.960 mm^{-1}	
F(000)	672	
Crystal size	0.43 x 0.38 x 0.08 mm^3	
Theta range for data collection	2.65 to 28.00°.	
Index ranges	-7<=h<=7, -5<=k<=10, -38<=l<=40	
Reflections collected	19233	
Independent reflections	3372 [R(int) = 0.0321]	
Completeness to theta = 28.00°	99.9 %	
Max. and min. transmission	0.789 and 0.361	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3372 / 0 / 173	
Goodness-of-fit on F^2	1.070	
Final R indices [I>2sigma(I)]	R1 = 0.0240, wR2 = 0.0514	
R indices (all data)	R1 = 0.0268, wR2 = 0.0525	
Absolute structure parameter	0.002(7)	
Largest diff. peak and hole	0.384 and -0.409 $e.Å^{-3}$	

Synthesis of (*S*)-methyl 2-(4-fluorophenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3d)



2.3d

A solution of methyl 2-(4-fluorophenyl)-2-diazoacetate (**2.1d**) (97 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 μL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 30:1) yielded the title compound (*S*)-**2.3d** (53 mg, 0.21 mmol, 41%) as translucent oil.

A racemic sample was prepared using $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3d** (70 mg, 0.28 mmol).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 5.41 (d, *J* = 8.1 Hz, 1H), 5.23 (dd, *J* = 6.2, 1.4 Hz, 1H), 5.14 (dd, *J* = 6.3, 1.4 Hz, 2H), 5.01 (d, *J* = 6.3 Hz, 1H), 3.92 (d, *J* = 8.1 Hz, 1H), 3.70 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.7 (CO), 162.7 (d, $^2J_{C\text{-}F}$ = 247.0 Hz, C_q), 130.6 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 128.8 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, C_q), 115.8 (d, $^3J_{C\text{-}F}$ = 21.6 Hz, CH), 101.6 (CH), 93.5 (CH_2), 93.4 (CH_2), 55.4 (CH_3), 52.5 (CH).

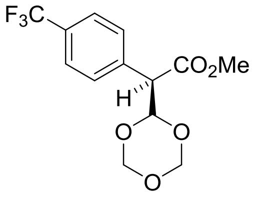
^{19}F NMR (282 MHz, Chloroform-*d*) δ -113.6 (m).

MS (GC-MS) *m/z* (relative intensity) = 256 (2) [M^+], 225 (1), 168 (44), 136 (47), 109 (75), 89 (100), 61 (36).

HRMS (EI, m/z) calcd. For $C_{12}H_{13}O_5F_1$ $[M]^+$: 256.0742; found: 256.0743.

$[\alpha]_D^{22}$ = -45.25° (*c* = 1.5, CH_2Cl_2)

Synthesis of (*R*)-methyl 2-(4-(trifluoromethyl)phenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3e)



2.3e

A solution of methyl 2-(4-trifluoromethylphenyl)-2-diazoacetate (**2.1e**) (122 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*R*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound (*R*)-**2.3e** (55 mg, 0.18 mmol, 36%) as translucent oil. Recrystallization from MeOH afforded a colorless solid.

A racemic sample was prepared using $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3e** (67 mg, 0.22 mmol, 44%).

m.p.: 74 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 5.47 (d, *J* = 7.9 Hz, 1H), 5.24 (dd, *J* = 6.3, 1.3 Hz, 1H), 5.15 (d, *J* = 6.3 Hz, 1H), 5.13 (dd, *J* = 6.3, 1.3 Hz, 1H), 5.01 (d, *J* = 6.3 Hz, 1H), 4.01 (d, *J* = 7.9 Hz, 1H), 3.71 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.1(C_q) , 137.0 (C_q), 130.5 (q, $^2J_{C–F}$ = 32.6 Hz, C_q), 129.5 , 125.7 (q, $^3J_{C–F}$ = 3.8 Hz, CH), 124.1 (q, $^1J_{C–F}$ = 272.1 Hz), 101.4 (CH), 93.5 (CH_2), 93.4 (CH_2), 56.1 (CH_3), 52.7 (CH).

^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.3 (s).

MS (GC-MS) *m/z* (relative intensity) = 247 (2) [M$^+$], 218 (24), 186 (39), 159 (29), 127 (10), 89 (100), 61 (37).

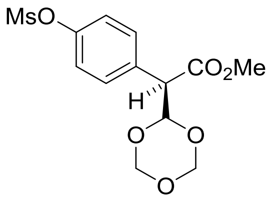
HRMS (EI, m/z) calcd. For $C_{11}H_{10}O_3F_3$ [M]$^+$: 247.0577; found: 247.0582.

IR (ATR, neat, cm^{-1}): 2961 (w), 2861 (w), 1732 (m), 1320 (s), 1159 (s), 1110 (s), 1063 (s), 1018 (m), 1992 (m), 944 (m), 838 (m), 761 (w), 600 (w).

HPLC: Cellulose2, *n*-heptane/EtOH = 90:10, 0.3 mL/min, 220 nm, 94% *ee* (t_R (major) = 10.2 min, t_R (minor) = 12.5 min).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +36.74° (*c* = 2.5, $CHCl_3$)

Synthesis of (*R*)-methyl 2-(4-((methylsulfonyl)oxy)phenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3f)



2.3f

A solution of methyl 2-(4- methylsulfonylphenyl)-2-diazoacetate (**2.1f**) (135 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh$_2$(*R*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 μL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 10:1 → 5:1 → 2:1) yielded the title compound (*R*)-**2.3f** (63 mmg, 0.19 mmol, 38%) as colorless solid. Recrystallization from MeOH afforded a colorless solid.

A racemic sample was prepared using Rh$_2$(esp)$_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3f** (86 mg, 0.26 mmol, 52%).

m.p.: 144 °C (recrystallized from MeOH)

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 5.42 (d, *J* = 8.0 Hz, 1H), 5.22 (d, *J* = 6.3 Hz, 1H), 5.14 (d, *J* = 6.3 Hz, 1H), 5.13 (d, *J* = 6.3 Hz, 1H), 5.00 (d, *J* = 6.3 Hz, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.70 (s, 3H), 3.14 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.1 (CO$_2$), 148.8 (C$_q$), 132.2 (C$_q$), 130.5 (CH), 122.1 (CH), 101.2 (CH), 93.3 (CH$_{2)}$, 93.2 (CH$_2$), 55.4 (CH$_3$), 52.5 (CH), 37.4 (CH$_3$).

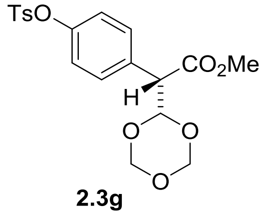
MS (GC-MS) *m/z* (relative intensity) = 332 (1) [M$^+$], 256 (16), 244 (60), 165 (100), 133 (42), 89 (64).

HRMS (EI, m/z) calcd. For $C_{13}H_{16}O_8S_1$ [M]$^+$: 332.0560; found: 332.0569.

IR (ATR, neat, cm^{-1}): 3018 (w), 3001 (w), 2877 (w), 1722 (m), 1508 (w), 1366 (m), 1144 (s), 1061 (m), 969 (m), 876 (s), 789 (m), 523 (s).

$[\alpha]_D^{22}$ = +42.63° (*c* = 1.0, CH$_2$Cl$_2$)

Synthesis of (*S*)-methyl 2-(4-((tosylsulfonyl)oxy)phenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3g)



2.3g

A solution of methyl 2-(4-tosylsulfonylphenyl)-2-diazoacetate (173 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound (*S*)-**2.3g** (110 mg, 0.27 mmol, 54%) as colorless solid. Recrystallization from MeOH afforded a colorless solid.

A racemic sample was prepared using Rh_2(esp)$_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3g** (124 mg, 0.31 mmol, 61%).

m.p.: 112-113 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.27 (m, 4H), 6.95 (d, *J* = 8.6 Hz, 2H), 5.37 (d, *J* = 8.0 Hz, 1H), 5.20 (d, *J* = 6.5, 1.2 Hz, 1H), 5.11 (d, *J* = 6.2 Hz, 1H), 5.09 (d, *J* = 6.5, 1.2 Hz, 1H), 4.98 (d, *J* = 6.3 Hz, 1H), 3.89 (d, *J* = 8.0 Hz, 1H), 3.68 (s, 2H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.3 (C_q), 149.4 (C_q), 145.5 (C_q), 132.6 (C_q), 132.0 (C_q), 130.3 (CH), 129.9 (CH), 128.5 (CH), 122.6 (CH), 101.4 (CH), 93.4 (CH_2), 93.3 (CH_2), 55.6 (CH_3), 52.6 (CH), 21.8 (CH_3).

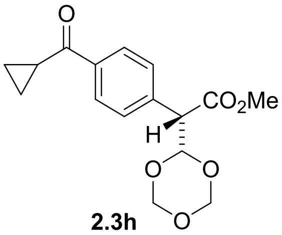
MS (GC-MS) *m/z* (relative intensity) = 408 (1) [M^+], 332 (15), 320 (41), 289 (5), 165 (100), 137 (21), 91 (43).

HRMS (EI, m/z) calcd. For $C_{19}H_{20}O_8S_1$ $[M]^+$: 408.0873; found: 408.0877.

IR (ATR, neat, cm^{-1}): 2958 (w), 2871 (w), 1733 (m), 1470 (w), 1367 (m), 1177 (m), 1153 (s), 10681 (m), 862 (s), 657 (m), 550 (s).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{22}}$ = -31.97° (*c* = 3.5, $CHCl_3$)

Synthesis of (S)-Methyl 2-(4-(cyclopropanecarbonyl)phenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3h)



2.3h

A solution of methyl 2-(4-(cyclopropanecarbonyl)phenyl)-2-diazoacetate (**2.1h**) (73 mg, 0.3 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (5.6 mg, 1.0 mol%) and 1,3,5-trioxane (286 mg, 3.18 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 10:1 → 7:1 → 5:1) yielded the title compound **2.3h** (21 mg, 0.07 mmol, 23%) as translucent oil.

A racemic sample was prepared using 2-(4-(cyclopropanecarbonyl)phenyl)-2-diazoacetate (110 mg, 0.45 mmol, 1.0 equiv.) and $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3h** (47 mg, 0.153 mmol, 34%).

^{1}H NMR (300 MHz, Chloroform-d) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 5.49 (d, *J* = 8.0 Hz, 1H), 5.23 (dd, *J* = 6.1, 1.3 Hz, 1H), 5.15 (d, *J* = 6.3 Hz, 1H), 5.12 (dd, *J* = 6.4, 1.3 Hz, 1H), 5.00 (d, *J* = 6.3 Hz, 1H), 4.01 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H), 2.64 (tt, *J* = 7.9, 4.5 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 0H), 1.22 (dt, *J* = 4.5, 3.3 Hz, 2H), 1.03 (dt, *J* = 7.9, 3.3 Hz, 2H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 200.1 (C_q), 170.2 (C_q), 137.8 (C_q), 129.2 (CH), 128.4 (CH), 101.4 (CH), 93.5 (CH_2), 93.4 (CH_2), 56.2 (CH), 52.6 (CH_3), 17.3 (CH), 11.8 (CH_2).

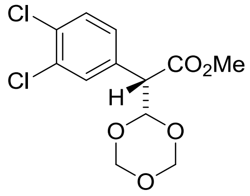
MS (GC-MS) *m/z* (relative intensity) = 306 (3) [M^+], 276 (4), 218 (63), 186 (15), 145 (46), 89 (100), 61 (29).

HRMS (EI, m/z) calcd. For $C_{16}H_{18}O_6$ $[M+H]^+$: 307.1176; found: 307.1179.

HPLC: Cellulose2, *n*-heptane/EtOH = 95:5, 1.0 mL/min, 220 nm, 91% *ee* (t_R (minor) = 15.30 min, t_R (major) = 20.32 min).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = -47.85° (*c* = 0.5, *i*-PrOH)

Synthesis of (*S*)-methyl 2-(3,4-dichlorophenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3i)



A solution of methyl 2-(3,4-dichlorophenyl)-2-diazoacetate (**2.1i**) (123 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound (*S*)-**3i** (54 mg, 0.18 mmol, 35%) as translucent oil. Recrystallization from MeOH afforded a colorless solid.

A racemic sample was prepared using Rh_2(esp)$_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3i** (80 mg, 0.26 mmol, 52%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 2.1 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.40 (d, *J* = 7.8 Hz, 1H), 5.22 (dd, *J* = 6.3, 1.2 Hz, 1H), 5.18 – 5.08 (m, 2H), 5.01 (d, *J* = 6.3 Hz, 1H), 3.89 (d, *J* = 7.8 Hz, 1H), 3.71 (s, 3H).

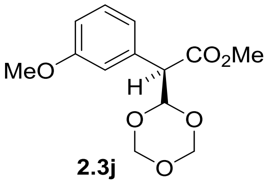
^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.0 (CO), 133.1 (C_q), 132.8 (C_q), 132.6 (C_q), 131.0 (C_q), 130.6 (CH), 128.6 (CH), 101.1 (CH), 93.4 (CH_2), 93.3 (CH_2), 55.3 (CH), 52.7 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 306 (1) [M^+], 247 (1), 218 (23), 186 (25), 159 (19), 123 (22), 89 (100).

HPLC: Chiracel OD-H, *n*-heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 220 nm, 77% *ee* (t_R (minor) = 13.1 min, t_R (major) = 16.3 min).

$[\alpha]_D^{28}$ = -23.14° (*c* = 1.25, $CHCl_3$)

Synthesis of (*R*)-methyl 2-(3-methoxyphenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3j)



2.3j

A solution of methyl 2-(3-methoxyphenyl)-2-diazoacetate (**2.1j**) (103 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*R*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 20:1 → 10:1) yielded the title compound (*R*)-**2.3j** (27 mg, 0.10 mmol, 20%) as translucent oil.

A racemic sample was prepared using $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3j** (64 mg, 0.24 mmol, 48%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.63 – 7.51 (m, 1H), 7.32 – 7.21 (m, 2H), 7.17 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 5.77 (d, *J* = 8.3 Hz, 1H), 5.55 (dd, *J* = 6.3, 1.2 Hz, 1H), 5.47 (d, *J* = 6.2 Hz, 1H), 5.45 (dd, *J* = 6.3, 1.2 Hz, 1H), 5.32 (d, *J* = 6.4 Hz, 1H), 4.22 (d, *J* = 8.3 Hz, 1H), 4.12 (s, 3H), 4.01 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.7 (C_q), 159.8 (C_q), 134.5 (C_q), 129.8 (CH), 121.2 (CH), 114.7 (CH), 113.6 (CH), 101.7 (CH), 93.6 (CH_2), 93.4 (CH_2), 56.3 (CH), 55.3 (CH_3), 52.5 (CH_3).

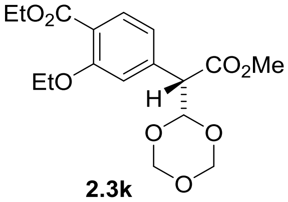
MS (GC-MS) *m/z* (relative intensity) = 268 (8) [M^+], 192 (63), 180 (22), 148 (100), 121 (29), 89 (30), 61 (28).

HRMS (EI, m/z) calcd. For $C_{13}H_{16}O_6$ $[M]^+$: 268.0941; found: 268.0940.

HPLC: Chiracel OD-H, *n*-heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 220 nm, 76% *ee* (t_R (major) = 29.8 min, t_R (minor) = 34.4 min).

$[\alpha]_D^{28}$ = +53.5° (*c* = 1.0, $CHCl_3$)

Synthesis of (*S*)-ethyl 2-ethoxy-4-(2-methoxy-2-oxo-1-(1,3,5-trioxan-2-yl)ethyl)benzoate (2.3k)



2.3k

A solution of methyl ethyl 2-ethoxy-4-(2-methoxy-2-oxoethyl)-2-diazoacetate (**2.1k**) (146 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 20:1 → 10:1 → 5:1) yielded the title compound as (*S*)-**2.3k** (60 mg, 0.17 mmol, 34%) pale yellow oil.

A racemic sample was prepared using $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3k** (98 mg, 0.28 mmol, 55%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.3 Hz, 1H), 7.00 – 6.92 (m, 2H), 5.42 (d, *J* = 8.1 Hz, 1H), 5.22 (dd, *J* = 6.3, 1.2 Hz, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 5.10 (dd, *J* = 6.3, 1.2 Hz, 1H), 4.98 (d, *J* = 6.4 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.91 (d, *J* = 8.1 Hz, 1H), 3.69 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.2 (C_q), 166.2 (C_q), 158.5 (C_q), 138.3 (C_q), 131.7 (CH), 120.7 (C_q), 120.5 (CH), 114.1 (CH), 101.4 (CH), 93.5 (CH_2), 93.4 (CH_2), 64.7 (CH_2), 60.9 (CH_2), 56.3 (CH), 52.6 (CH_3), 14.8 (CH_3), 14.4 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 354 (6) [M^+], 309 (22), 278 (69), 220 (100), 187 (13), 161 (30), 89 (59).

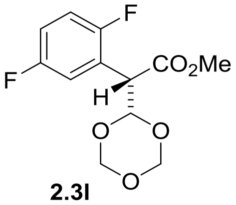
HRMS (EI, m/z) calcd. For $C_{17}H_{22}O_8$ $[M+H]^+$: 355.13874; found: 355.13879.

IR (ATR, neat, cm^{-1}): 2976 (w), 2866 (w), 1734 (m), 1611 (w), 1297 (m), 1267 (m), 1162 (s), 1114 (s), 1067 (s), 947 (m), 746 (w).

HPLC: Cellulose2, *n*-heptane/EtOH = 98:2, 0.8 mL/min, 220 nm, 67% *ee* (t_R (minor) = 24.7 min, t_R (major) = 32.5 min).

$[\alpha]_D^{22}$ = -35.9° (*c* = 1.0, $CHCl_3$)

Synthesis of (*S*)-Methyl 2-(2,5-difluorophenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3l)



2.3l

A solution of methyl 2-(2,5-difluorophenyl)-2-diazoacetate (**2.1l**) (106 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*S*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 20:1 → 10:1 → 5:1) yielded the title compound **2.3l** (30 mg, 0.11 mmol, 21%) as pale yellow oil.

