Published in final edited form as:
J Am Chem Soc. 2013 June 19; 135(24): 9000–9009. doi:10.1021/ja402848c.

Overcoming Product Inhibition in Catalysis of the Intramolecular Schmidt Reaction

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Abstract

A method for carrying out the intramolecular Schmidt reaction of alkyl azides and ketones using a substoichiometric amount of catalyst is reported. Following extensive screening, the use of the strong hydrogen bond donating solvent hexafluoro-2-propanol was found to be consistent with low catalyst loadings, which range from 2.5 mol% for favorable substrates to 25 mol% for more difficult cases. Reaction optimization, broad substrate scope, and preliminary mechanistic studies of this improved version of the reaction are described.

INTRODUCTION

The intramolecular Schmidt reaction is a useful method for the preparation of lactams from azidoalkyl ketones[1,2] that has been applied to alkaloid synthesis and natural product-inspired libraries.[3] One limitation of the reaction has been the requirement of excess Lewis or Brønsted acid[1a,4] in order to achieve complete conversion, which often renders it unsuitable for strongly acid-sensitive substrates and limits scalability. In addition, a version of this reaction that would employ vastly smaller amounts of metal may well be cleaner and more efficient, even as it minimized the generation of metal waste.[5] Two representative examples are shown in Figures 1a and 1b. Indeed, we are unaware of any examples that proceed to high conversion with less than a full equivalent of promoter. This can be attributed to strong product inhibition, which is intrinsic to any reaction that converts a ketone to an amide. The first step in a hypothetical catalytic cycle for the intramolecular Schmidt reaction is the activation of a substrate **S** with a Lewis or Brønsted acid **LA** to form complex **S**–**LA** (Figure 1c).[6] The tethered azide then attacks the activated carbonyl, forming the azidohydrin intermediate **A**, which upon antiperiplanar bond migration and nitrogen extrusion results in the formation of a product **P**. The lactam produced is strongly Lewis-basic and sequesters the catalyst in an unproductive manner. We propose that this unfavorable catalyst-product interaction results in product inhibition deterring the progress of reaction and necessitating the use of super-stoichiometric amount of catalyst. [4a,7]

A fundamental challenge in designing a catalytic variant for this reaction lies in the inherent strength of the complex formed between the catalyst and the product, which is a hard acid–

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures for new compounds and mechanistic experiments; list of known compounds; additional screening data for reaction optimization experiments; and copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

hard base interaction. Related reactions such as the Beckmann rearrangement and Ritter reaction, which generate amide or lactam products, have also suffered in the past from the requirement of a stoichiometric amount of strong acids and harsh reaction conditions.[8,10] The role of lactam in product inhibition has been demonstrated for Beckmann rearrangement using a microchemical system.[9] However, recent catalytic developments for these reactions have allowed for the use of substoichiometric amounts of Brønsted or Lewis acid, improving efficiency and expanding scope of those processes.[8,10] The use of ionic liquids[11] and extensive screening of catalysts and solvents led to the realization of these catalytic reactions. We envisioned that catalysis in the intramolecular Schmidt reaction might be more efficient if condition were identified wherein a ligand, solvent, or additive is capable of competing with the catalyst in forming a complex with the Lewis-basic lactam, thus allowing catalyst turnover. Herein, we disclose a first report of the catalytic intramolecular Schmidt reaction that is superior in essentially every way to the version that we and others have been exploring since 1991.[1,2d,4]

RESULTS AND DISCUSSIONS

Screening

We sought to replace the stoichiometric Schmidt reaction by identifying conditions that would (1) require low, sub-stoichiometric amounts of catalyst, (2) be mild, efficient, and proceed at room temperature, and (3) would have broad substrate scope. We initially focused on catalyst and additive screening. Early on, we found that 10–25 mol% of scandium(III) triflate could efficiently promote the reaction of **1c** to **2c**, but only at unacceptably high temperatures (Scheme 1; see Supporting Information for details of these and all other early attempts). Moreover, these reaction conditions were plagued with extremely limited substrate scope and low yields. For example, higher catalyst loadings were generally necessary for cyclopentanone **1a** (we had in the interim found that MeCN was a better solvent than H_2O, either alone or with phase-transfer catalysts) and the reaction of **1d** under the same conditions failed (<5% product yields). Reactions of substrates like **1a** or **1d** require longer reaction times than **1c** in the stoichiometric reaction and are often poorer yielding as well.[1,12]