A racemic sample was prepared using $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **3l** (72 mg, 0.26 mmol, 53%).

m.p.: 69-70 °C

^{13}C NMR (75 MHz, Chloroform-*d*) δ 169.5 (C_q), 158.5 (dd, $^1J_{C-F}$ 242.3, $^4J_{C-F}$ = 2.4 Hz), 157.1 (dd, $^1J_{C-F}$ = 243.8, $^4J_{C-F}$ = 2.5 Hz), 116.8 (dd, $^2J_{C-F}$ = 25.2, $^3J_{C-F}$ = 3.5 Hz, CH), 116.4 (dd, $^3J_{C-F}$ = 8.6, $^4J_{C-F}$ = 3.6 Hz), 122.0 (dd, $^2J_{C-F}$ = 17.2, $^3J_{C-F}$ = 8.4 Hz), 116.4 (dd, J = 53.3, 8.7 Hz), 100.8 (d, J = 1.7 Hz), 93.4 , 93.3 , 52.7, 48.2 , 49.2 – 46.7 (m).

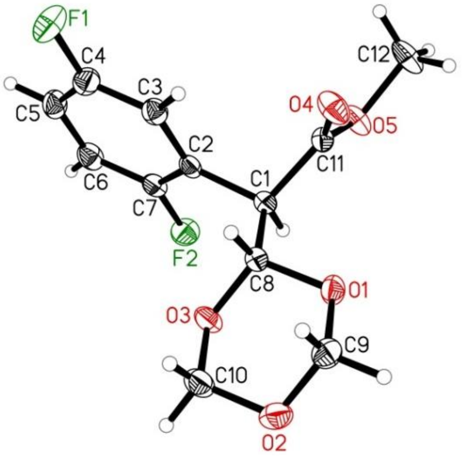
^{19}F NMR (282 MHz, Chloroform-*d*) δ -117.4 – -118.3 (m), -122.1 – -123.1 (m).

MS (GC-MS) *m/z* (relative intensity) = 274 (1) [M^+], 215 (2), 186 (40), 154 (63), 127 (62), 89 (100), 61 (38).

IR (ATR, neat, cm^{-1}): 3008 (w), 2928 (w), 2823 (w), 1664 (m), 1381 (m), 1224 (w), 1096 (s), 991 (s), 825 (m), 742 (m).

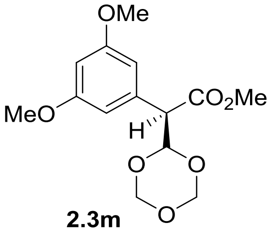
HPLC: Chiracel OD-H, *n*-heptane/*i*PrOH = 99.5:0.5, 1.5 mL/min, 220 nm, 70% *ee* (t_R (minor) = 11.4 min, t_R (major) = 13.1 min).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = -36.2° (*c* = 1.25, $CHCl_3$)



Empirical formula	$C_{12}H_{12}F_2O_5$	
Formula weight	274.22	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 7.9463(7) Å	α= 104.074(2)°.
	b = 8.7658(8) Å	β= 104.446(2)°.
	c = 10.3812(10) Å	γ = 112.083(2)°.
Volume	601.39(10) $Å^3$	
Z	2	
Density (calculated)	1.514 Mg/m^3	
Absorption coefficient	0.137 mm^{-1}	
F(000)	284	
Crystal size	0.50 x 0.36 x 0.14 mm	
Theta range for data collection	2.19 to 28.00°.	
Index ranges	-10<=h<=10, -11<=k<=11, -13<=l<=13	
Reflections collected	16835	
Independent reflections	2911 [R(int) = 0.0389]	
Completeness to theta = 28.00°	100.0 %	
Max. and min. transmission	1.000 and 0.855	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2911 / 0 / 173	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2sigma(I)]	R1 = 0.0412, wR2 = 0.1225	
R indices (all data)	R1 = 0.0527, wR2 = 0.1358	
Largest diff. peak and hole	0.374 and -0.271 $e^{\cdot}Å^{-3}$	

Synthesis of (*R*)-methyl 2-(3,5-dimethoxyphenyl)-2-(1,3,5-trioxan-2-yl)acetate (2.3m)


2.3m

A solution of methyl 2-(3,5-dimethoxyphenyl)-2-diazoacetate (**2.1m**) (118 mg, 0.50 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of Rh_2(*R*-DOSP)$_4$ (9.5 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 0°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 20:1 → 10:1) yielded the title compound as (*R*)-**2.3m** (26 mg, 0.87 mmol, 17%) translucent oil. Recrystallization from MeOH afforded a colorless solid.

A racemic sample was prepared using **1m** (113 mg, 0.48 mol), $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) at 40°C under otherwise identical reaction conditions, yielding **2.3m** (80 mg, 0.27 mmol, 56%).

m.p.: 101-102 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.53 (d, *J* = 2.3 Hz, 2H), 6.40 (dd, *J* = 2.3 Hz, 1H), 5.43 (d, *J* = 8.3 Hz, 1H), 5.22 (dd, *J* = 6.3, 1.2 Hz, 1H), 5.14 (m, 2H), 5.00 (d, *J* = 6.3 Hz, 1H), 3.85 (d, *J* = 8.3 Hz, 1H), 3.77 (s, 6H), 3.68 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.5 (C_q), 160.9 (C_q), 135.0 (C_q), 107.0 (CH), 101.6 (CH_2), 100.1 (CH_2), 56.4 (CH_3), 55.4 (CH_3), 52.4 (CH).

MS (GC-MS) *m/z* (relative intensity) = 298 (29) [M^+], 222 (97), 178 (100), 151 (28), 121 (18), 89 (43).

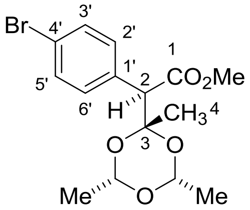
HRMS (EI, m/z) calcd. For $C_{14}H_{18}O_7$ $[M+H]^+$: 298.1047; found: 298.1041.

IR (ATR, neat, cm^{-1}): 2966 (w), 2864 (w), 1729 (m), 1597 (m), 1463 (w), 1323 (w), 1202 (m), 1161 (s), 1137 (s), 1051 (s), 947 (m), 835 (m), 688 (m), 531 (m).

HPLC: Cellulose2, *n*-heptane/*i*PrOH = 98:2, 1.0 mL/min, 220 nm, 53% *ee* (t_R (major) = 25.25 min, t_R (minor) = 29.07 min).

$[\alpha]_D^{22}$ = -17.0° (*c* = 0.5, $CHCl_3$)

Synthesis of *rac*-methyl 2-(4-bromophenyl)-2-2,4,6-trimethyl-1,3,5-trioxan-2-yl)acetate (2.5)



A solution of methyl 2-(4-bromophenyl)-2-diazoacetate (**2.1b**) (127 mg, 0.5 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.0 mL) was added dropwise to a styrring solution of $Rh_2(esp)_2$ (3.6 mg, 1.0 mol%) and 1,3,5-trioxane (450 mg, 5 mmol, 10 equiv.) in 1,2-dichloroethane (5.0 mL) at 40°C within 90 min. The reaction mixture was stirred for additional 30 min. Volatiles were removed under reduced pressure. Mesitylene (20 µL) was added as internal standard. Purification by flash chromatography (*n*-pentane:EtOAc = 40:1) yielded the title compound **2.5** (90 mg, 0.25 mmol, 50%) as colorless oil.

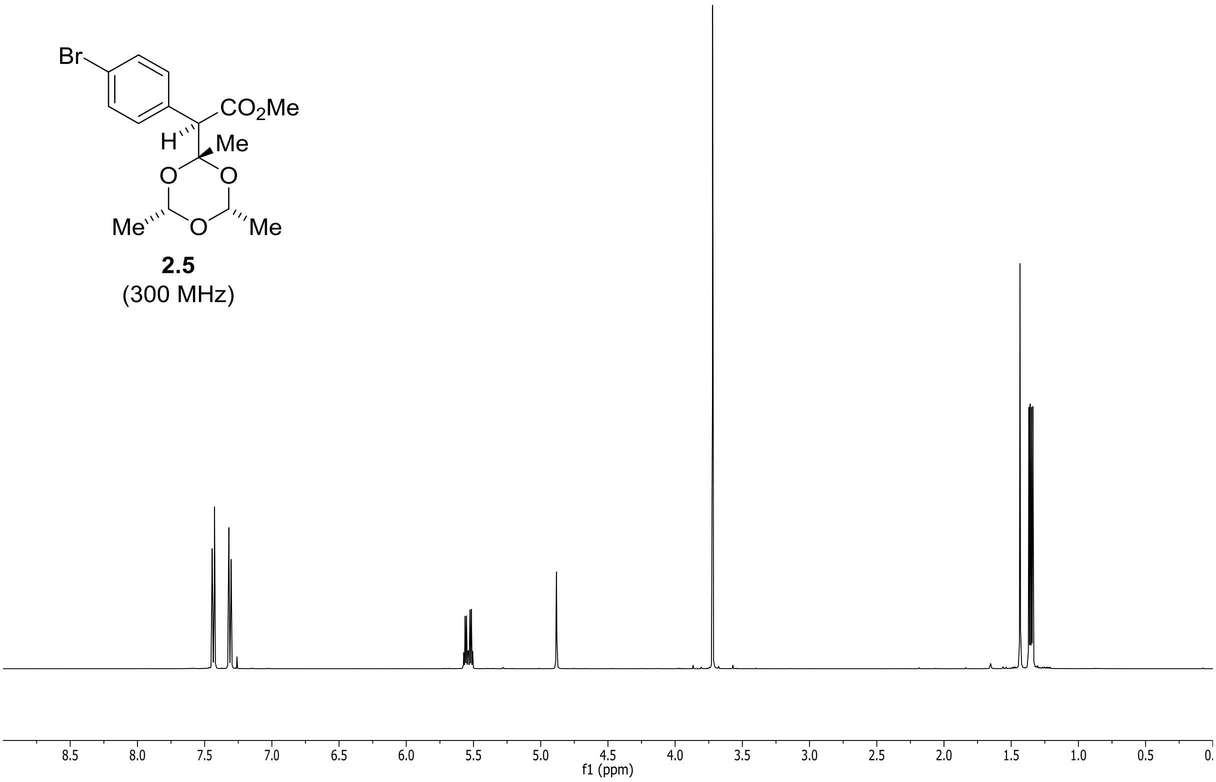
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.5 Hz, 2H, H-3’, H-5’), 7.31 (d, *J* = 8.5 Hz, 2H, H-2’, H-6’), 5.56 (q, *J* = 5.0 Hz, 1H), 5.52 (q, *J* = 5.0 Hz, 1H), 4.88 (s, 3H, H-2), 1.43 (s, 3H, H-4), 1.36 (d, *J* = 5.0 Hz, 3H), 1.34 (d, *J* = 5.0 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.2 (CO), 133.1 (C_q), 131.5 (CH), 131.2 (CH), 122.0 (C_q), 100.9 (C_q), 93.0 (CH), 92.4 (CH), 52.2 (CH_3), 50.6 (CH), 24.3 (CH_3), 21.1 (CH_3), 21.0 (CH_3).

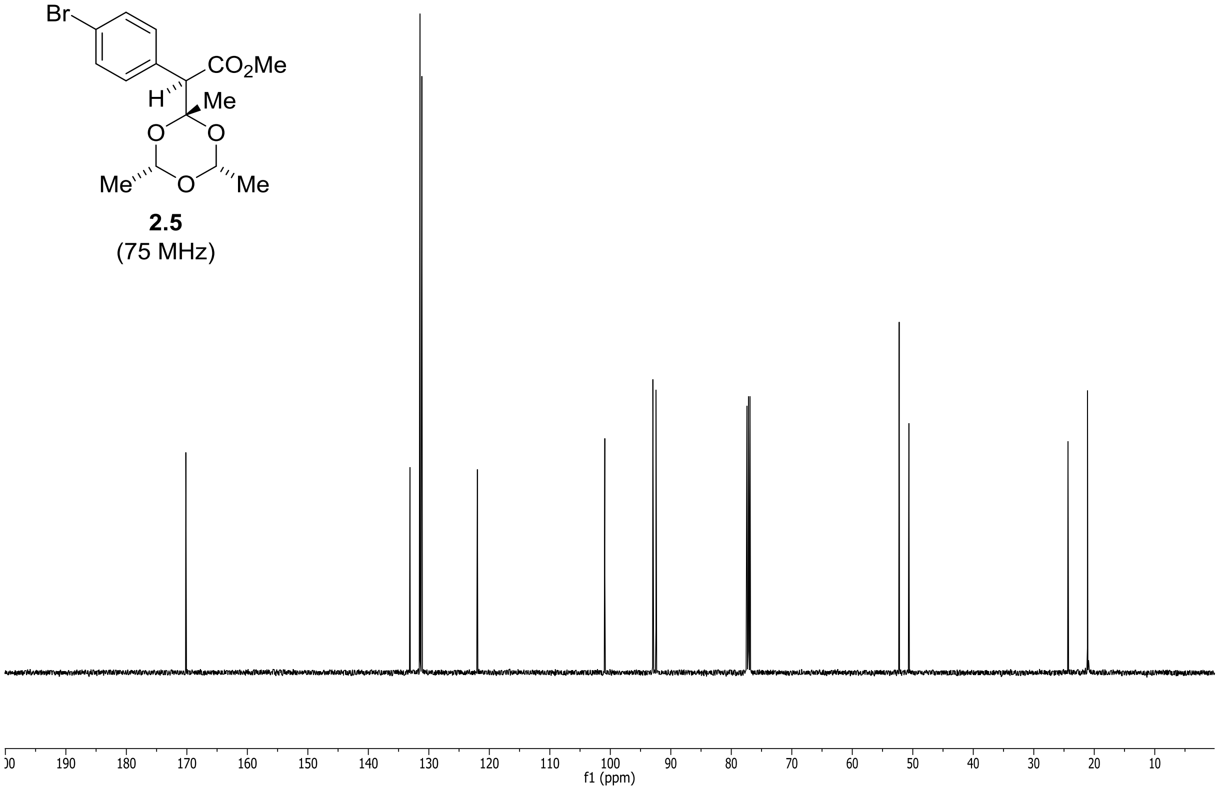
MS (GC-MS) *m/z* (relative intensity) = 359 (0) [M^+], 315 (1), 272 (5), 228 (56), 196 (17), 131 (48), 87 (58), 43 (100).

HRMS (EI, m/z) calcd. For $C_{15}H_{19}BrO5$ $[M+Na]^+$: 381.0308; found: 381.0307.

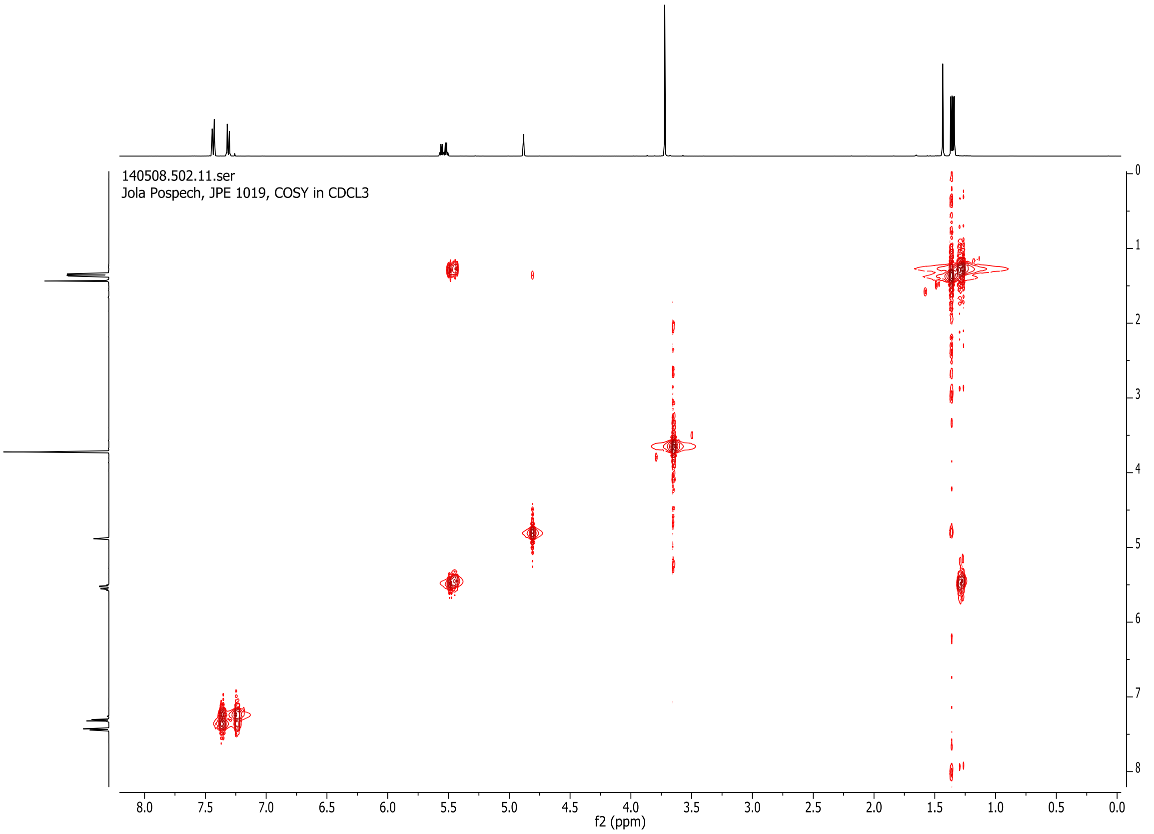
IR (ATR, neat, cm^{-1}): 2995 (w), 2950 (w), 1738 (m), 1490 (m), 1391 (m), 1178 (s), 1094 (s), 979 (s), 951 (m), 845 (m), 527 (m).

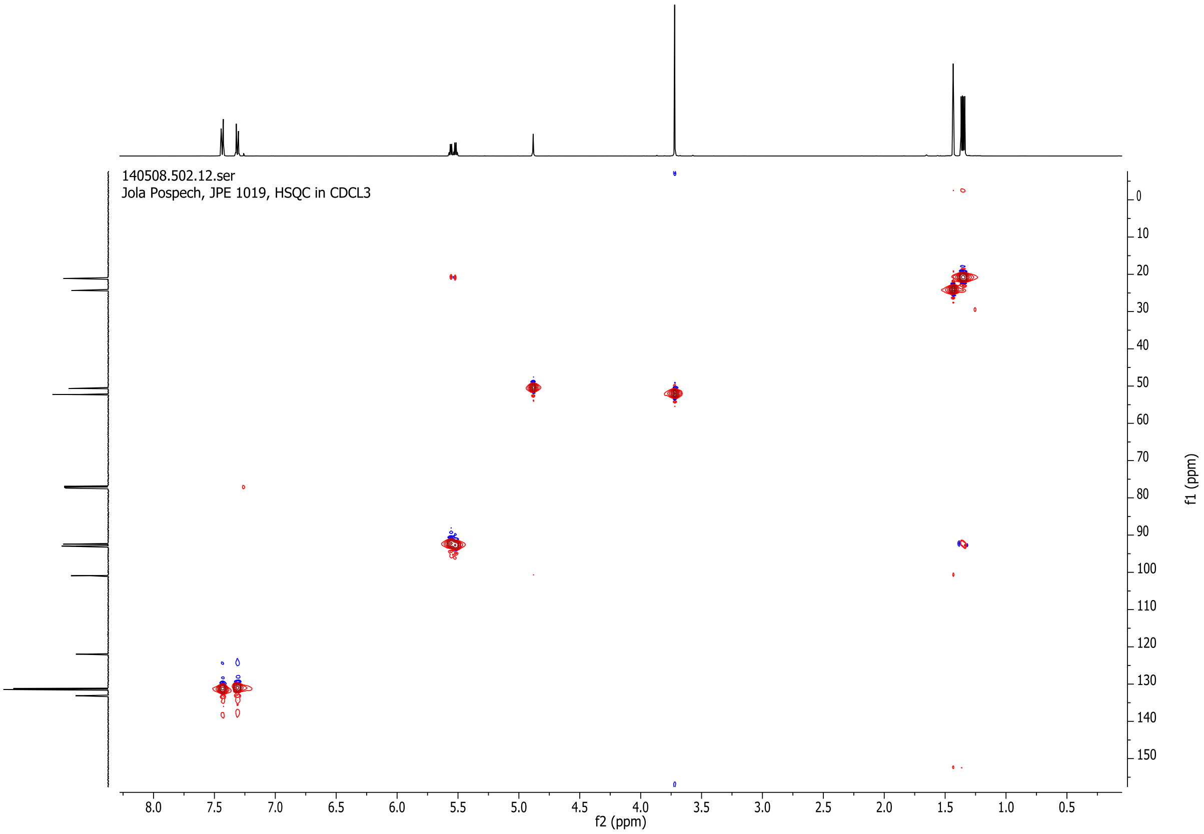


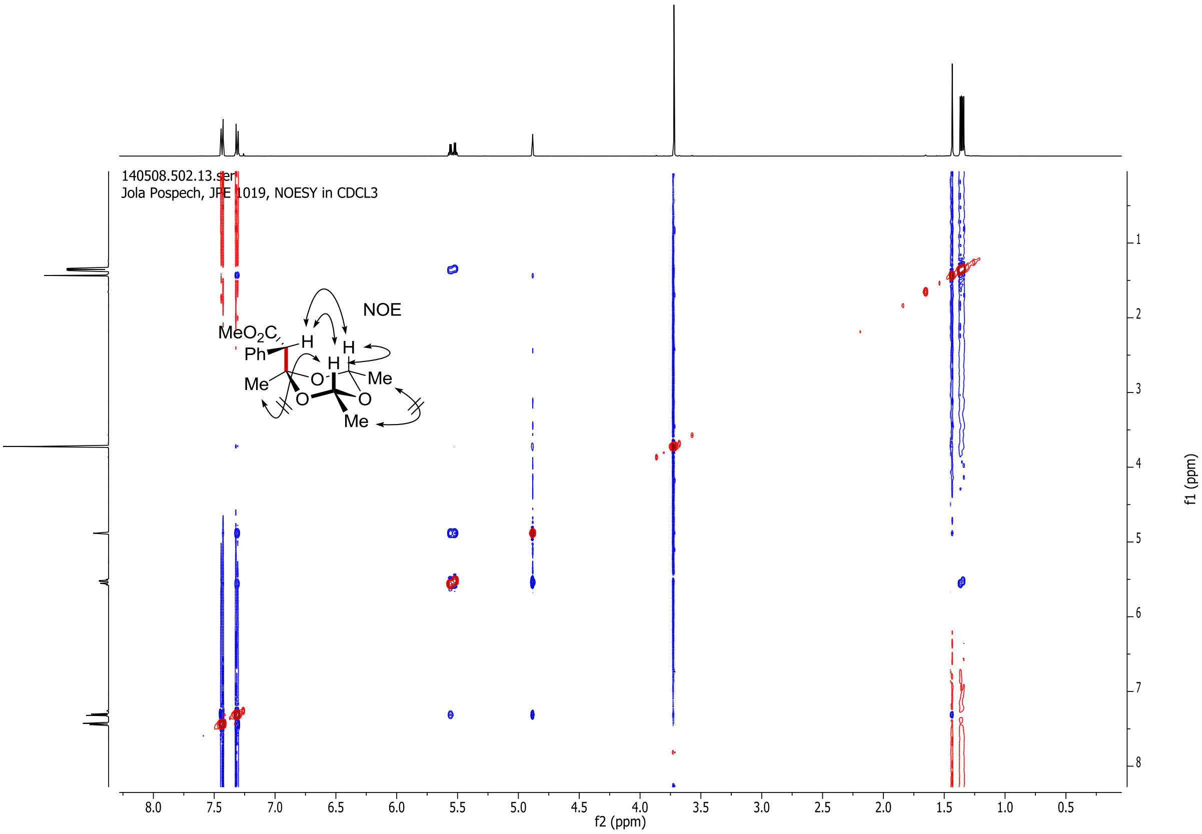
2.5
(300 MHz)



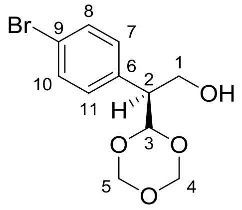
2.5
(75 MHz)


140508.502.11.ser
Jola Pospech, JPE 1019, COSY in CDCL3
f2 (ppm)
f1 (ppm)
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
0
1
2
3
4
5
6
7
8


140508.502.12.ser
Jola Pospech, JPE 1019, HSQC in CDCL3
f2 (ppm)
f1 (ppm)
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
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150


140508.502.13.ser
Jola Pospech, JPE 1019, NOESY in CDCL3
NOE
MeO2C
Ph
H
H
H
Me
Me
Me
O
O
O
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
f2 (ppm)
1
2
3
4
5
6
7
8
f1 (ppm)

Synthesis of (*S*)-2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)ethanol (2.6)



(*R*)-methyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate (**2.3b**) (200 mg, 0.63 mmol) was dissolved in THF (12 mL) and treated with a suspension of $LiAlH_4$ (120 mg, 2 M in THF, 5 equiv.) at 0°C. The conversion was monitored by TLC and judged complete after 30-45 min. The reaction mixture was quenched by dropwise addition of MeOH (2 mL), followed by a saturated, aqueous solution of NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3x15 mL). The combined organic layer were washed with brine and dried over Na_2SO_4. Purification by flash chromatography (*n*-pentane:EtOAc = 5:1 → 2:1) and drying under reduced pressure yielded the title compound **2.6** (164 mg, 0.57 mmol, 90%) as colorless solid.

m.p.: 84-85 °C

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.4 Hz, 2H, C-8, C-10), 7.17 (d, *J* = 8.4 Hz, 2H, C-7, C-11), 5.27 (dd, *J* = 6.2, 1.2 Hz, 1H), 5.2 (dd, *J* = 6.3, 1.3 Hz, 1H), 5.2 (d, *J* = 5.0 Hz, 1H), 5.10 (d, *J* = 6.2 Hz, 1H), 5.05 (d, *J* = 6.3 Hz, 1H), 4.09 (ddd, *J* = 11.2, 7.0, 5.0 Hz, 1H, H-1b), 3.86 (ddd, *J* = 11.2, 7.3, 5.2, 2.1 Hz, 1H, H-1a), 3.13 (dt, *J* = 7.0, 5.0 Hz, 1H, H-2), 2.13 (dd, *J* = 7.3, 5.2 Hz, 1H, OH).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 136.4 (C_q, C-9), 131.8 (C-H, C-8, C-10), 130.7 (CH, C-7,C-11), 121.6 (C-6), 103.2 (CH, C-3), 93.6 (C4/5), 93.5 (C4/5), 63.0 (CH_2, C-1), 51.5 (CH, C-2).

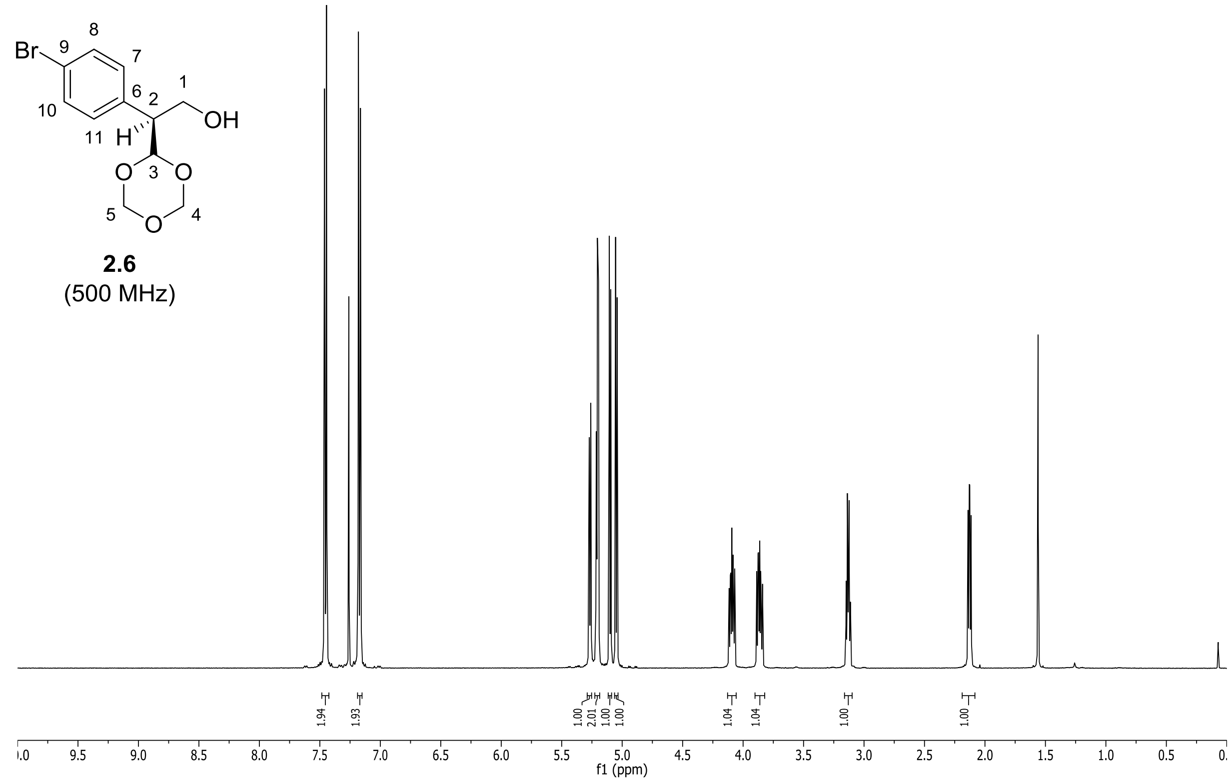
MS (GC-MS) *m/z* (relative intensity) = 288 (1) [M^++H], 229 (1), 212 (7), 198 (68), 182 (76), 169 (87), 120 (38), 89 (100), 61 (70).

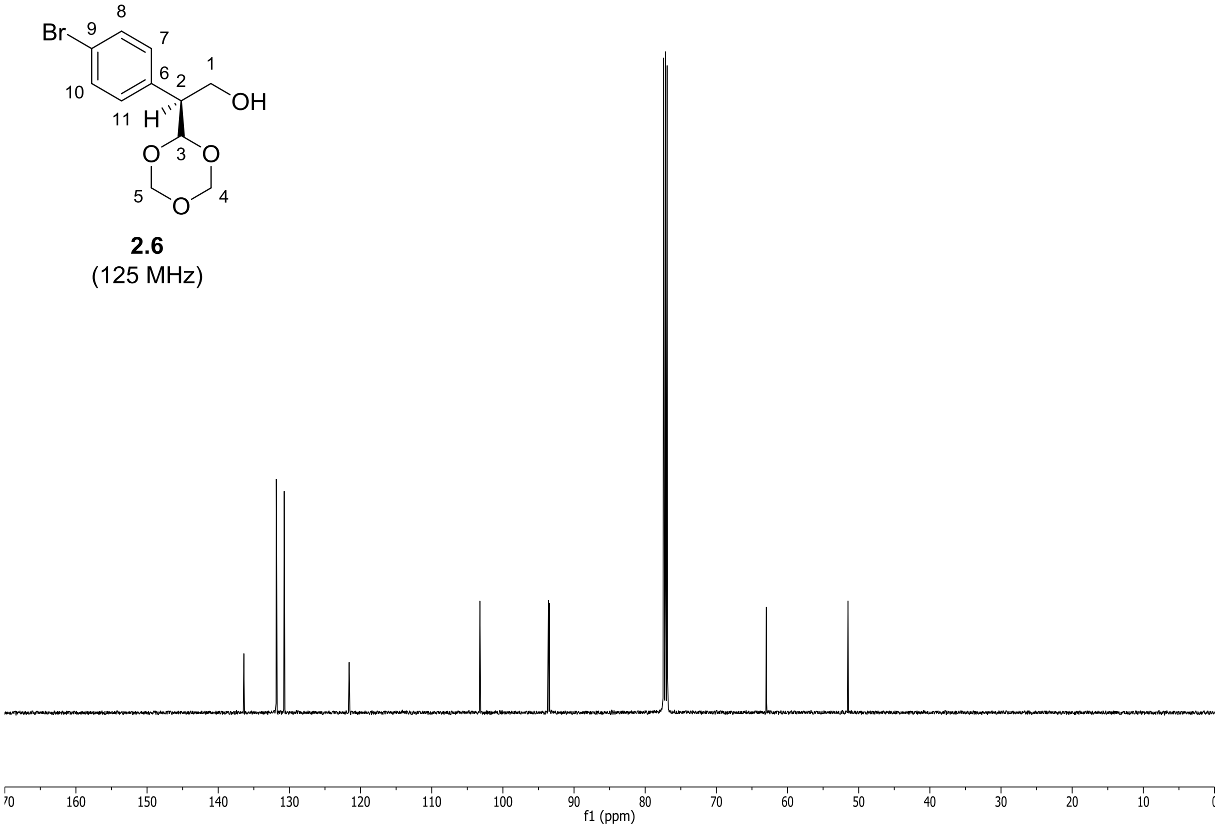
HRMS (EI, m/z) calcd. For $C_{11}H_{13}O_4Br$ $[M]^+$: 287.9992; found: 287.9992.

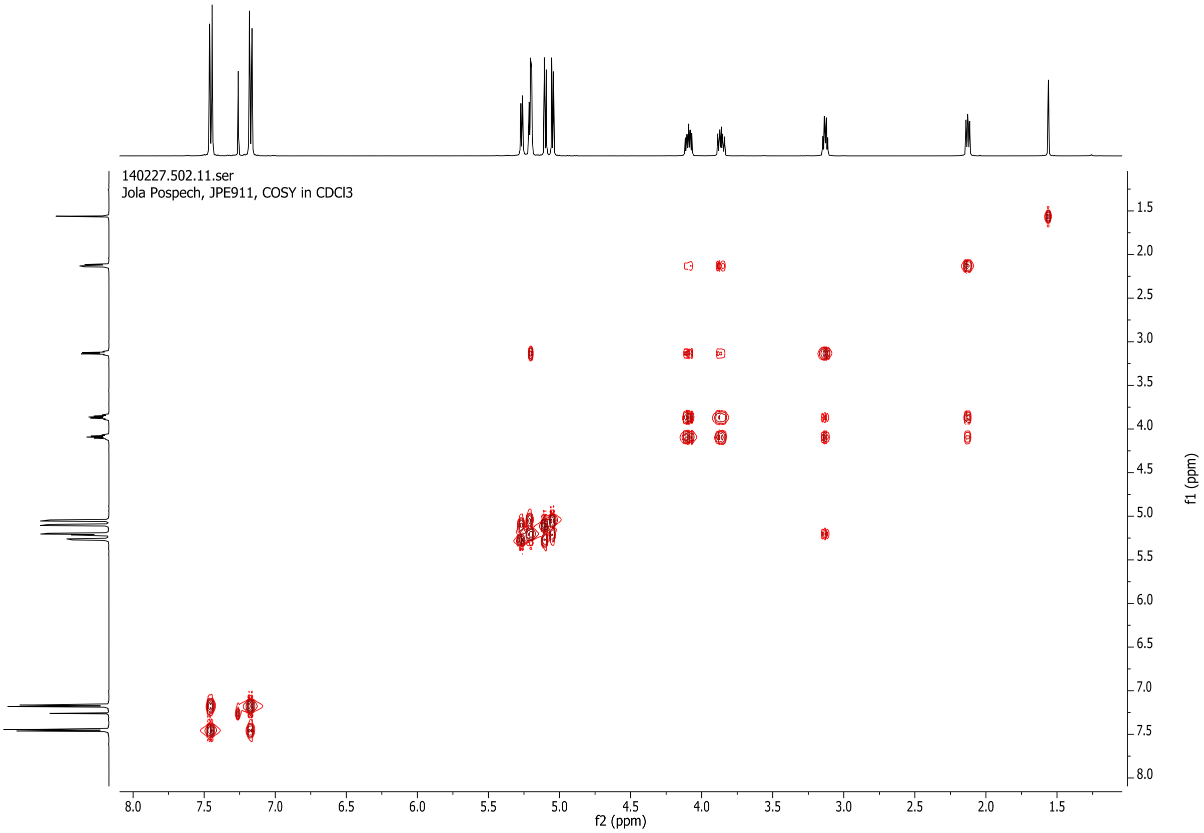
IR (ATR, neat, cm^{-1}): 3244 (w, OH), 2870 (w), 2855 (w), 1488 (m), 1392 (w), 1189 (m), 1160 (s), 1123 (m), 1041 (s), 952 (s), 820 (m), 733 (m), 544 (m).