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

Figure 2 depicts the results of preliminary screening of reaction conditions (see Supporting Information for details). Examination of 23 different solvents was first carried out using 20 mol% of $Sc(OTf)_3$ at 150 °C. Only five solvents (nitromethane, benzonitrile, acetic acid, trifluoroethanol (TFE), and the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate) gave product in high yields. When the $Sc(OTf)_3$ loading was reduced to 10 mol%, only TFE resulted in complete conversion. We then focused our attention on catalyst screening using 10 mol% of catalyst with TFE as a solvent at 80 °C. In total, 51 catalysts were screened, which included 44 Lewis acids that represented 31 different elements and 7 Brønsted acids. Of these, a number of transition metals such as $TiCl_4$, $ZrCl_4$, and $Fe(OTf)_3$, some post-transition metals like $In(OTf)_3$ and $Bi(OTf)_3$, and metalloids such as $SiCl_4$ and $SbCl_5$ have

results that were good enough for further screening. Further evaluation at 10 mol% loading of these selected catalysts in TFE at lower temperatures (50 and 25 °C) revealed $TiCl_4$ and $SiCl_4$ to be most effective. The identification of $TiCl_4$ was notable, as it has been a catalyst of choice for many stoichiometric intramolecular Schmidt reactions.[1b,4,14]

Identification of TFE as nearly unique in permitting catalyst turnover prompted us to more completely examine the effect of solvents using **1e** as the substrate and 10 mol% of $TiCl_4$ as catalyst (Table 1). Again, TFE was observed to give the best results with respect to both conversion and stereochemical retention (cf. entries 1–3 with entry 4). The results with TFE prompted us to consider other fluorinated alcohols, specifically hexafluoro-2-propanol (HFIP). Compared to their non-fluorinated alcohol analogues, TFE and HFIP have low nucleophilicity, low pKa, high ionizing power, high polarity, ability to solvate anions, and are strong hydrogen bond donors.[15] Accordingly, they are often used as solvent, co-solvent, or a Lewis acid substitute[15e,16] in oxidations,[17] or in ring opening reactions of oxiranes, cycloaddition, and deprotection reactions.[15b,l5d,l5f] Their utility has been attributed to the strong hydrogen bond donor ability of these solvents.[15b,c,17b,18] Moreover, the use of these solvents to denature proteins and induce α-helical secondary structures provided some ancillary expectation that they might prove useful in modifying the ability of our product lactams to coordinate with acid promoters.[19] Owing to the strong H-bond donor ability and high ionizing power of HFIP compared to TFE; HFIP often provides superior results both in reaction rate enhancement[15b,15e,16,20] and as a helix-inducing co-solvent.[19a]

Using HFIP as a substitute for $TiCl_4$ in a control experiment did not afford any product and substrate **1e** was recovered almost quantitatively (entry 5). Using one equivalent of HFIP as an additive with CH_3CN as a solvent did not improve the yield (entry 6). However, when HFIP was used as solvent in combination with 10 mol% of $TiCl_4$, complete conversion and negligible epimerization was observed with increased catalyst turnover compared to TFE (cf. entries 7 and 4). Lowering the catalyst loading to 5 mol% of $TiCl_4$ produced similar results as with 10 mol% of $TiCl_4$ but at the expense of longer reaction times (entry 8). Changing the concentration of reaction mixture had minimal effect on yield (entries 9 and 10).