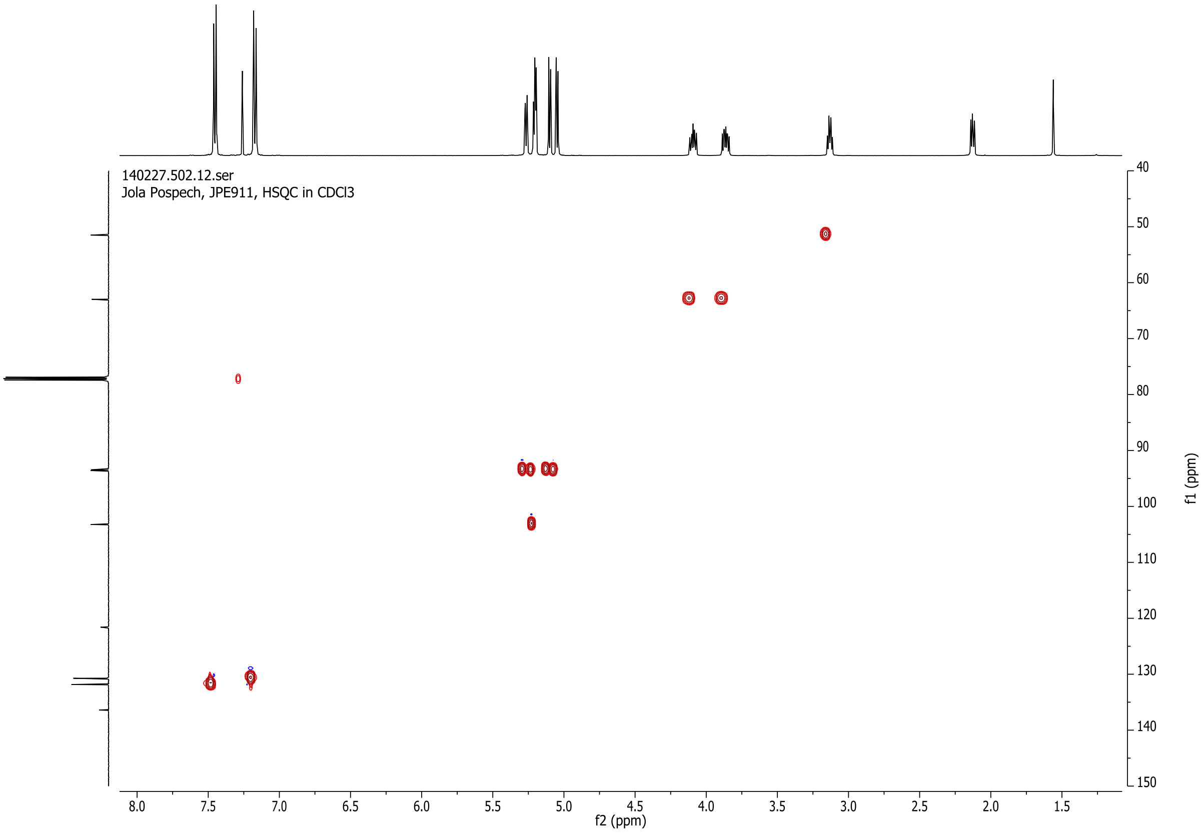
HPLC: Chiralpak AD-H, *n*-heptane/EtOH = 90:10, 1.0 mL/min, 220 nm, 97% *ee* (t_R (major) = 20.99 min, t_R (minor) = 27.26 min).

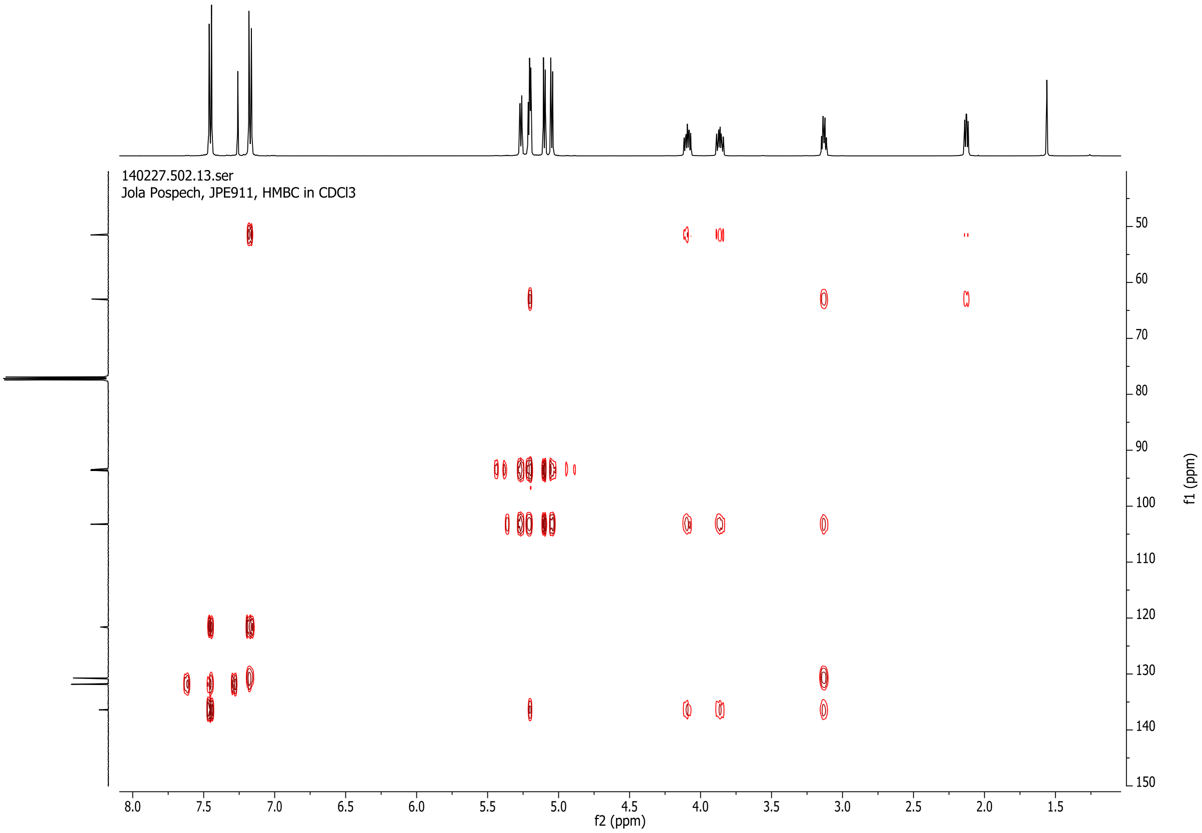
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +27.52° (*c* = 0.6, $CHCl_3$)

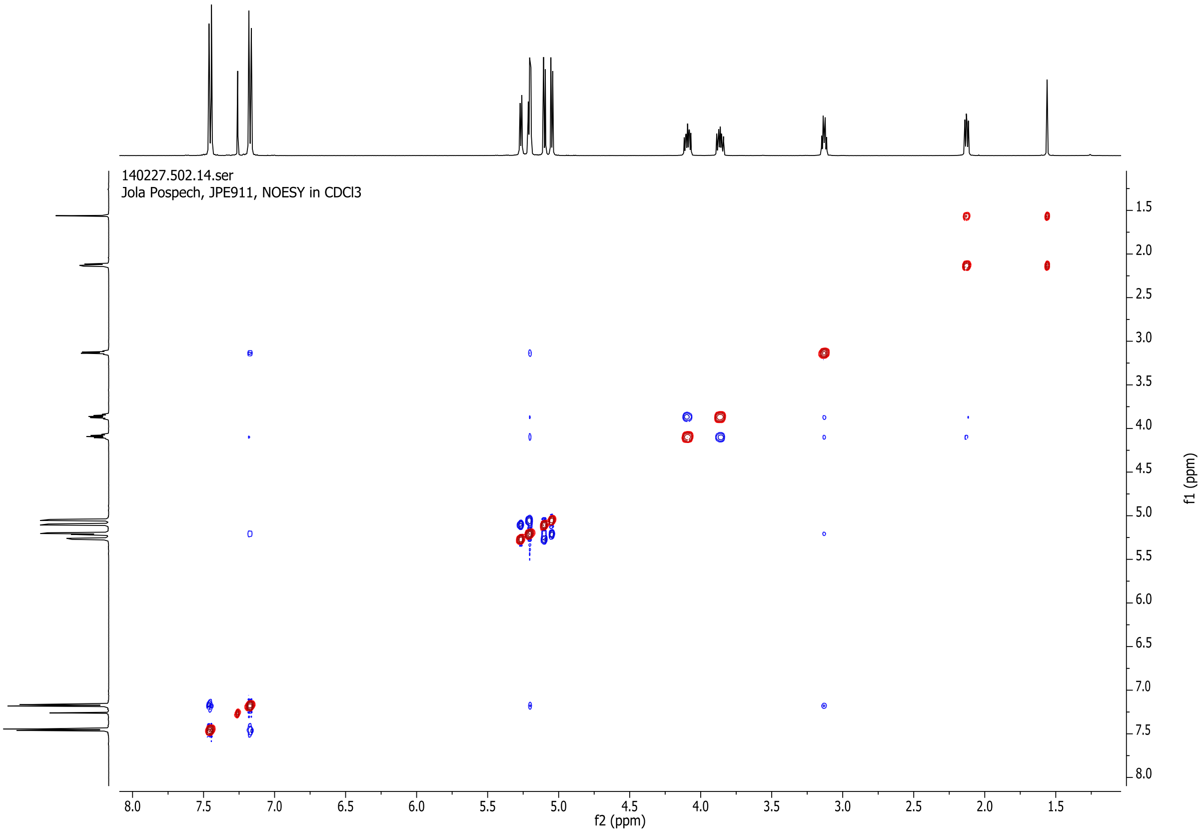

2.6
(500 MHz)


2.6
(125 MHz)

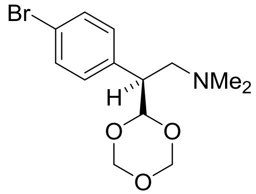

140227.502.11.ser
Jola Pospech, JPE911, COSY in CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


140227.502.12.ser
Jola Pospech, JPE911, HSQC in CDCl3
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
f2 (ppm)
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)


140227.502.13.ser
Jola Pospech, JPE911, HMBC in CDCl3
f1 (ppm)
f2 (ppm)
50
60
70
80
90
100
110
120
130
140
150
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


140227.502.14.ser
Jola Pospech, JPE911, NOESY in CDCl3
f1 (ppm)
f2 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
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

Synthesis of (*S*)-2-(4-Bromophenyl)-*N*,*N*-dimethyl-2-(1,3,5-trioxan-2-yl)ethanamine (2.7)



2.7

(*S*)-2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)ethanol (**2.6**) (40 mg, 0.14 mmol) was dissolved in dichloromethane (2 mL) and cooled to 0 °C. Pyridine (0.1 µL, 0.21 mmol, 1.5 equiv.) was added via syringe followed by dropwise addition of triflic anhydride (25 µL, 0.15 mmol, 1.1 equiv.). The reaction mixture was stirred for 1 h at 0 °C; conversion was monitored by TLC. NaI (25 mg, 0.16 mmol, 1.2 equiv.) was added followed by dimethylamine (2 M in THF, 0.35 mL, 5.0 equiv.). The resulting mixture was stirred for additional 90 min at 0 °C at which point full conversion was reached judged by TLC. The reaction mixture was quenched with H_2O and extracted with dichloromethane (3 x 15 mL), combined organic layer were washed with sat. $NaHCO_3$ (10 mL) and dried over Na_2SO_4. Purification by flash chromatography afforded **2.7** (31 mg, 0.1 mmol, 71%) as yellowish solid.

m.p.: 84-85 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 5.19 (ddd, *J* = 6.2, 3.1, 1.2 Hz, 2H), 5.07 (d, *J* = 4.0 Hz, 1H), 5.04 (d, *J* = 6.3 Hz, 1H), 3.09 (ddd, *J* = 8.7, 6.2, 4.0 Hz, 1H), 2.83 (dd, *J* = 12.5, 6.2 Hz, 1H), 2.66 (dd, *J* = 12.5, 8.7 Hz, 1H), 2.23 (s, 4H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 137.7 (C_q), 131.5 (CH), 131.0 (CH), 121.2 (C_q), 102.7 (CH), 93.5 (CH_2), 93.4 (CH_2), 59.5 (CH_2), 47.7 (CH), 46.0 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 315 (0) [M^+], 254 (1), 198 (1), 184 (2), 169 (3), 103 (4), 89 (4), 58 (100).

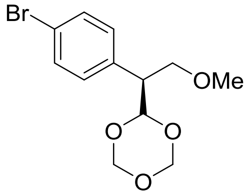
HRMS (ESI^+, m/z) calcd. For $C_{13}H_{18}BrNO_3$ $[M+H]^+$: 316.0543; found: 316.0545.

IR (ATR, neat, cm^{-1}): 2943 (w), 2856 (w), 2782 (w), 1489 (m), 1378 (m), 1265 (m), 1164 (s), 1106 (s), 1056 (s), 1011 (s), 930 (s), 854 (m), 524 (s).

HPLC: Chiralpak OD-H, *n*-heptane/EtOH = 99:1, 1.0 mL/min, 220 nm, 94% *ee* (t_R (major) = 20.99 min, t_R (minor) = 27.26 min).

$[\alpha]_D^{25}$ = -23.3° (*c* = 0.5, $CHCl_3$)

Synthesis of (*S*)-2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)ethanol (2.8)



2.8

(*S*)-2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)ethanol (**2.6**) (84 mg, 0.29 mmol, 1.0 equiv.) was dissolved in THF (5 mL); NaH (60wt% in mineral oil, 35 mg, 0.87 mmol, 3 equiv.) and MeI (247 mg, 108 µL, 6 equiv.) were added at 0 °C. The reaction mixture was stirred over night at ambient temperature. The reaction mixture was quenched with H_2O and extracted with dichloromethane (3 x 15 mL), combined organic layer were washed with sat. $NaHCO_3$ (10 mL) and dried over Na_2SO_4. Purification by flash chromatography (*n*-pentane/EtOAc = 2:1) afforded **2.8** (75 mg, 0.25 mmol, 85%) as colorless solid.

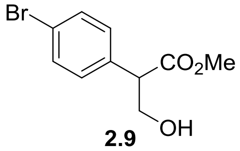
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 5.20 (ddd, *J* = 6.1, 4.4, 1.2 Hz, 2H), 5.16 (d, *J* = 5.0 Hz, 1H), 5.06 (dd, *J* = 9.1, 6.4 Hz, 2H), 3.82 – 3.63 (m, 1H), 3.31 (s, 3H), 3.14 (dt, *J* = 6.9, 5.3 Hz, 1H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 136.9 (C_q), 131.5 (CH), 131.1 (CH), 121.3 (C_q), 101.7 (CH), 93.5 (CH_2), 93.5 (CH_2), 71.8 (CH), 59.2 (CH_3), 49.6 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 303 (1) [M^+], 213 (6), 184 (54), 171 (13), 134 (32), 89 (100), 61 (28).

HRMS (ESI^+, m/z) calcd. For $C_{12}H_{15}O_4Br$ $[M+Na]^+$: 325.0046; found: 325.0048.

Synthesis of (*R*)-methyl 2-(4-bromophenyl)-3-hydroxypropanoate (2.9)



2.9

(*R*)-methyl 2-(4-bromophenyl)-2-(1,3,5-trioxan-2-yl)acetate (**2.3b**) (75 mg, 0.24 mmol, 1.0 equiv.) was dissolved in THF/H_2O (1:1, 3 mL); $NaBH_4$ (45 mg, 1.2 mmol, 5 equiv.) and LiOH (7 mg, 0.3 mmol, 1.2 equiv.) were consecutively added at 0 °C. The reaction mixture was stirred for 3 hours at 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (2 mL) and diluted with CH_2Cl_2 (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL). Phases were separated and the organic layer was dried over Na_2SO_4. Purification of the crude product by flash chromatography (*n*-pentane/EtOAc = 4:1, $KMnO_4$-stain) yielded the title compound **2.9** (40 mg, 0.154 mmol, 65%) as a colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.10 (dd, *J* = 12.8, 10.1 Hz, 1H), 3.82 (dd, *J* = 12.9, 5.2 Hz, 1H), 3.81 (dd, *J* = 10.1, 5.2 Hz, 1H), 3.71 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.3 (CO), 134.8 (C_q), 132.2 (CH), 130.1 (CH), 122.0 (C_q), 64.5 (CH_2), 53.4 (CH), 52.5 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 258 (3) [M^+], 240 (3), 228 (100), 196 (37), 169 (17), 134 (27), 120 (31), 89 (51).

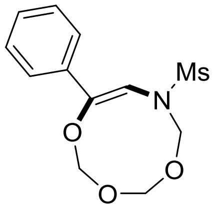
HRMS (HR(EI), m/z) calcd. For $C_{10}H_{11}O_3Br$ [M^+]: 257.98861; found: 257.98813.

IR (ATR, neat, cm^{-1}): 3424 (w), 2950 (w), 2876 (w), 1734 (s), 1490 (m), 1436 (m), 1251 (w), 1199 (w), 1167 (m), 1072 (m), 1011 (s).

$[\alpha]_D^{24}$ = -1.4° (*c* = 1.5, $CHCl_3$)

6.2.3 Experimental part to Chapter 3

Synthesis of (Z)-7-(methylsulfonyl)-9-(phenyl)-6,7-dihydro-1,3,5,7-trioxazonine (3.3a)



3.3a

Following general procedure **E**, **3.3a** (103 mg, 0.36 mmol, 72%) was isolated as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.41 (m, 2H, CH), 7.41 – 7.31 (m, 3H, CH), 6.51 (s, 1H, CH), 5.54 (s, 2H, CH_2), 5.00 (s, 2H, CH_2), 4.93 (s, 2H, CH_2), 3.13 (s, 3H, CH_3).

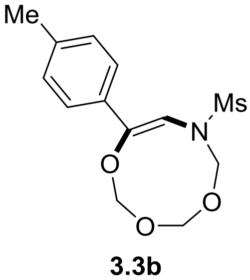
^{13}C NMR (75 MHz, Chloroform-*d*) δ 142.5 (C_q), 133.4 (C_q), 128.9 (CH), 128.9 (CH), 125.9 (CH), 113.8 (CH), 96.7 (CH_2), 93.9 (CH_2), 77.9 (CH_2), 41.9 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 285 (13) [M^+], 255 (8), 225 (6), 146 (100), 105 (78), 91 (83), 77 (37).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{15}NSO_5$ $[M+Na]^+$ calc.: 308.0563; found: 308.0566.

IR (ATR, neat, cm^{-1}): 2964 (w), 2936 (w), 2895 (w), 1343 (s), 1147 (s), 1100 (m), 1056 (s), 929 (s), 773 (s), 697 (m), 509 (s).

Synthesis of (Z)-7-(methylsulfonyl)-9-(p-tolyl)-6,7-dihydro-1,3,5,7-trioxazonine (3.3b)



3.3b

Following general procedure **E**, **3.3b** (108 mg, 0.36 mmol, 72%) was isolated as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 30:1).

m.p.: 122-123 °C

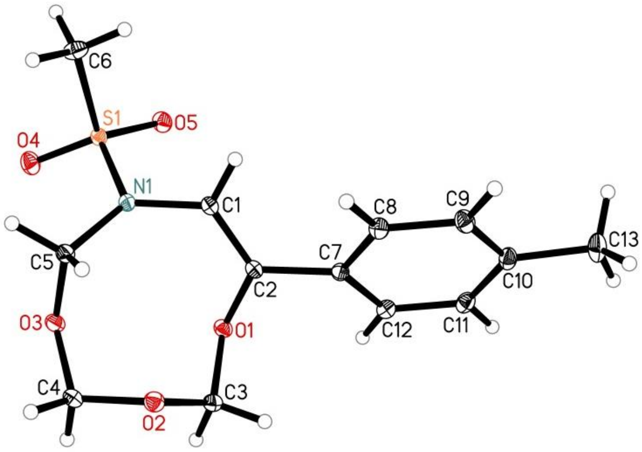
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.2 Hz, 2H, CH), 7.17 (d, *J* = 7.8 Hz, 1H, CH), 6.45 (s, 1H, CH), 5.50 (s, 2H, CH_2), 5.00 (s, 2H, CH_2), 4.94 (s, 2H, CH_2), 3.13 (s, 3H, CH_3), 2.36 (s, 3H, CH_3).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.5 (C_q), 139.1 (C_q), 130.4 (C_q), 129.6 (CH), 126.0 (CH), 113.2 (CH), 96.6 (CH_2), 93.9 (CH_2), 77.8 (CH_2), 41.8 (CH_3), 21.4 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 299 (6) [M$^+$], 269 (3), 160 (71), 119 (59), 105 (100), 91 (38).

HRMS (ESI-TOF, m/z) calcd. For $C_{13}H_{17}NSO_5$ [M]$^+$ calc.: 299.0822; found: 299.0823.

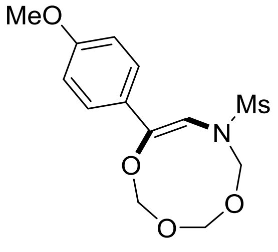
IR (ATR, neat, cm^{-1}): 2956 (w), 2901 (w), 1332 (m), 1323 (m), 1145 (m), 1145 (s). 1109 (s), 1072 (s), 927 (s), 814 (s), 767 (m), 516 (s).



Empirical formula	$C_{13}H_{17}NO_5S$	
Formula weight	299.33	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 5.6464(2) Å	α= 71.157(1)°.
	b = 11.2363(4) Å	β= 80.731(1)°.
	c = 11.4977(4) Å	γ = 85.869(1)°.
Volume	681.20(4) Å^3	
Z	2	
Density (calculated)	1.459 Mg/m^3	
Absorption coefficient	0.257 mm^{-1}	
F(000)	316	
Crystal size	0.433 x 0.233 x 0.120 mm	
Theta range for data collection	1.892 to 27.996°.	
Index ranges	-7<=h<=7, -14<=k<=14, -15<=l<=15	
Reflections collected	24709	
Independent reflections	3289 [R(int) = 0.0204]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.90	
Data / restraints / parameters	3289 / 0 / 183	
Goodness-of-fit on F^2	1.065	

Final R indices [I>2sigma(I)]	R1 = 0.0305, wR2 = 0.0807
R indices (all data)	R1 = 0.0333, wR2 = 0.0835
Largest diff. peak and hole	0.394 and -0.376 $e^{\cdot}Å^{-3}$

Synthesis of (Z)-7-(methylsulfonyl)-9-(p-anisyl)-6,7-dihydro-1,3,5,7-trioxazonine (3.3c)



3.3c

Following general procedure **E**, **3.3c** (95 mg, 0.3 mmol, 60%) was isolated as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1 → 10:1).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29 (d, 2H, CH), 6.84 (d, 2H, CH), 6.28 (s, 1H, CH), 5.38 (s, 2H, CH_2), 4.92 (d, *J* = 12,7 Hz, 4H, CH_2), 3.76 (s, 3H, CH_3), 3.05 (s, 3H, CH_3).

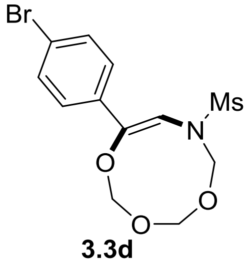
^{13}C NMR (75 MHz, Chloroform-*d*) δ 160.36, 144.50, 127.55, 125.33, 114.22, 112.47, 96.42, 93.69, 78.09, 55.40, 41.66.

MS (GC-MS) *m/z* (relative intensity) = 315 (10) [M^+], 252 (19), 250 (13), 235 (11), 207 (21), 177 (19), 176 (100), 175 (69).

HRMS (EI, m/z) calcd. For $C_{13}H_{17}NO_6S_1$ $[M]^+$: 316.3422; found: 316.0849.

IR (ATR, neat, cm^{-1}): 2962 (w), 2840 (w), 1683 (m), 1599 (s), 1511 (s), 1147 (s), 830 (w), 506 (m).

Synthesis of (Z)-7-(methylsulfonyl)-9-(4-bromophenyl)-6,7-dihydro-1,3,5,7-trioxazonine (3.3d)



3.3d

Following general procedure **E**, **3.3d** (108 mg, 0.36 mmol, 77%) was isolated as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

m.p.: 141-142 °C

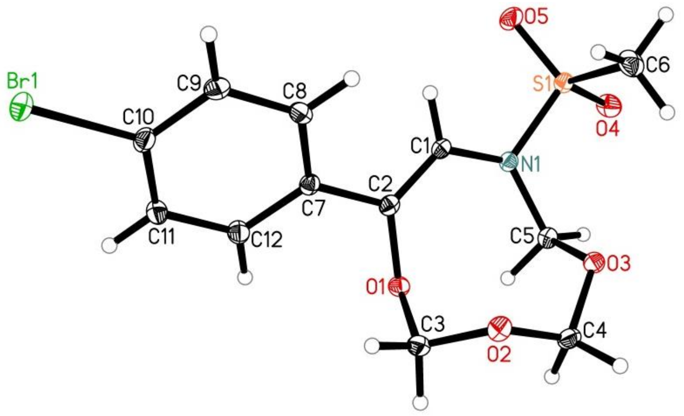
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.7 Hz, 1H, CH), 7.30 (d, *J* = 8.7 Hz, 1H, CH), 6.53 (s, 1H, CH), 5.56 (s, 2H, CH_2), 5.01 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 3.13 (s, 3H, CH_3).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 140.4 (C_q), 132.6 (C_q), 132.1 (C_q), 127.3 (CH), 122.8 (CH), 114.2 (CH), 96.9 (CH_2), 94.0 (CH_2), 77.8 (CH_2), 42.0 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 363 (6) [M^+], 333 (5), 303 (2), 224 (100), 183 (57), 169 (99), 155 (33).

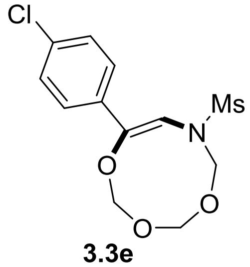
HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{14}BrNO_5S$ $[M]^+$: 303.0571; found: 303.0568.

IR (ATR, neat, cm^{-1}): 2961 (w), 2895 (w), 1670 (w), 1478 (w), 1341 (s), 1219 (m), 1145 (s), 1049 (s), 998 (s), 969 (s), 904 (s), 832 (s). 812 (s), 512 (s), 475 (m).



Empirical formula	$C_{12}H_{14}BrNO_5S$	
Formula weight	364.21	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 16.4002(6) Å	α= 90°.
	b = 6.0352(2) Å	β= 118.104(1)°.
	c = 16.0983(6) Å	γ = 90°.
Volume	1405.51(9) $Å^3$	
Z	4	
Density (calculated)	1.721 Mg/m^3	
Absorption coefficient	3.091 mm^{-1}	
F(000)	736	
Crystal size	0.404 x 0.139 x 0.096 mm	
Theta range for data collection	2.531 to 27.998°.	
Index ranges	-21<=h<=21, -7<=k<=7, -20<=l<=21	
Reflections collected	15921	
Independent reflections	3380 [R(int) = 0.0508]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.76 and 0.57	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3380 / 0 / 182	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0320, wR2 = 0.0623	
R indices (all data)	R1 = 0.0538, wR2 = 0.0683	
Largest diff. peak and hole	0.499 and -0.506 $e^{.}Å^{-3}$	

Synthesis of (Z)-7-(methylsulfonyl)-9-(4-chlorophenyl)-6,7-dihydro-1,3,5,7-trioxazonine (3.3e)



3.3e

Following general procedure **E**, **3.3e** (108 mg, 0.36 mmol, 77%) was isolated as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29 (m, 4H), 6.45 (s, 1H), 5.49 (s, 2H), 4.94 (s, 2H), 4.84 (s, 2H), 3.06 (s, 3H).

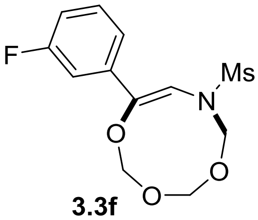
^{13}C NMR (75 MHz, Chloroform-*d*) δ 140.54, 134.59, 132.04, 129.05, 127.01, 114.08, 96.79, 93.85, 41.90.

MS (GC-MS) *m/z* (relative intensity) = 319 (5) [M$^+$], 180 (82), 139 (61), 125 (100), 111 (36).

HRMS (EI, m/z) calcd. For $C_{12}H_{14}NO_5S_1$ [M]$^+$: 319.0281; found: 319.0274.

IR (ATR, neat, cm^{-1}): 2975 (w), 2795 (w), 1636 (w), 1488 (m), 1325 (s), 1151 (s), 833 (m), 688 (w), 511 (m).

Synthesis of (Z)-9-(3-fluorophenyl)-7-(methylsulfonyl)-6,7-dihydro-1,3,5,7-trioxazonine (3.3f)



3.3f

Following general procedure **E**, **3.3f** (121 mg, 0.4 mmol, 80%) was isolated as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

m.p.: 118-119 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.33 (td, *J* = 8.0, 5.8 Hz, 1H, CH), 7.22 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H, CH), 7.15 – 7.09 (m, 1H, CH), 7.01 (tdd, *J* = 8.3, 2.6, 1.1 Hz, 1H, CH), 6.59 (s, 1H, CH), 5.59 (d, *J* = 2.1 Hz, 2H, CH$_2$), 5.02 (s, 2H, CH$_2$), 4.92 (s, 2H, CH$_2$), 3.13 (s, 3H, CH$_3$).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.2 (d, $^1J_{C\text{-}F}$ = 246.3 Hz, C$_q$), 139.8 (d, $^4J_{C\text{-}F}$ = 2.7 Hz, C$_q$), 136.2 (d, $^3J_{C\text{-}F}$ = 7.6 Hz, C$_q$), 130.5 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, CH), 121.4 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, CH), 115.6 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, CH), 114.7 (CH), 112.6 (d, $^2J_{C\text{-}F}$ = 23.1 Hz, CH), 97.0 (CH$_2$), 94.1 (CH$_2$), 77.8 (CH$_2$), 42.0 (CH$_3$).

^{19}**F NMR** (282 MHz, Chloroform-*d*) δ -111.9 (dd, *J* = 9.5, 6.0 Hz).

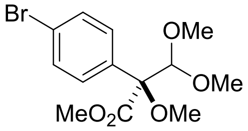
MS (GC-MS) *m/z* (relative intensity) = 303 (3) [M$^+$], 273 (4), 164 (89), 123 (53), 109 (100), 95 (42).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{14}NFSO_5$ [M]$^+$: 303.0571; found: 303.0568.

IR (ATR, neat, cm^{-1}): 3015 (w), 2925 (w), 1361 (m), 1347 (m), 1146 (s), 1052 (m), 968 (m), 906 8s), 795 8m), 768 (s). 508 (s).

6.2.4 Experimental part to Chapter 4

Synthesis of methyl 2-(4-bromophenyl)-2,3,3-trimethoxypropanoate (4.3a)



4.3a

Following general procedure **F**, the title compound **4.3a** (123 mg, 0.33 mmol, 83%) was isolated as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

m.p.: 83 °C

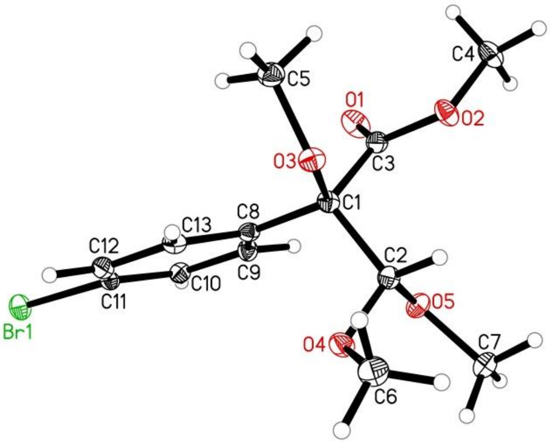
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.9 Hz, 1H, CH), 7.41 (d, *J* = 8.9 Hz, 1H, CH), 4.78 (s, 1H, CH_3), 3.83 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 3.37 (s, 3H, CH_3).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.3 (CO_2R), 134.0 (C_q), 130.9 (CH), 130.1 (CH), 122.6 (C_q), 108.4 (CH), 87.0 (C_q), 58.6 (CH_3), 58.0 (CH_3), 54.7 (CH_3), 52.5 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 301 (1) [M^+-31], 275 (2), 201 (7), 183 (10), 155 (5), 105 (3), 75 (100).

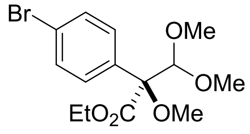
HRMS (ESI-TOF, m/z) calcd. For $C_{13}H_{17}Br_2O_2$ $[M+Na]^+$: 355.01516; found: 355.01527.

IR (ATR, neat, cm^{-1}): 2956 (w), 2935 (w), 1741 (s), 1226 (m), 1175 (m), 1097 (m), 1076 (s), 1008 (m), 975 (m), 910 (m), 800 (m).



Empirical formula	$C_{13}H_{17}BrO_5$	
Formula weight	333.17	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	*Pna*2$_1$	
Unit cell dimensions	a = 14.3578(16) Å	α= 90°.
	b = 11.7005(14) Å	β= 90°.
	c = 8.2619(9) Å	γ = 90°.
Volume	1387.9(3) Å^3	
Z	4	
Density (calculated)	1.594 Mg/m^3	
Absorption coefficient	2.975 mm^{-1}	
F(000)	680	
Crystal size	0.490 x 0.298 x 0.145 mm	
Theta range for data collection	2.245 to 28.701°.	
Index ranges	-19<=h<=19, -15<=k<=15, -11<=l<=10	
Reflections collected	21187	
Independent reflections	3366 [R(int) = 0.0327]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.67 and 0.48	
Data / restraints / parameters	3366 / 1 / 176	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2sigma(I)]	R1 = 0.0219, wR2 = 0.0472	
R indices (all data)	R1 = 0.0262, wR2 = 0.0483	
Absolute structure parameter	0.021(5)	
Largest diff. peak and hole	0.377 and -0.281 e.Å^{-3}	

Synthesis of ethyl 2-(4-bromophenyl)-2,3,3-trimethoxypropanoate (4.3b)



4.3b

Following general procedure **F**, the title compound **4.3b** (75 mg, 0.21 mmol, 54%) was isolated as a colorless oil. Purification was performed by preparative TLC (*n*-pentane:EtOAc = 40:1).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 9.0 Hz, 2H, CH), 7.42 (d, *J* = 8.9 Hz, 2H, CH), 4.78 (s, 1H, CH), 4.31 (d, *J* = 7.1 Hz, 2H, CH_2), 3.51 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 1.33 (t, *J* = 7.1 Hz, 3H, CH_3).

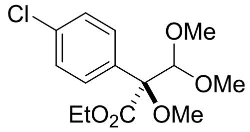
^{13}C NMR (75 MHz, Chloroform-*d*) δ 169.7 (CO), 134.1 (C_q), 130.9 (CH), 130.2 (CH), 122.5 (C_q), 108.4 (CH), 86.9 (C_q), 61.6 (CH_2), 58.6 (CH_3), 57.9 (CH_3), 54.6 (CH_3), 14.3 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 317 (1) [M^+-31], 273 (3), 244 (1), 227 (1), 199 (8), 183 (9), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{19}BrO_5$ $[M+Na]^+$: 369.0308; found: 369.0307.

IR (ATR, neat, cm^{-1}): 2937 (w), 2833 (w), 1734 (m), 1488 (m), 1181 (m), 1072 (s), 1009 (m), 937 (m), 731 (m), 503 (m).

Synthesis of ethyl 2-(4-chlorophenyl)-2,3,3-trimethoxypropanoate (4.3c)



4.3

Following general procedure **F**, the title compound **4.3c** (82 mg, 0.27 mmol, 68%) was obtained as a colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

m.p.: 122-123 °C

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.9 Hz, 1H, CH), 7.32 (d, *J* = 8.8 Hz, 1H, CH), 4.78 (s, 1H, CH), 4.32 (qd, *J* = 7.1, 1.0 Hz, 2H, CH_2), 3.51 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 1.33 (t, *J* = 7.1 Hz, 3H, CH_3).

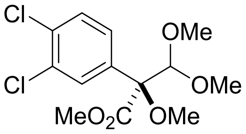
^{13}C NMR (75 MHz, Chloroform-*d*) δ 169.8 (C_q), 134.2 (C_q), 133.5 (C_q), 129.8 (CH), 127.9 ,(CH) 108.4 (CH), 86.8 (C_q), 61.6 (CH_2), 58.6 (CH_3), 57.9 (CH_3), 54.6 (CH_3), 14.3 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 271 (1) [M^+-31], 229 (5), 183 (3), 155 (16), 139 (16), 111 (11), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{19}Cl_2O_5$ $[M+Na]^+$: 325.0813; found: 325.0815.

IR (ATR, neat, cm^{-1}): 2938 (w), 2834 (w), 1731 (m), 1491 (m), 1181 (m), 1076 (s), 1038 (m), 1014 (s), 963 (m). 733 (m), 507 (m).