We speculated that reaction of HFIP with $TiCl_4$ might generate HCl in situ along with $Ti[OCH(CF_3)_2]_4$. If so, then 5 mol% of $TiCl_4$ should be capable of generating 20 mol% of HCl in situ. To test this hypothesis, we ran the reaction in the presence of 10 and 20 mol% of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a proton scavenger (entries 11 and 12). Significant catalyst inhibition was observed resulting in lower yields but reaction to some extent was still observed when 20 mol% of DTBMP was used. This could mean that the catalytically active species is in situ generated HCl or that DTBMP, being a base, is having some other deleterious effect on the reaction.[21] Reaction in HFIP with $SiCl_4$ provided lactam in good yield but $Sc(OTf)_3$ provided product in only 28% yield (entries 13 and 14). The reaction with Brønsted acids (5–20 mol%) delivered comparative lower yield of the product than 5 mol% of $TiCl_4$ (entries 15–18). Interestingly, reaction with 20 mol% of HCl in ether gave a lower yield compared to 5 mol% of $TiCl_4$ (cf. entries 8 and 16). The use of a chiral phosphoric acid[4b] neither provided good yield nor led to any degree of kinetic resolution (entry 18). Reaction with $Ti(^iOPr)_4$ resulted in only a trace amount of product with quantitative recovery of substrate **1e** (entry 19). Although this supported our supposition that in situ generated HCl could be the active catalyst, it was hard to reconcile with the reduced yield obtained with HCl added as a solution in ether, possibly due to concentration errors in the commercial product (see Table 4 and associated discussion for more on this point).

Scope

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

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

Substrate **1o** containing a tertiary amine – a possible additional source of catalyst inactivation – required 35 mol% of $TiCl_4$ to provide pyrrolodiazepinone **2o** (entry 8).[22] Typically, for the intramolecular Schmidt reaction, nitrogen gas evolution is observed immediately upon addition of the catalyst. However, when $TiCl_4$ was added slowly to a solution of substrate **1o** in HFIP, a yellow precipitate was initially observed, with effervescence only commencing upon the addition of 25 mol% of $TiCl_4$.[23] This observation suggests that the initial 25 mol% of $TiCl_4$, capable of generating 100 mol% of HCl, formed a salt with the basic amine and the remaining 10 mol% of $TiCl_4$ was responsible for the desired transformation into lactam **2o**. Azidoaldehyde **1p** only required 5 mol% of $TiCl_4$ to provide 3-benzylpyrrolidinone **2p** in good yield (entry 9). Unfortunately, extending the tether length between carbonyl and the azide moiety from the usual four to five carbons resulted in a sluggish reaction with only 11% of lactam **2q** being obtained, even when 20 mol% of $TiCl_4$ was employed (entry 10). This is consistent with the stringent dependence of the intramolecular Schmidt reaction on tether length observed since the initial discovery of the reaction.[1,2d]

Given the requirement of relatively high catalyst loading for these less reactive substrates, we sought to further optimize our reaction conditions using substrate **1a** (Table 4). After evaluation of a series of Lewis and Brønsted acids, $TiCl_4$ was still found to be the most effective catalyst for this substrate (entries 1–14). However, the combination of $TiCl_4$ with other Lewis or Brønsted acids, while not initially promising (entries 15–20 and 28), ultimately revealed acetyl chloride (CH_3COCl) as an effective promoter of this reaction even in the absence of $TiCl_4$ (entries 21–25). Thus, reaction with 80 mol% of acetyl chloride gave comparable results as did 20 mol% of $TiCl_4$ (cf. entries 1 and 25). We realized that this would support the case that HCl is the active catalytic species, provided we could show that HFIP was capable of generating HCl from acetyl chloride (an ironic notion given the low

nucleophilicity of HFIP[15b]). To address this, we combined one 1 equiv of acetyl chloride (AcCl) and 2 equiv of HFIP and monitored the reaction by ^{1}H NMR in $CDCl_3$ (Figure 3; see Supporting Information for details). Within 6 min, ca. 50% conversion to HFIP acetate was observed. The rate slowed down after 20 min and the reaction took 4 h to reach >95% conversion. Conversely, we were not able to obtain any evidence for the in situ generation of HCl from $TiCl_4$.