Synthesis of methyl 2-(3,4-dichlorophenyl)-2,3,3-trimethoxypropanoate (4.3d)



4.3d

Following general procedure **F**, the title compound **4.3d** (92 mg, 0.28 mmol, 71%) was obtained as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

m.p.: 78 °C

^{1}**H NMR** (300 MHz, Chloroform-*d*) δ 7.65 (dd, *J* = 2.1, 0.5 Hz, 1H, CH), 7.42 (dd, *J* = 8.5, 0.5 Hz, 1H, CH), 7.37 (dd, *J* = 8.5, 2.1 Hz, 1H, CH), 4.77 (s, 1H, CH), 3.85 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 3.37 (s, 3H, CH_3).

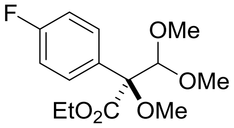
^{13}**C NMR** (75 MHz, Chloroform-*d*) δ 169.9 (CO), 135.1 (C_q), 132.4 (C_q), 132.0 (C_q), 130.6 (CH), 129.6 (CH), 128.0 (CH), 108.2 (CH), 86.6 (C_q), 58.9 (CH_3), 57.9 (CH_3), 54.7 (CH_3), 52.7 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 324 (1) [M$^+$], 291 (2), 263 (3), 219 (2), 189 (12), 173 (13), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{13}H_{16}Cl_2O_5$ [M+Na]$^+$: 345.0267; found: 345.0268.

IR (ATR, neat, cm^{-1}): 2935 (w), 1898 (w), 2834 (w), 1742 (s), 1225 (m), 1191 (m), 1180 (m), 1106 (s), 1084 (s), 1049 (m), 979 (m), 921 (m), 797 (m), 718 (m), (674 (m), 517 (m).

Synthesis of ethyl 2-(4-fluorophenyl)-2,3,3-trimethoxypropanoate (4.3e)



4.3e

Following general procedure **F**, the title compound **4.3e** (104 mg, 0.38 mmol, 76%) was obtained as colorless oil. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

^{1}**H NMR** (300 MHz, Chloroform-*d*) δ 7.51 (dd, *J* = 9.0, 5.4 Hz, 1H, CH), 7.04 (dd, *J* = 9.0, 8.5 Hz, 1H, CH), 4.78 (s, 1H, CH), 3.84 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 3.37 (s, 3H, CH_3).

^{13}**C NMR** (75 MHz, Chloroform-*d*) δ 170.6 (CO), 162.7 (d, *J* = 246.9 Hz, C_q), 130.7 (d, *J* = 3.5 Hz, C_q), 130.1 (d, *J* = 8.1 Hz, CH), 114.8 (d, *J* = 21.3 Hz, CH), 108.5 (CH), 86.9 (C_q), 58.5 (CH_3), 58.0 (CH_3), 54.6 (CH_3), 52.5 (CH_3).

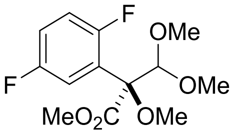
^{19}**F NMR** (282 MHz, Chloroform-*d*) δ -112.7 – -117.0 (m).

MS (GC-MS) *m/z* (relative intensity) = 271 (1) [M^+-31], 229 (5), 183 (3), 155 (16), 139 (16), 111 (11), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{19}Cl_2O_5$ [M+Na]$^+$: 325.0813; found: 325.0815.

IR (ATR, neat, cm^{-1}): 2952 (w), 2836 (w), 1735 (m), 1508 (m), 1225 (m), 1076 (s), 911 (m), 727 (s).

Synthesis of methyl 2-(2,5-difluorophenyl)-2,3,3-trimethoxypropanoate (4.3f)



4.3f

Following general procedure **F**, the title compound **4.3f** (120 mg, 0.41 mmol, 83%) was obtained as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 1H, CH), 7.06 – 6.90 (m, 2H, CH), 4.95 (d, *J* = 1.2 Hz, 1H, CH), 3.82 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 3.36 (d, *J* = 0.5 Hz, 3H).

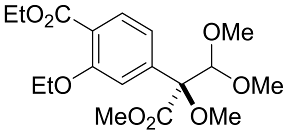
^{13}C NMR (75 MHz, Chloroform-*d*) δ 169.5 (C_q), 158.4 (dd, *J* = 241.6, 2.0 Hz, C_q), 156.7 (dd, *J* = 244.3, 2.5 Hz, C_q), 125.0 (dd, *J* = 14.6, 7.8 Hz, C_q), 117.1 (dd, *J* = 26.6, 4.0 Hz, CH), 116.7 (dd, *J* = 27.0, 8.8 Hz, CH), 116.7 (dd, *J* = 24.3, 9.3 Hz, CH), 106.5 (d, *J* = 2.7 Hz, CH), 83.9 (d, *J* = 3.2 Hz, C_q), 58.3 (CH_3), 57.9 (CH_3), 54.1 (CH_3), 52.6 (CH_3).

^{19}F NMR (282 MHz, Chloroform-*d*) δ -115.8 – -116.2 (m), -118.0 – -118.8 (m).

MS (GC-MS) *m/z* (relative intensity) = 259 (1) [M^+-31], 228 (2), 197 (8), 159 (10), 138 (18), 75 (100).

IR (ATR, neat, cm^{-1}): 3087 (w), 2954 (w), 2834 (w), 1733 (s), 1491 (m), 1248 (m), 1166 (m), 1069 (s), 986 (m), 818 (m), 768 (m), 718 (m).

Synthesis of methyl 2-ethoxy-4-(1,1,2,3-tetramethoxy-3-oxopropan-2-yl)benzoate (4.3g)



4.3g

Following general procedure **F**, the title compound **4.3g** (123 mg, 0.33 mmol, 83%) was isolated as a colorless oil. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 10:1 → 5:1).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 8.2 Hz, 1H, CH), 7.22 (d, *J* = 1.6 Hz, 1H, CH), 7.11 (dd, *J* = 8.2, 1.6 Hz, 1H, CH), 4.80 (s, 1H, CH), 4.34 (q, *J* = 7.1 Hz, 2H, CH_2), 4.13 (q, *J* = 7.0 Hz, 2H, CH_2), 3.82 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 1.44 (t, *J* = 7.0 Hz, 3H, CH_3), 1.36 (t, *J* = 7.1 Hz, 3H, CH_3).

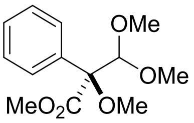
^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.4 (C_q), 166.4 (C_q), 158.1 (C_q), 140.9 (C_q), 130.8 (CH), 120.6 (C_q), 119.6 (CH), 113.4 (CH), 108.7 (CH), 86.9 (C_q), 64.8 (CH_2), 60.9 (CH_2), 58.4 (CH_3), 58.2 (CH_3), 55.1 (CH_3), 52.5 (CH_3), 14.8 (CH_3), 14.4 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 370 (1) [M^+-31], 311 (2), 237 (6), 221 (4), 147 (3), 119 (5), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{18}H_{26}O_8$ $[M+H]^+$: 371.17004; found: 371.17003.

IR (ATR, neat, cm^{-1}): 2981 (w), 2938 (w), 2835 (w), 1728 (s), 1610 (m), 1417 (m) 1293 (m), 1240 (s), 1074 (s), 1040 (m), 982 (m), 770 (m).

Synthesis of methyl 2,3,3-trimethoxy-2-phenylpropanoate (4.3h)



4.3h

Following general procedure **F**, the title compound **4.3h** (67 mg, 0.26 mmol, 66%) as colorless oil. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 20:1).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.58 – 7.48 (m, 2H), 7.42 – 7.28 (m, 3H), 4.83 (s, 1H, CH), 3.83 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 3.40 (s, 3H, CH_3).

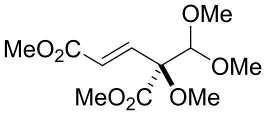
^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.9 (C_q), 135.2 (C_q), 128.3 (CH), 128.0 (CH), 128.0 (CH), 108.8 (CH), 87.2 (C_q), 58.3 (CH_3), 58.0 (CH_3), 54.8 (CH_3), 52.4 (CH_3)

MS (GC-MS) *m/z* (relative intensity) = 223 (1) [M^+-31], 195 (5), 179 (2), 149 (4), 121 (20), 105 (25), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{13}H_{18}O_5$ $[M+Na]^+$: 277.1046; found: 277.1046.

IR (ATR, neat, cm^{-1}): 2951 (w), 2834 (w), 1733 (m), 1190 (m), 1106 (m), 1076 (s), 910 (m), 726 (s), 698 (m), 646 (m).

Synthesis of dimethyl (*E*)-4-(dimethoxymethyl)-4-methoxypent-2-enedioate (4.6a)



4.6a

Following general procedure **F** on a 0.2 mmol scale, the title compound **4.6a** (28 mg, 0.11 mmol, 53%) was obtained as colorless solid. Purification was performed by flash chromatograohy (*n*-pentane:EtOAc = 5:1).

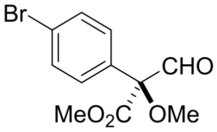
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.09 (d, *J* = 16.1 Hz, 1H, CH), 6.17 (d, *J* = 16.1 Hz, 1H, CH), 4.54 (s, 1H, CH), 3.82 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 3.33 (s, 3H, CH_3).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.5 (C_q), 166.4 (C_q), 141.2 (CH), 124.5 (CH), 108.1 (CH), 86.3 (C_q), 58.6 (CH_3), 57.6 (CH_3), 54.2 (CH_3), 52.7 (CH_3), 51.9 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 230 (2) [M^+-31], 199 (8), 171 (4), 113 (13), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{11}H_{18}O_7$ $[M+Na]^+$: 285.0945; found: 285.0946.

Synthesis of methyl 2-(4-bromophenyl)-2-methoxy-3-oxopropanoate (4.7a)



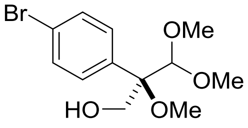
4.7a

Dimethylacetale **4.3a** (50 mg, 0.15 mmol, 1.0 equiv.) was dissolved in acetone (3 mL). Iodine (114 mg, 0.45 mmol, 3.0 equiv.) was added. The reaction mixture was stirred for 2 hours at 60 °C. The crude mixture was concentrated and quenched with $Na_2S_2O_3$ and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (*n*-pentane/EtOAc = 20:1) yielded the title compound **4.7a** (42 mg, 0.15 mmol, 99%) as colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.77 (s, 1H), 7.55 (d, *J* = 8.47 Hz, 2H), 7.35 (d, *J* = 8.51 Hz, 2H), 3.88 (s, 3H, CH_3), 3.49 (s, 3H, CH_3).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 194.1 (CHO), 168.9 (CO_2R), 132.7 (CH), 132.5 (C_q), 129.0 (CH), 124.3 (C_q), 89.0 (C_q), 55.6 (CH_3), 54.8 (CH_3).

Synthesis of 2-(4-Bromophenyl)-2,3,3-trimethoxypropan-1-ol (4.8a)



4.8a

Dimethylacetale **4.3a** (50 mg, 0.15 mmol, 1.0 equiv.) was dissolved in dry THF (3 mL) and cooled to 0 °C. $LiAlH_4$ (23 mg, 0.6 mmol, 4.0 equiv.) was added in two portions. The reaction mixture was stirred for 0 °C for 30 min. The crude mixture was quenched by dropwise addition of MeOH (2 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (*n*-pentane/EtOAc = 20:1) yielded the title compound **4.8a** (42 mg, 0.15 mmol, 99%) as translucid oil.

^{1}**H NMR** (300 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 4.35 (d, *J* = 11.9 Hz, 1H), 4.23 (d, *J* = 0.7 Hz, 1H), 3.85 (d, *J* = 11.9 Hz, 1H), 3.46 (s, 3H), 3.17 (s, 3H), 3.16 (s, 3H).

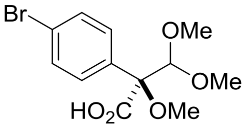
^{13}**C NMR** (75 MHz, Chloroform-*d*) δ 137.4 (C_q), 131.3 (CH), 129.0 (CH), 121.9 (C_q), 110.8 (CH), 81.5 (C_q), 61.7 (CH_2), 58.3 ($2CH_3$), 50.9 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 273 (1) [M^+-31], 229 (2), 199 (8), 183 (6), 155 (5), 118 (7), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{17}BrO_4$ $[M+Na]^+$: 327.0202; found: 327.0208.

IR (ATR, neat, cm^{-1}): 3456 (w), 2934 (w), 2832 (w), 1488 (w), 1189 (w), 1098 (m), 1071 (s), 1008 (m), 969 (w), 823 (w).

Synthesis of 2-(4-Bromophenyl)-2,3,3-trimethoxypropanoic acid (4.9a)



4.9a

Dimethylacetale **4.3a** (50 mg, 0.15 mmol, 1.0 equiv.) and LiOH were dissolved in THF/H_2O (3 mL) and stirred at 80 °C for 16 hours. The reaction mixture was allowed to cool to ambient temperature and extracted with Et_2O (3 x 10 mL). The aqueous layer was acidified to pH 1 with 1M HCl (2 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layer were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The title compound **4.9a** (42 mg, 0.15 mmol, 99%) was obtained as colorless solid.

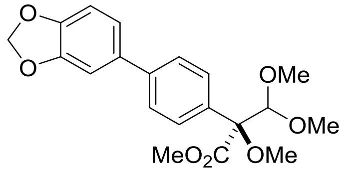
^{1}**H NMR** (300 MHz, Acetone-d_6) δ 7.46 (m, 4H, 2 CH_3), 4.87 (s, 1H, CH), 3.46 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 3.34 (s, 3H, CH_3).

^{13}C NMR (75 MHz, Acetone-d_6) δ 170.7 (CO), 136.2 (C_q) , 131.4 (CH), 131.0 (CH), 122.1 (C_q), 109.0 (CH), 87.0 (C_q), 58.7 (CH_3), 57.6 (CH_3), 54.5 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 287 (1) [M^+-31], 275 (2), 242 (11), 227 (8), 183 (12), 148 (14), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{12}H_{15}BrO_5$ $[M\text{-}H]^+$: 317.0030; found: 317.0035.

Synthesis of methyl -2-(4-(benzo[*d*][1,3]dioxol-5-yl)phenyl)-2,3,3-trimethoxypropanoate (4.11)



JPE1126

Benzo[*d*][1,3]dioxol-5-ylboronic acid **4.10** (52.3 mg, 0.32 mmol, 1.2 equiv.), Na_2CO_3 (89 mg, 0.84 mmol,4.0 equiv.) and $Pd(PPh_3)_4$ (24 mg, 10 mol%) were dissolved in DME (3.8 mL) and H_2O (0.8 mL). Methyl 2-(4-bromophenyl)-2,3,3-trimethoxypropanoate (**4.3a**) (70 mg, 0.21 mmol, 1.0 equiv.) was added in one portion. The reaction mixture was placed in a pre-heated oil bath and stirred at 100 °C for 5 hrs. The reaction mixture was quenched with EtOAc/H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (*n*-hexane/EtOAc = 20:1) yielded the title compound **4.11** (71 mg, 0.19 mmol, 90%) as colorless solid.

m.p.: 122 °C

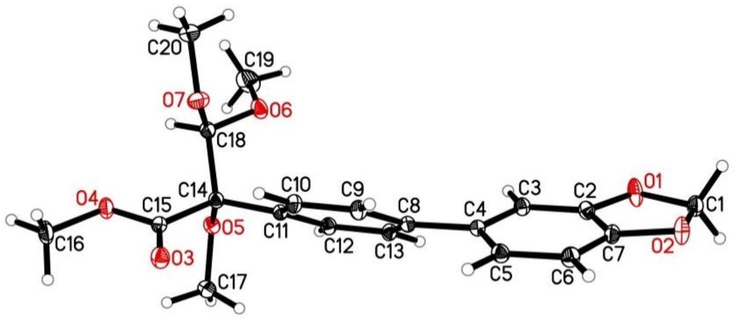
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.6 (d, *J* = 8.8 Hz, 2H), 7.5 (d, *J* = 8.8 Hz, 2H), 7.1 – 7.0 (m, 2H), 6.9 (d, *J* = 8.6 Hz, 1H), 6.0 (s, 2H), 4.9 (s, 1H), 3.9 (s, 3H), 3.5 (s, 3H), 3.5 (s, 3H), 3.4 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.8 (C_q), 148.2 (C_q), 147.2 (C_q), 140.7 (C_q), 135.1 (C_q), 133.7 (C_q), 128.6 (CH), 126.3 (CH), 125.1 (C_q), 120.8 (CH), 108.7 (CH), 107.7 (CH), 101.3 (CH_2), 87.2 (C_q), 58.5 (CH_3), 58.0 (CH_3), 54.7 (CH_3), 52.4 (CH_3).

MS (GC-MS) *m/z* (relative intensity) = 374 (1) [M^+], 343 (2), 299 (6), 241 (8), 139 (25), 75 (100).

HRMS (ESI-TOF, m/z) calcd. For $C_{20}H_{22}O_7$ $[M+Na]^+$: 397.1258; found: 397.1259.

IR (ATR, neat, cm^{-1}): 2884 (w), 2827 (w), 1741 (s), 1477 (m), 1227 (s), 1178 (m), 1103 (s), 1085 (s), 1036 (m), 935 (m), 911 (m), 811 (s), 799 (s), 535 (m).



Empirical formula	$C_{20}H_{22}O_7$	
Formula weight	374.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.7096(3) Å	α= 90°.
	b = 7.1009(2) Å	β= 100.031(1)°.
	c = 26.6401(7) Å	γ = 90°.
Volume	1808.67(9) $Å^3$	
Z	4	
Density (calculated)	1.375 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	792	
Crystal size	0.478 x 0.440 x 0.162 mm	
Theta range for data collection	2.136 to 28.000°.	
Index ranges	-12<=h<=12, -9<=k<=9, -35<=l<=35	
Reflections collected	35963	
Independent reflections	4368 [R(int) = 0.0314]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.91	
Data / restraints / parameters	4368 / 0 / 248	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0445, wR2 = 0.1103	
R indices (all data)	R1 = 0.0555, wR2 = 0.1182	
Largest diff. peak and hole	0.515 and -0.231 $e^{\cdot}Å^{-3}$	

7 References

[1] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420.

[2] a) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133; b) X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009; c) X.-F. Wu, X. Fang, L. Wu, R. Jackstell, H. Neumann, M. Beller, *Acc. Chem. Res.* **2014**, *47*, 1041–1053.

[3] a) A. Tlili, J. Schranck, J. Pospech, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 6293–6297; b) J. Pospech, A. Tlili, A. Spannenberg, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 3135–3141.

[4] a) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315–319; b) M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19090–19093; c) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955; d) C. Huang, N. Ghavtadze, B. Chattopadhyay, V. Gevorgyan, *J. Am. Chem. Soc.* **2011**, *133*, 17630–17633; e) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569; f) H. Ren, W. D. Wulff, *J. Am. Chem. Soc.* **2011**, *133*, *5656–5659*; g) H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *134*, 134–137; h) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518–522.

[5] a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417–424; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2009**, *110*, 624–655; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; d) A. S. Borovik, *Chem. Soc. Rev.* **2011**, *40*, 1870–1874; e) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926–1936; f) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976–1991; g) J. F. Hartwig, *Chem. Soc. Rev.* **2011**, *40*, 1992–2002; h) J. C. Lewis, P. S. Coelho, F. H. Arnold, *Chem. Soc. Rev.* **2011**, *40*, 2003–2021; i) H. Lu, X. P. Zhang, *Chem. Soc. Rev.* **2011**, *40*, 1899–1909; j) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898.

[6] a) *Handbook of C–H Transformations: Applications in Organic Synthesis*, Wiley-VCH, Weinheim, Germany **2005**; b) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514; c) E. M. Ferreira, *Nat. Chem.* **2014**, *6*, 94–96.

[7] a) D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749–823; b) M. Lersch, M. Tilset, *Chem. Rev.* **2005**, *105*, 2471–2526; c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1770.

[8] G. Dyker, *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712.

[9] F. K. S. Murai, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529−531.

[10] a) B.–J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, *2008*, 949–957; b) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2011**, *45*, 788–802; c) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936–946; d) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2011**, *45*, 814–825.

[11] L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.

[12] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.

[13] J. Oxgaard, W. J. Tenn, R. J. Nielsen, R. A. Periana, W. A. Goddard, *Organometallics* **2007**, *26*, 1565–1567.

[14] a) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5887–5893; b) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831.

[15] a) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed.* **2011**, *50*, 10788–10799; b) X.-F. Wu, H. Neumann, *ChemCatChem* **2012**, *4*, 447–458.

[16] E. J. Moore, W. R. Pretzer, T. J. O'Connell, J. Harris, L. LaBounty, L. Chou, S. S. Grimmer, *J. Am. Chem. Soc.* **1992**, *114*, 5888–5890.

[17] a) M. I. Bruce, M. G. Humphrey, M. R. Snow, E. R. T. Tiekink, R. C. Wallis, *J. Organomet. Chem.* **1986**, *314*, 311–322; b) E. C. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 12066–12067.

[18] T. Fukuyama, N. Chatani, J. Tatsumi, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1998**, *120*, 11522–11523.

[19] N. Chatani, S. Yorimitsu, T. Asaumi, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2002**, *67*, 7557–7560.

[20] a) M. A. Campo, R. C. Larock, *Org. Lett.* **2000**, *2*, 3675–3677; b) M. A. Campo, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 5616–5620.

[21] X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 7316–7319.

[22] a) L. Zhang, J. Cheng, T. Ohishi, Z. Hou, *Angew. Chem. Int. Ed.* **2010**, *49*, 8670–8673; b) L. Ackermann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3842–3844; c) Y. Tsuji, T. Fujihara, *Chem. Commun.* **2012**, *48*, 9956–9964; d) H. Inomata, K. Ogata, S.-i. Fukuzawa, Z. Hou, *Org. Lett.* **2012**, *14*, 3986–3989.

[23] H. Zhang, R. Shi, P. Gan, C. Liu, A. Ding, Q. Wang, A. Lei, *Angew. Chem. Int. Ed.* **2012**, *51*, 5204–5207.

[24] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348–1349.

[25] M. E. Burnett, S. Q. Wang, *Photodermatol. Photoimmunol. Photomed.* **2011**, *27*, 58–67.

[26] G. T. Carroll, N. J. Turro, J. T. Koberstein, *J. Colloid Interface Sci.* **2010**, *351*, 556–560.

[27] M. B. Smith, *March's Advanced Organic Chemistry*, 7th *Ed.* , Wiley New York, **2013**.

[28] a) T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, N. Miyaura, *J. Org. Chem.* **1998**, *63*, 4726–4731; b) R. Skoda-Földes, Z. Székvölgyi, L. Kollár, Z. Berente, J. Horváth, Z. Tuba, *Tetrahedron* **2000**, *56*, 3415–3418; c) S. Couve-Bonnaire, J.-F. Carpentier, A. Mortreux, Y. Castanet, *Tetrahedron Lett.* **2001**, *42*, 3689–3691; d) M. B. Andrus, Y. Ma, Y. Zang, C. Song, *Tetrahedron Lett.* **2002**, *43*, 9137–9140; e) M. Medio-Simón, C. Mollar, N. Rodríguez, G. Asensio, *Org. Lett.* **2005**, *7*, 4669–4672; f) L. Bartali, A. Guarna, P. Larini, E. G. Occhiato, *Eur. J. Org. Chem.* **2007**, *2007*, 2152–2163; g) P. Prediger, A. V. Moro, C. W. Nogueira, L. Savegnago, P. H. Menezes, J. B. T. Rocha, G. Zeni, *J. Org. Chem.* **2006**, *71*, 3786–3792; h) W. Qin, S. Yasuike, N. Kakusawa, J. Kurita, *J. Organomet. Chem.* **2008**, *693*, 2949–2953; i) H. Neumann, A. Brennführer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645–3652; j) X.-F. Wu, H. Neumann, M. Beller, *Tetrahedron Lett.* **2010**, *51*, 6146–6149.

[29] a) Y. Tamaru, H. Ochiai, Y. Yamada, Z.-i. Yoshida, *Tetrahedron Lett.* **1983**, *24*, 3869–3872; b) B. M. O'Keefe, N. Simmons, S. F. Martin, *Org. Lett.* **2008**, *10*, 5301–5304; c) K. Yasui, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1995**, *60*, 1365–1380; d) Q. Wang, C. Chen, *Tetrahedron Lett.* **2008**, *49*, 2916–2921.

[30] a) M. Tanaka, *Tetrahedron Lett.* **1979**, *20*, 2601–2602; b) A. M. Echavarren, J. K. Stille, *J. Am. Chem. Soc.* **1988**, *110*, 1557–1565; c) H. B. Kwon, B. H. McKee, J. K. Stille, *J. Org. Chem.* **1990**, *55*, 3114–3118; d) J. Lindh, A. Fardost, M. Almeida, P. Nilsson, *Tetrahedron Lett.* **2010**, *51*, 2470–2472; e) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1993**, *115*, 9293–9294; f) R. Shimizu, T. Fuchikami, *Tetrahedron Lett.* **1996**, *37*, 8405–8408;

g) Chen, K. Wilcoxen, Y.-F. Zhu, K.-i. Kim, J. R. McCarthy, *J. Org. Chem.* **1999**, *64*, 3476–3482; h) F. Garrido, S. Raeppel, A. Mann, M. Lautens, *Tetrahedron Lett.* **2001**, *42*, 265–266.

[31] a) S. Goubert-Renaudin, R. Schneider, A. Walcarius, *Tetrahedron Lett.* **2007**, *48*, 2113–2116; b) Y. Hatanaka, S. Fukushima, T. Hiyama, *Tetrahedron* **1992**, *48*, 2113–2126.

[32] a) K. J. T. Carr, D. L. Davies, S. A. Macgregor, K. Singh, B. Villa-Marcos, *Chem. Sci.* **2014**, *5*, 2340–2346; b) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2011**, *77*, 658–668.

[33] L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332–3335.

[34] S. Dadiboyena, *European J. Med. Chem.* **2012**, *51*, 17–34.

[35] a) K. Yamanaka, K. S. Ryan, T. A. M. Gulder, C. C. Hughes, B. S. Moore, *J. Am. Chem. Soc.* **2012**, *134*, 12434–12437; b) A. A. Kanakis, V. Sarli, *Org. Lett.* **2010**, *12*, 4872–4875; c) P. Cheng, D. L. J. Clive, S. Fernandopulle, Z. Chen, *Chem. Commun.* **2013**, *49*, 558–560; d) D. L. J. Clive, P. Cheng, *Tetrahedron* **2013**, *69*, 5067–5078.

[36] a) C. C. Hughes, A. Prieto-Davo, P. R. Jensen, W. Fenical, *Org. Lett.* **2008**, *10*, 629–631; b) C. C. Hughes, C. A. Kauffman, P. R. Jensen, W. Fenical, *J. Org. Chem.* **2010**, *75*, 3240–3250.

[37] N. M. Haste, C. C. Hughes, D. N. Tran, W. Fenical, P. R. Jensen, V. Nizet, M. E. Hensler, *Antimicrobial Agents and Chemotherapy* **2011**, *55*, 3305–3312.

[38] K. C. Nicolaou, N. L. Simmons, J. S. Chen, N. M. Haste, V. Nizet, *Tetrahedron Lett.* **2011**, *52*, 2041–2043.

[39] a) M. J. Scanlan, I. H. Hillier, A. A. MacDowell, *J. Am. Chem. Soc.* **1983**, *105*, 3568–3571; b) D. E. Metzler, C. M. Harris, R. J. Johnson, D. B. Siano, J. A. Thomson, *Biochemistry* **1973**, *12*, 5377–5392.

[41] For notable exceptions, which are however limited in scope, see: a) S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita, K. Kondo, *J. Org. Chem.* **1979**, *44*, 2408–2417; b) Y. Na, S. Park, S. B. Han, H. Han, S. Ko, S. Chang, *J. Am. Chem. Soc.* **2003**, *126*, 250–258; c) S. Park, M. Kim, D. H. Koo, S. Chang, *Adv. Synth. Catal.* **2004**, *346*, 1638–1640.

[42] a) L. Ackermann, *Acc. Chem. Res.* **2013**, *47*, 281–295; b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; c) S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886–896.

[43] a) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113–3119; b) S. Oi, R. Funayama, T. Hattori, Y. Inoue, *Tetrahedron* **2008**, *64*, 6051–6059.

[44] M. A. M. M. P. Doyle, T. Ye, Wiley, New York, **1998**.

[45] a) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857–1869; b) H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070.

[46] a) M. Berthelot, F. Besseau, C. Laurence, *Eur. J. Org. Chem.* **1998**, *1998*, 925–931; b) L. Bellon, R. W. Taft, J.-L. M. Abboud, *J. Org. Chem.* **1980**, *45*, 1166–1168; c) J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 9052–9067.

[47] a) D. D. A. A. K. Ghosh, *Future Med. Chem.* **2011**, *3*, 1181–1203; b) A. K. Ghosh, S. Gemma, A. Baldridge, Y.-F. Wang, A. Y. Kovalevsky, Y. Koh, I. T. Weber, H. Mitsuya, *J. Med. Chem.* **2008**, *51*, 6021–6033.

[48] B. Chemie, Heidelberg, Germany, **2005**.

[49] A. B. Concepcion, H. Yamamoto, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, **2001**.

[50] D. Chaturvedi, A. Goswami, P. Pratim Saikia, N. C. Barua, P. G. Rao, *Chem. Soc. Rev.* **2010**, *39*, 435–454.

[51] a) I. Rosenthal, D. Elad, *J. Org. Chem.* **1968**, *33*, 805–811; b) M. Matsukawa, J. Inanaga, M. Yamaguchi, *Tetrahedron Lett.* **1987**, *28*, 5877–5878; c) S. H. Brown, R. H. Crabtree, *J. Chem. Soc., Chem. Commun.* **1987**, 970–971.

[52] a) A. Plodek, S. Raeder, F. Bracher, *Tetrahedron* **2012**, *68*, 4693–4700; b) L. Pokhrel, Y. Kim, T. D. T. Nguyen, A. M. Prior, J. Lu, K.-O. Chang, D. H. Hua, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3480–3484.

[53] S. H. Brown, R. H. Crabtree, *J. Am. Chem. Soc.* **1989**, *111*, 2946–2953.

[54] a) D. C. Beshore, A. B. Smith, *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149; b) D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

[55] a) C. D. Shacklett, H. A. Smith, *J. Am. Chem. Soc.* **1951**, *73*, 766–768; b) M. Selva, F. Trotta, P. Tundo, *Synthesis* **1991**, *1991*, 1003–1004; c) Y. L. Hu, Q. Ge, Y. He, M. Lu, *ChemCatChem* **2010**, *2*, 392–396.

[56] G. Pasquale, D. Ruiz, J. Autino, G. Baronetti, H. Thomas, G. Romanelli, *Comptes Rendus Chimie* **2012**, *15*, 758–763.

[57] a) E. Nadeau, D. L. Ventura, J. A. Brekan, H. M. L. Davies, *J. Org. Chem.* **2010**, *75*, 1927–1939; b) J. Hansen, J. Autschbach, H. M. L. Davies, *J. Org. Chem.* **2009**, *74*, 6555–6563; c) E. Nadeau, Z. Li, D. Morton, H. M. L. Davies, *Synlett* **2009**, *2009*, 151–154; d) Y. Lian, K. I. Hardcastle, H. M. L. Davies, *Angew. Chem. Int. Ed.* **2011**, *50*, 9370–9373; e) S. Chuprakov, J. A. Malik, M. Zibinsky, V. V. Fokin, *J. Am. Chem. Soc.* **2011**, *133*, 10352–10355; f) M. E. Harvey, D. G. Musaev, J. Du Bois, *J. Am. Chem. Soc.* **2011**, *133*, 17207–17216; g) M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 9721–9726.

[58] M. P. Doyle, M. A. McKervey, T. Ye, *Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, NY., **1998**.

[59] H. M. L. Davies, Y. Lian, *Acc. Chem. Res.* **2012**, *45*, 923–935.

[60] Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2012**, *46*, 236–247.

[61] H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050.

[62] a) M. Kennedy, M. A. McKervey, A. R. Maguire, G. H. P. Roos, *J. Chem. Soc., Chem. Commun.* **1990**, 361–362; b) M. A. McKervey, T. Ye, *J. Chem. Soc., Chem. Commun.* **1992**, 823–824.

[63] H. M. L. Davies, T. Hansen, *J. Am. Chem. Soc.* **1997**, *119*, 9075–9076.

[64] K. Kosswig, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2005**.

[65] a) H. M. L. Davies, Q. Jin, *Org. Lett.* **2004**, *6*, 1769–1772; b) H. M. L. Davies, Q. Jin, P. Ren, A. Y. Kovalevsky, *J. Org. Chem.* **2002**, *67*, 4165–4169; c) H. M. L. Davies, Q. Jin, *Tetrahedron: Asymm.* **2003**, *14*, 941–949.

[66] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) M. Kaupp, P. v. R. Schleyer, H. Stoll, H. Preuss, *J. Chem. Phys.* **1991**, *94*, 1360–1366.

[67] J. Hansen, H. M. L. Davies, *Coord. Chem. Rev.* **2008**, *252*, 545–555.

[68] H. M. L. Davies, A. Ni, *Chem. Commun.* **2006**, 3110–3112.

[69] a) H. M. L. Davies, E. G. Antoulinakis, *Org. Lett.* **2000**, *2*, 4153–4156; b) H. M. L. Davies, E. G. Antoulinakis, T. Hansen, *Org. Lett.* **1999**, *1*, 383–386; c) H. M. L. Davies, R. E. J. Beckwith, E. G. Antoulinakis, Q. Jin, *J. Org. Chem.* **2003**, *68*, 6126–6132.

[70] a) H. M. L. Davies, T. Hansen, D. W. Hopper, S. A. Panaro, *J. Am. Chem. Soc.* **1999**, *121*, 6509–6510; b) H. M. L. Davies, C. Venkataramani, T. Hansen, D. W. Hopper, *J. Am. Chem. Soc.* **2003**, *125*, 6462–6468; c) H. M. L. Davies, C. Venkataramani, *Org. Lett.* **2001**, *3*, 1773–1775; d) J. M. Axten, R. Ivy, L. Krim, J. D. Winkler, *J. Am. Chem. Soc.* **1999**, *121*, 6511–6512.

[71] H. M. L. Davies, J. Yang, J. Nikolai, *J. Organomet. Chem.* **2005**, *690*, 6111–6124.

[72] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

[73] H. M. L. Davies, J. Yang, *Adv. Synth. Catal.* **2003**, *345*, 1133–1138.

[74] Samples of 1,3,5-trioxane and **2.3b** were dissolved in THF-d_8 (0.4 mL) and 10%-DCl in D_2O (0.2 mL). No degradation of either material was evident according to ^{1}H-NMR spectroscopy (>7 d).

[75] a) P. G. M. W. T. W. Green, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, **1999**; b) R. Dalpozzo, A. De Nino, L. Maiuolo, A. Procopio, A. Tagarelli, G. Sindona, G. Bartoli, *J. Org. Chem.* **2002**, *67*, 9093–9095; c) S. A. Ruider, S. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2013**, *52*, 11908–11911; d) B. T. Gregg, K. C. Golden, J. F. Quinn, *J. Org. Chem.* **2007**, *72*, 5890–5893; e) J. Sun, Y. Dong, L. Cao, X. Wang, S. Wang, Y. Hu, *J. Org. Chem.* **2004**, *69*, 8932–8934; f) P. S. Kumar, A. Banerjee, S. Baskaran, *Angew. Chem. Int. Ed.* **2010**, *49*, 804–807.

[76] W. K. Busfield, I. D. Grice, I. D. Jenkins, *J. Chem. Soc., Perkin Trans. 2* **1994**, 1079–1086.

[77] M. P. Byrn, C. J. Curtis, S. I. Khan, P. A. Sawin, R. Tsurumi, C. E. Strouse, *J. Am. Chem. Soc.* **1990**, *112*, 1865–1874.

[78] S. Wolfe, B. M. Pinto, V. Varma, R. Y. N. Leung, *Can. J. Chem.* **1990**, *68*, 1051–1062.

[79] a) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2009**, *110*, 704–724; b) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2904.

[80] T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 14972–14974.

[81] H. M. L. Davies, J. S. Alford, *Chem. Soc. Rev.* **2014**, *43*, 5151–5162.

[82] a) P. A. Evans, B. Holmes, *Tetrahedron* **1991**, *47*, 9131–9166; b) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95–102; c) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3008.