Additional experiments were carried out to gather further detail about the effect of various sources of H^+ on these Schmidt reactions. In our initial survey, we had first tried adding HCl in ether to the HFIP solvent (Table 1, entries 15 and 16, and Table 4, entry 10). Neither that method nor adding aqueous HCl[15f] (Table 4, entry 11) gave good results in our hands. On the other hand, when HCl gas was separately generated and infused into the HFIP (Table 4, entry 12), a range of results were obtained. The non-reproducibility of these experiments can be blamed on the ease with which the HCl gas escapes the solution, making it difficult to accurately gauge exactly how much acid is present in a particular experiment. For example, markedly reduced yields (on the low end noted in entry 12) were obtained when HCl/HFIP solutions were aged for even a few minutes. We also examined whether HBr, generated by the addition of AcBr to HFIP, was a suitable substitute for HCl and initial evidence suggests that it is (cf. entries 26 and 27 with 22 and 25). We still prefer using AcCl-generated HCl because AcCl is generally easier to handle and more resistant to hydrolysis in air. Moreover, we have observed very little differences in the source of AcCl in the reaction (i.e., freshly opened vs. older bottles of reagent, cf. entries 25 and 24). Taking into account both efficiency and practicality, we prefer using $TiCl_4$ or AcCl as HCl sources among all of the methods tested so far.

We decided to further explore the substrate scope with this new reaction condition in hand that utilizes acetyl chloride as a pro-catalyst. The substrate scope was comparable to that described for $TiCl_4$ and lactams were obtained in good to excellent yields (entries 1–10, Table 5). Although higher amounts of acetyl chloride than $TiCl_4$ were required to achieve complete conversion, the use of acetyl chloride was convenient. In addition, both HFIP and its acetate ester byproduct were volatile, which eased work-up. Finally, no metal waste was produced.

Mechanism

Based on precedent,[15b–e,18] we propose the involvement of HFIP as a strong hydrogen bond donor with the lactam carbonyl (Figure 4). As proposed above, we believe that association of a Lewis or Brønsted acid with the Lewis-basic lactam product inhibits the catalytic reaction carried out in CH_2Cl_2. Hexafluoro-2-propanol solvent can potentially form complexes with the substrate, intermediates, and product. Critically, the hydrogen bonding of HFIP with the lactam carbonyl through the displacement of Lewis or Brønsted acids allows for the regeneration of catalyst – most likely, a proton. In addition, one cannot rule out coordination between HFIP and catalyst to produce a catalytically more reactive species, like $[HFIP{\bullet}H]^+$.[25] We note that cursory pH measurement of the reaction mixture by pH indicator strips (non-bleeding) gave a reading of pH = 4 for the present version, as opposed to pH = 1 for an intramolecular Schmidt reaction carried out with $TiCl_4$ in CH_2C1_2 (the pH of pure HFIP was 5 by this method), suggesting an overall buffering effect of the solvent.

HFIP has been shown to form aggregates, such as trimers, having potential hydrogen bonds of strengths comparable to those of covalent linkages.[15c] Such a strong hydrogen bonding could well explain the role of HFIP in the catalysis of the intramolecular Schmidt reaction. Job's method of continuous variation was used to determine the stoichiometry of binding for HFIP-substrate and HFIP-product complexes (Figure 5).[15c,26] Job plots based on ^{1}H NMR data provide good evidence that HFIP forms a 1:1 complex with both substrate **la** and

product **2a**. Although the stoichiometry of binding was similar, complexation shift (?δ) of the HFIP hydroxyl resonance for lactam **2a** was significantly higher compared to azidoketone **la**, consistent with the expected stronger complexation of HFIP with lactam over the ketone.

In order to gain more insight into the different behaviors of different classes of azidoalkyl ketones, a competition experiment between cyclohexanone- and cyclopentanone-derived **1f** and **la** was performed (Figure 6 and Scheme 3a). Treating an equimolar mixture of **1f** and **1a** in HFIP with 20 mol% of acetyl chloride resulted in complete conversion of substrate **1f** to lactam **2f** within 3 h (also see entry 2, Table 5). In sharp contrast, the conversion of **la** to lactam **2a** was only 13% complete after 12 h (also see entry 7, Table 5). These results could be explained by an innate kinetic difference between the substrates, a difference in the degree of product inhibition, or a combination of the two.

With respect to the latter point, we made note of the requirement of different catalyst loadings for different substrate classes. This could be attributed to the difference in basicity of different lactam products, with a more basic lactam requiring higher catalyst loadings.[27] In order to demonstrate different degrees of product inhibition with different lactams, ^{1}H NMR experiments were carried out to determine the effect of adding two different product lactams at the outset on a single, relatively fast, reaction. For this, we chose the product of the quicker reaction leading to **2f** (and a case that succeeds with 10 mol% of AcCl pro-catalyst) and **2a**, the product of a much slower reaction (and one that requires 80 mol% of AcCl to reach completion). In the first case, the facile substrate azidoketone **1f** was combined with an equimolar amount of its lactam product **2f** and then treated with 20 mol% of acetyl chloride in HFIP (Figure 6 and Scheme 3b). The time it took for quantitative conversion of **1f** to **2f** was ca. 6 h. In contrast, the reaction of a 1:1 mixture of **1f** and **2a** with 20 mol% of acetyl chloride in HFIP required >24 h to attain completion (Figure 6 and Scheme 3c). These results suggested significantly more product inhibition by lactam **2a** than **2f**, which is consistent with the need for higher catalyst loadings with relatively recalcitrant substrates.[7c] More detailed series of kinetic studies is necessary to fully address the relative roles of kinetics vs. product inhibition and will be reported in due course.

CONCLUSIONS

In summary, we have demonstrated a catalytic intramolecular Schmidt reaction with broad substrate scope and utility. Two versions of the reaction, one using $TiCl_4$ and the other with AcCl, have been identified as having strong synthetic utility that is as good or better than all previous versions of this process. In either case, the strong hydrogen-bonding ability of hexafluoro-2-propanol was critical to the development of these substoichiometric reactions. The discovery of conditions employing acetyl chloride as a pro-catalyst in the presence of hexafluoro-2-propanol provided evidence for HCl being an active catalytic species as well as providing a metal-free catalytic reaction. Prior to this discovery, the primary metal-free variations of the intramolecular Schmidt reaction used either trifluoracetic acid as solvent, or TfOH or $ClSO_3H$ as a stoichiometric reagent.

The most favorable examples utilize attractively low loadings of catalyst – as low as 2.5% for the $TiCl_4$-promoted version or 10 mol% of AcCl. Although some of the least cooperative substrates needed as much as 100 mol% of "H^+" catalyst added (either via the addition of 25 mol% of $TiCl_4$ or the straightahead addition of 100 mol% of AcCl), we note that these conditions still measure up very favorably to those previously reported for analogous substrates. For example, the reaction of **1a** in CH_2Cl_2 needed 4.5 equiv of $TiCl_4$ to afford a 67% yield,[1b] while the same reaction carried out with 20 mol% of $TiCl_4$ or 80 mol% of AcCl gave 87% and 90% yields of product, respectively. Although we did not quantitatively

compare the purity of products obtained in these various reactions, we note informally that the presently reported procedures tend to provide products requiring little additional purification.

In addition, ^{1}H NMR experiments were performed to exhibit different degree of product inhibition with different lactams. That such structurally similar lactams have substantially different effects on the rate of a given reaction is, minimally, provocative, and might point to a role in understanding the role of product inhibition in this and other reactions that afford lactam or amide products. Future efforts will be directed to extend the scope of this reaction and elucidate further mechanistic details. In the meantime, we consider the method reported herein as the best means of preparatively carrying out this variation of the intramolecular Schmidt reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of General Medical Sciences (GM-049093) and University of Kansas for financial support. We thank Sarah Neuenswander and Justin Douglas for assistance with NMR, and Ryan Altman and an anonymous reviewer of this manuscript for helpful suggestions.