[83] a) K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem. Int. Ed.* **1994**, *33*, 15–44; b) K. C. Nicolaou, R. K. Guy, *Angew. Chem. Int. Ed.* **1995**, *34*, 2079–2090.

[84] a) T. Nakata, *Chem. Rev.* **2005**, *105*, 4314–4347; b) M. Inoue, *Chem. Rev.* **2005**, *105*, 4379–4405; c) M. Sasaki, H. Fuwa, *Nat. Prod. Rep.* **2008**, *25*, 401–426; d) K. C. Nicolaou, M. O. Frederick, R. J. Aversa, *Angew. Chem. Int. Ed.* **2008**, *47*, 7182–7225.

[85] a) A. Parenty, X. Moreau, J. M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939; b) U. Nubbemeyer, in *Stereoselective Heterocyclic Synthesis III, Vol. 216* (*Ed.* : P. Metz), Springer Berlin Heidelberg, **2001**, pp. 125–196.

[86] M. E. Maier, *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077.

[87] a) N. J. Lawrence, *Preparation of Alkenes: A Practical Approach*, Oxford University Press, Oxford, **1996**; b) H.-J. Cristau, *Chem. Rev.* **1994**, *94*, 1299–1313; c) D. G. Gilheany, *Chem. Rev.* **1994**, *94*, 1339–1374.

[88] a) S. N. Lakeev, I. O. Maydanova, F. Z. Galin, G. A. Tolstikov, *Russian Chem. Rev.* **2001**, *70*, 655–672; b) V. K. Aggarwal, C. L. Winn, *Acc. Chem. Res.* **2004**, *37*, 611–620.

[89] a) W. Kirmse, R. Lelgemann, K. Friedrich, *Chemische Berichte* **1991**, *124*, 1853–1863; b) W. Kirmse, *Eur. J. Org. Chem.* **2005**, *2005*, 237–260; c) T. A. Young, C. O'Rourke, N. B. Gray, B. D. Lewis, C. A. Dvorak, K. S. Kuen, J. P. DeLuca, *J. Org. Chem.* **1993**, *58*, 6224–6228; d) T. Sueda, T. Nagaoka, S. Goto, M. Ochiai, *J. Am. Chem. Soc.* **1996**, *118*, 10141–10149; e) S. Kim, J.-Y. Yoon, C. M. Cho, *Chem. Commun.* **1996**, 909–910; f) J. W. Cubbage, B. L. Edelbach, K. S. Kuen, J. P. DeLuca, *Tetrahedron* **1997**, *53*, 9823–9834; g) F. P. Marmsäter, J. A. Vanecko, F. G. West, *Org. Lett.* **2004**, *6*, 1657–1660.

[90] J.-L. Mieusset, U. H. Brinker, *Eur. J. Org. Chem.* **2008**, *2008*, 3363–3368.

[91] W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2010**, *49*, 7253–7256.

[92] a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734–736; b) H. B. Buergi, J. D. Dunitz, *Acc. Chem. Res.* **1983**, *16*, 153–161.

[93] a) J. S. Clark, C. Guerot, C. Wilson, A. J. Blake, *Chem. Commun.* **2007**, 4134–4136; b) J. B. Sweeney, *Chem. Soc. Rev.* **2009**, *38*, 1027–1038.

[94] M. Vishe, R. Hrdina, L. Guénée, C. Besnard, J. Lacour, *Adv. Synth. Catal.* **2013**, *355*, 3161–3169.

[95] R. Ballesteros-Garrido, D. Rix, C. Besnard, J. Lacour, *Chem. Eur. J.* **2012**, *18*, 6626–6631.

[96] S. Cenini, G. Cravotto, G. B. Giovenzana, G. Palmisano, S. Tollari, *Tetrahedron* **1999**, *55*, 6577–6584.

[97] F. Medina, C. Besnard, J. Lacour, *Org. Lett.* **2014**, *16*, 3232–3235.

[98] H. K. Aldridge, X. Liu, M. C. Lin, C. F. Melius, *Int. J. Chem. Kinet.* **1991**, *23*, 947–956.

[99] R. T. Taylor, T. Snowden, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, **2001**.

[100] a) S. E. Denmark, N. G. Almstead, *J. Org. Chem.* **1991**, *56*, 6458–6467; b) M. Takasu, Y. Naruse, H. Yamamoto, *Tetrahedron Lett.* **1988**, *29*, 1947–1950; c) R. Gardi, R. Vitali, A. Ercoli, *Tetrahedron Lett.* **1961**, *2*, 448–451.

[101] a) B. Karimi, H. Seradj, G.-R. Ebrahimian, *Synlett* **1999**, *1999*, 1456–1458; b) N. M. Leonard, M. C. Oswald, D. A. Freiberg, B. A. Nattier, R. C. Smith, R. S. Mohan, *J. Org. Chem.* **2002**, *67*, 5202–5207; c) E. Fernández, S. Castillón, *Tetrahedron Lett.* **1994**, *35*, 2361–2364.

[102] R. Morrone, M. Piattelli, G. Nicolosi, *Eur. J. Org. Chem.* **2001**, *2001*, 1441–1443.

[103] a) R. M. Roberts, P. J. Vogt, *J. Am. Chem. Soc.* **1956**, *78*, 4778–4782; b) R. A. Crochet Jr, C. D. W. Blanton Jr, *Synthesis* **1974**, *1974*, 55–56; c) G. Jenkins, A. Knevel, C. Davis, *J. Org. Chem.* **1961**, *26*, 274–274; d) K. Kamata, I. Agata, A. I. Meyers, *J. Org. Chem.* **1998**, *63*, 3113–3116; e) P. Gmeiner, B. Bollinger, *Tetrahedron Lett.* **1991**, *32*, 5927–5930.

[104] a) W. E. R. Parham, L. J., *Org. Synth., Coll. Vol.* **1955**, *3*, 295; b) F. Perron-Sierra, M. A. Promo, V. A. Martin, K. F. Albizati, *J. Org. Chem.* **1991**, *56*, 6188–6199.

[105] a) W. Treibs, *Tetrahedron Lett.* **1967**, *8*, 4707–4709; b) H. Gross, A. Rieche, G. Matthey, *Chem. Ber.* **1963**, *96*, 308–313.

[106] J.-C. Hierso, E. Bouwman, D. D. Ellis, M. Perez Cabero, J. Reedijk, A. L. Spek, *J. Chem. Soc., Dalton Trans.* **2001**, 197–201.

[107] a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519; b) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096; c) T. Kusumi, T. Fukushima, I. Ohtani, H. Kakisawa, *Tetrahedron Lett.* **1991**, *32*, 2939–2942; d) B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. E. Christy, G. S. Ponticello, S. L. Varga, J. P. Springer, *J. Org. Chem.* **1986**, *51*, 2370–2374; e) B. M. Trost, R. C. Bunt, S. R. Pulley, *J. Org. Chem.* **1994**, *59*, 4202–4205.

[108] P. C. Gøtzsche, *Non-steroidal anti-inflammatory drugs, Vol. 320*, **2000**.

[109] L. D. L. J. M. Ritter, T. G. K. Mant, 4 *Ed.* , London: Arnold, London, **1999**, pp. 423–424.

[110] D. Tassinari, F. Drudi, M. Rosati, P. Tombesi, S. Sartori, M. Maltoni, *Palliat. Medicine* **2011**, *25*, 410–423.

[111] D. K. Thompson, N. Suzuki, L. S. Hegedus, Y. Satoh, *J. Org. Chem.* **1992**, *57*, 1461–1467.

[112] F. J. Moreno-Dorado, F. M. Guerra, M. a. J. Ortega, E. Zubía, G. M. Massanet, *Tetrahedron: Asymm.* **2003**, *14*, 503–510.

[113] A. Crespo-Peña, D. Monge, E. Martín-Zamora, E. Álvarez, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2012**, *134*, 12912–12915.

[114] a) A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263–309; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223–270; c) A. Padwa, *J. Org. Chem.* **2009**, *74*, 6421–6441.

[115] a) R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert, P. Teyssié, *Tetrahedron Lett.* **1973**, *14*, 2233–2236; b) R. Paulissen, E. Hayez, A. J. Hubert, P. Teyssie, *Tetrahedron Lett.* **1974**, *15*, 607–608.

[116] R. W. Ratcliffe, T. N. Salzmann, B. G. Christensen, *Tetrahedron Lett.* **1980**, *21*, 31–34.

[117] C. J. Moody, *Angew. Chem. Int. Ed.* **2007**, *46*, 9148–9150.

[118] L. Ferris, D. Haigh, C. J. Moody, *Tetrahedron Lett.* **1996**, *37*, 107–110.

[119] a) T. C. Maier, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 4594–4595; b) S.-F. Zhu, C. Chen, Y. Cai, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2008**, *47*, 932–934.

[120] Y. Liang, H. Zhou, Z.-X. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 17783–17785.

[121] J. Egger, E. M. Carreira, *Nat. Prod. Rep.* **2014**, *31*, 449–455.

[122] Z. Li, H. M. L. Davies, *J. Am. Chem. Soc.* **2009**, *132*, 396–401.

[123] Z. Li, B. T. Parr, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 10942–10946.

[124] Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 15497–15504.

[125] H. M. L. Davies, B. Hu, E. Saikali, P. R. Bruzinski, *J. Org. Chem.* **1994**, *59*, 4535–4541.

[126] H. M. L. Davies, E. Saikali, T. Jeffrey Clark, E. H. Chee, *Tetrahedron Lett.* **1990**, *31*, 6299–6302.

[127] a) Y. Sevryugina, B. Weaver, J. Hansen, J. Thompson, H. M. L. Davies, M. A. Petrukhina, *Organometallics* **2008**, *27*, 1750–1757; b) J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 457–461; c) D. Morton, A. R. Dick, D. Ghosh, H. M. L. Davies, *Chem. Commun.* **2012**, *48*, 5838–5840; d) A. G. Smith, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 18241–18244.

[128] a) X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 16402–16405; b) Y. Qian, X. Xu, X. Wang, P. J. Zavalij, W. Hu, M. P. Doyle, *Angew. Chem. Int. Ed.* **2012**, *51*, 5900–5903; c) X. Xu, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* **2013**, *52*, 12664–12668; d) X. Xu, P. Y. Zavalij, W. Hu, M. P. Doyle, *J. Org. Chem.* **2013**, *78*, 1583–1588; e) Y. Qian, P. J. Zavalij, W. Hu, M. P. Doyle, *Org. Lett.* **2013**, *15*, 1564–1567; f) J. Barluenga, G. Lonzi, L. Riesgo, L. A. López, M. Tomás, *J. Am. Chem. Soc.* **2010**, *132*, 13200–13202; g) V. V. Pagar, A. M. Jadhav, R.-S. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 20728–20731; h) Y. Yue, Y. Wang, W. Hu, *Tetrahedron Lett.* **2007**, *48*, 3975–3977.

[129] a) Y. Lian, H. M. L. Davies, *Org. Lett.* **2010**, *12*, 924–927; b) Y. Lian, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 1934–1937; c) J. H. Hansen, T. M. Gregg, S. R. Ovalles, Y. Lian, J. Autschbach, H. M. L. Davies, *J. Am. Chem. Soc.* **2011**, *133*, 5076–5085.

[130] D. Valette, Y. Lian, J. P. Haydek, K. I. Hardcastle, H. M. L. Davies, *Angew. Chem. Int. Ed.* **2012**, *51*, 8636–8639.

[131] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862.

[132] a) J. W. J. Kennedy, D. G. Hall, *Angew. Chem. Int. Ed.* **2003**, *42*, 4732–4739; b) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2794.

[133] M. Sugiura, K. Hirano, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 7182–7183.

[134] Statistically corrected value in parentheses.

[135] a) G. L. Heard, B. F. Yates, *J. Comput. Chem.* **1996**, *17*, 1444–1452; b) G. L. Heard, B. F. Yates, *J. Org. Chem.* **1996**, *61*, 7276–7284; c) G. Ghigo, S. Cagnina, A. Maranzana, G. Tonachini, *J. Org. Chem.* **2010**, *75*, 3608–3617.

[136] a) G. A. Olah, E. B. Baker, J. C. Evans, W. S. Tolgyesi, J. S. McIntyre, I. J. Bastien, *J. Am. Chem. Soc.* **1964**, *86*, 1360–1373; b) G. A. Olah, A. M. White, *J. Am. Chem. Soc.* **1968**, *90*, 1884–1889.

[137] a) C.-D. Lu, H. Liu, Z.-Y. Chen, W.-H. Hu, A.-Q. Mi., *Org. Lett.* **2005**, *7*, 83–86; b) H. Huang, X. Guo, W. Hu, *Angew. Chem. Int. Ed.*, **2007**, *46*, 1337–1339; c) X. Zhang, H. Huang, X. Guo, X. Guan, L. Yang, W. Hu, *Angew. Chem., Int. Ed.*, **2008**, *47*, 6647–6649; d) W. Hu, X. Xu, J. Zhou, W. Liu, H. Huang, J. Hu, L. Yang, L. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782–7783.

8 Curriculum Vitae

Jola Pospech

Born on December 21st, 1986 in Pinneberg, Germany.

Education

03/2012-01/2015	**PhD Thesis** with highest Honors (summa cum laude) Advisor: Prof. Dr. M. Beller Leibniz Institute for Catalysis at the University of Rostock Rostock, Germany.
09/2011-11/2011	**Research Assistant** Advisor: Prof. Dr. E. M. Carreira ETH Zürich, Switzerland.
04/2010-08/2011	**Master of Science** with Honors in Chemistry Advisor: Prof. Dr. L. Ackermann University of Göttingen, Germany.
08/2009-01/2010	**Exchange Student** Advisor: Prof. Dr. K. J. Szabó University of Stockholm, Schweden.
10/2006-06/2009	**Bachelor of Science** in Chemistry Advisor: Prof. Dr. L. Ackermann University of Göttingen, Germany.
06/2006	**Highschool Graduation** Ludwig-Meyn Gymnasium, Uetersen, Germany.
08/1993-07/1998	**Primary School** Grund- und Hauptschule am Roggenfeld, Uetersen, Germany.

Merits & Awards

08/2009-01/2010	**Erasmus Scholarship**
05/2013	**Scientific Communication Award** Young Scientists' Meeting "Rostock's 11", Rostock, Germany.
08/2013	**DAAD-Travel grant** IUPAC Meeting "OMCOS 17", Fort Collins, Colorado, USA.

Conferences and Workshops

05/22/2013	**Rostock's 11**, Young Scientists' Meeting, Rostock, Germany. *"Breaking C–H Bonds"* (Oral Presentation)
07/28-08/01/2013	**OMCOS 17**, Fort Collins, Colorado, USA. **J. Pospech**, A. Tlili, H. Neumann, M. Beller. *"Regioselective Ruthenium-catalyzed carbonylative direct Arylation of Heteroarenes"* (Poster Presentation)
09/03-04/2013	**CHEM 21 AGM**, Orion Pharma, Helsinki, Finland. **J. Pospech**, H. Neumann, M. Beller. *"Transition Metal-catalyzed Carbonylative Coupling Reactions and its Application in Organic Synthesis"* (Poster Presentation) *"Ruthenium-catalyzed Carbonylative Direct Arylation and its Application in Organic Synthesis"* (Poster Presentation)
09/16-18/2013	**Catalysis for Sustainable Synthesis (CaSuS) Workshop**, Joint Workshop of LIKAT Rostock and University of Göttingen, Rostock, Germany. *"Regioselective Ruthenium-catalyzed carbonylative direct Arylation of Heteroarenes"* (Oral Presentation)
10/11-14/2013	**iNANO Autumn School**, Aarhus University, Denmark. *invited* by Prof. T. Skrydstrup **J. Pospech**, A. Tlili, H. Neumann, M. Beller. *"Regioselective Ruthenium-catalyzed carbonylative direct Arylation of Heteroarenes"* (Poster Presentation)
01/24-25/2014	**Torkil Holm Symposium - Visions in Chemistry**, Kopenhagen, Denmark.
07/13-18/2014	**BOSS XIV**, 14th Belgium Organic Synthesis Symposium, Louvain-la-Neuve, Belgium. (Poster Presentation)

9 Publications

(9) **J. Pospech**, I. Fleischer, *RSC Adv.* **2015**, *5*, 493–496.
"Brønsted Acid-catalyzed Hydroarylation of Activated Olefins"

(8) A. Tlili, J. Schranck, **J. Pospech**, H. Neumann, M. Beller, *ChemCatChem* **2014**, *6*, 1562–1566.
„Ruthenium-catalyzed Carbonylative Hydroarylation of Styrene-derivatives using Arenes and Heteroarenes Bearing a N-directing Group"

(7) **J. Pospech**, A. Tlili, A. Spannenberg, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 3135–3141.
„Regioselective Ruthenium-Catalyzed Carbonylative Direct Arylation of 5-membered and condensed Heterocycles"

(6) A. Tlili, J. Schranck, **J. Pospech**, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 6293–6297.
"Ruthenium-Catalyzed Carbonylative C–C Coupling in Water by Directed C–H Bond Activation"

(5) **J. Pospech**, I. Fleischer, R. Franke, S. Buchholz, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 2852–2872. *Angew. Chem.* **2013**, *125*, 2922–2944.
„Alternative Metals in Homogenous Hydroformylation"

(4) L. Ackermann, **J. Pospech**, H.K. Potukuchi, *Org. Lett*. **2012**, *14*, 2146–2149.
"Well-Defined Ruthenium(II) Carboxylate as Catalyst for Direct C–H/C–O Bond Arylations with Phenols in Water"

(3) L. Ackermann, **J. Pospech**, K. Graczyk, K. Rauch, *Org. Lett.* **2012**, *14*, 930–933. (highlighted in *Synfacts* **2012**, 366.)
"Versatile Synthesis of Isocoumarins and α-Pyrones by Ruthenium-Catalyzed Oxidative C–H/O–H Bond Cleavages"

(2) L. Ackermann, **J. Pospech**, *Org. Lett.* **2011**, *13*, 4153–4155. (highlighted in *Synfacts* **2011**, 1167.
"Ruthenium-Catalyzed Oxidative C–H Bond Alkenylations in Water: Expedient Synthesis of Annulated Lactones"

(1) L. Ackermann, S. Barfüßer, **J. Pospech**, *Org. Lett.* **2010**, *12*, 724–726. (highlighted in *Synfacts* **2010**, 694.)

“Palladium-Catalyzed Direct Arylations, Alkenylations, and Benzylations through C-H Bond Cleavages with Sulfamates or Phosphates as Electrophiles”