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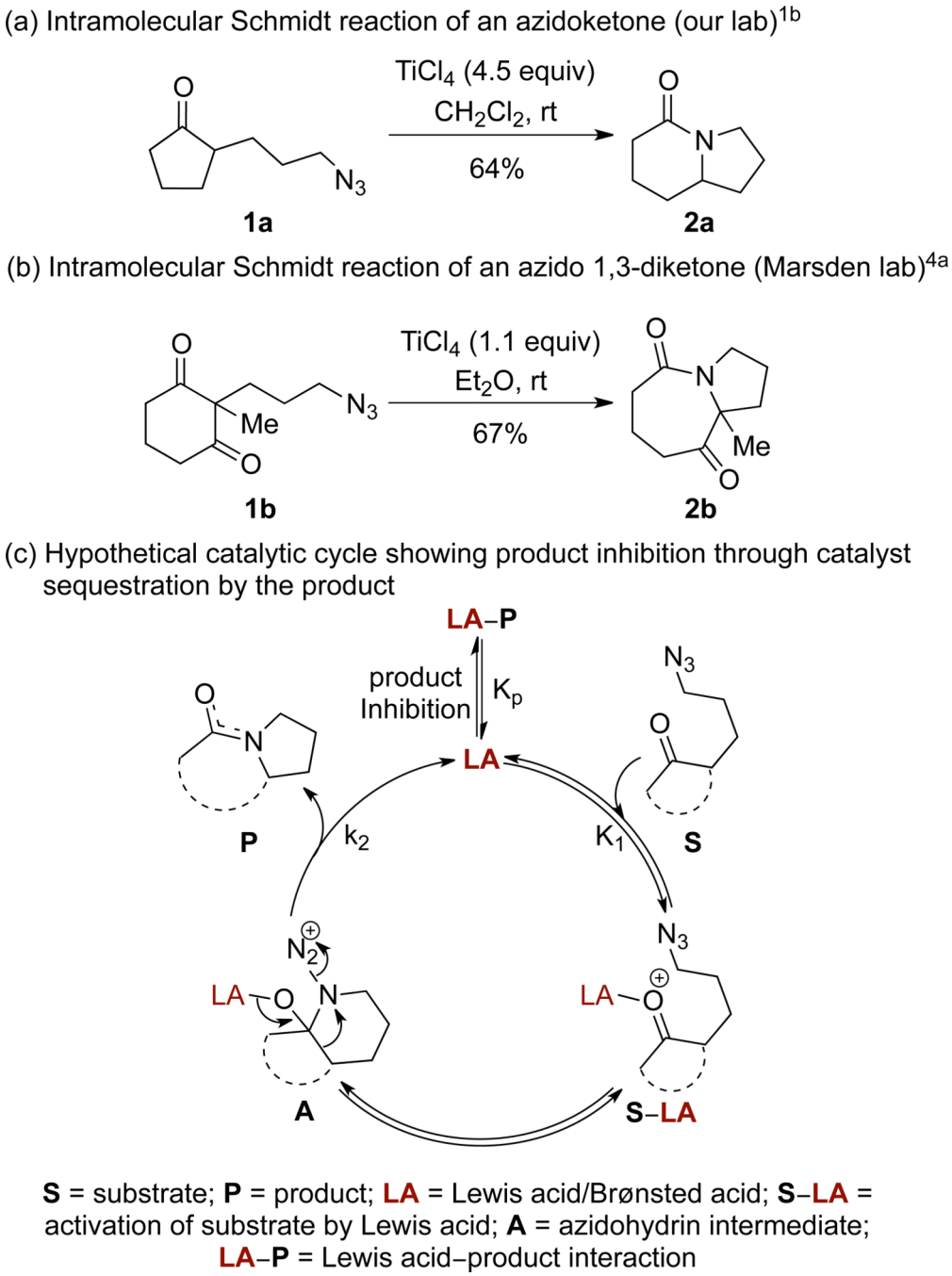


Figure 1.

(a) and (b) Examples of intramolecular Schmidt reactions requiring >1 equiv catalyst and (c) hypothetical catalytic cycle displaying product inhibition.

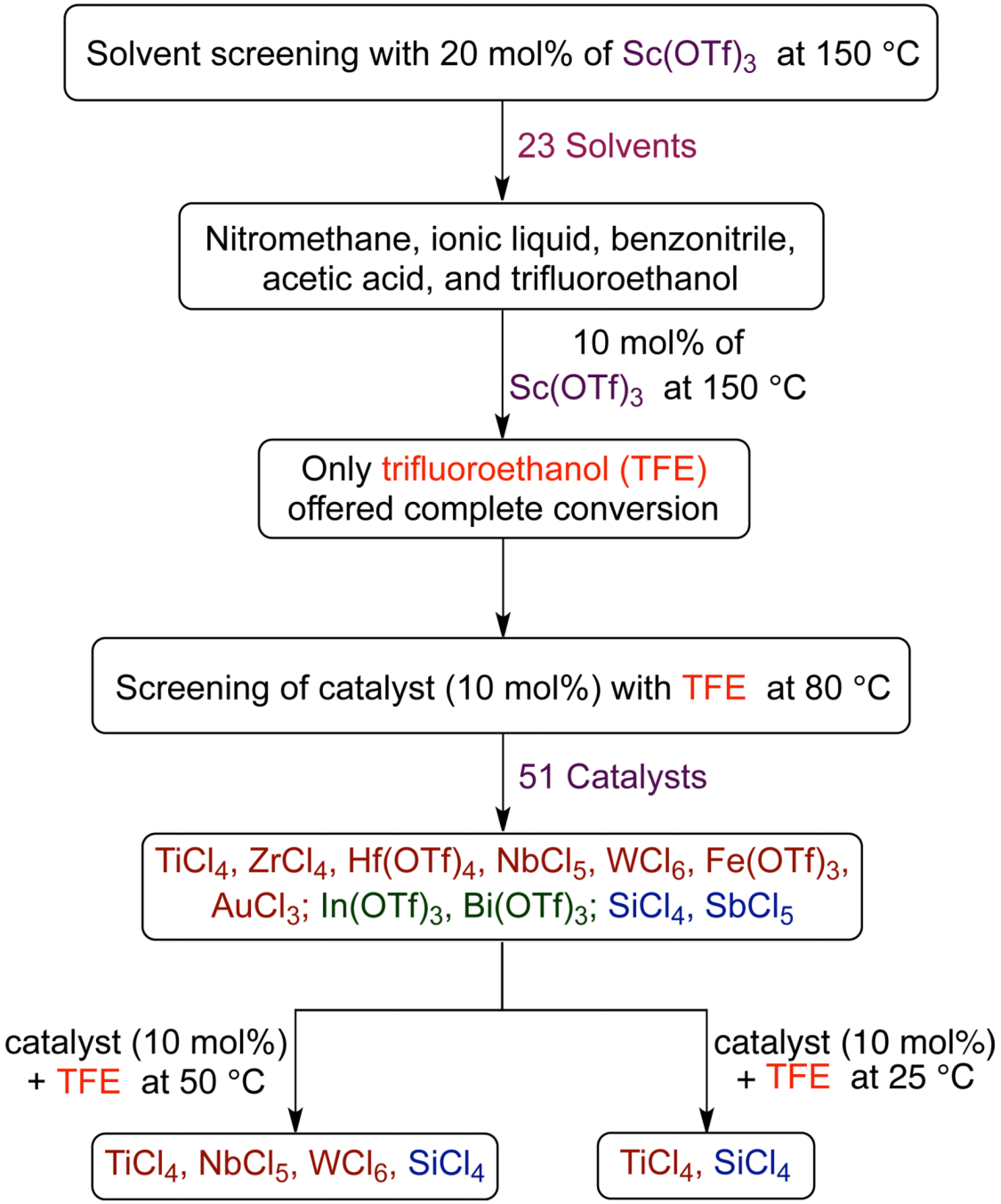


Figure 2.
Screening flowchart. See Supporting Information for details. Transition metals are depicted in deep red, post-transition metals in green, and metalloids in blue.

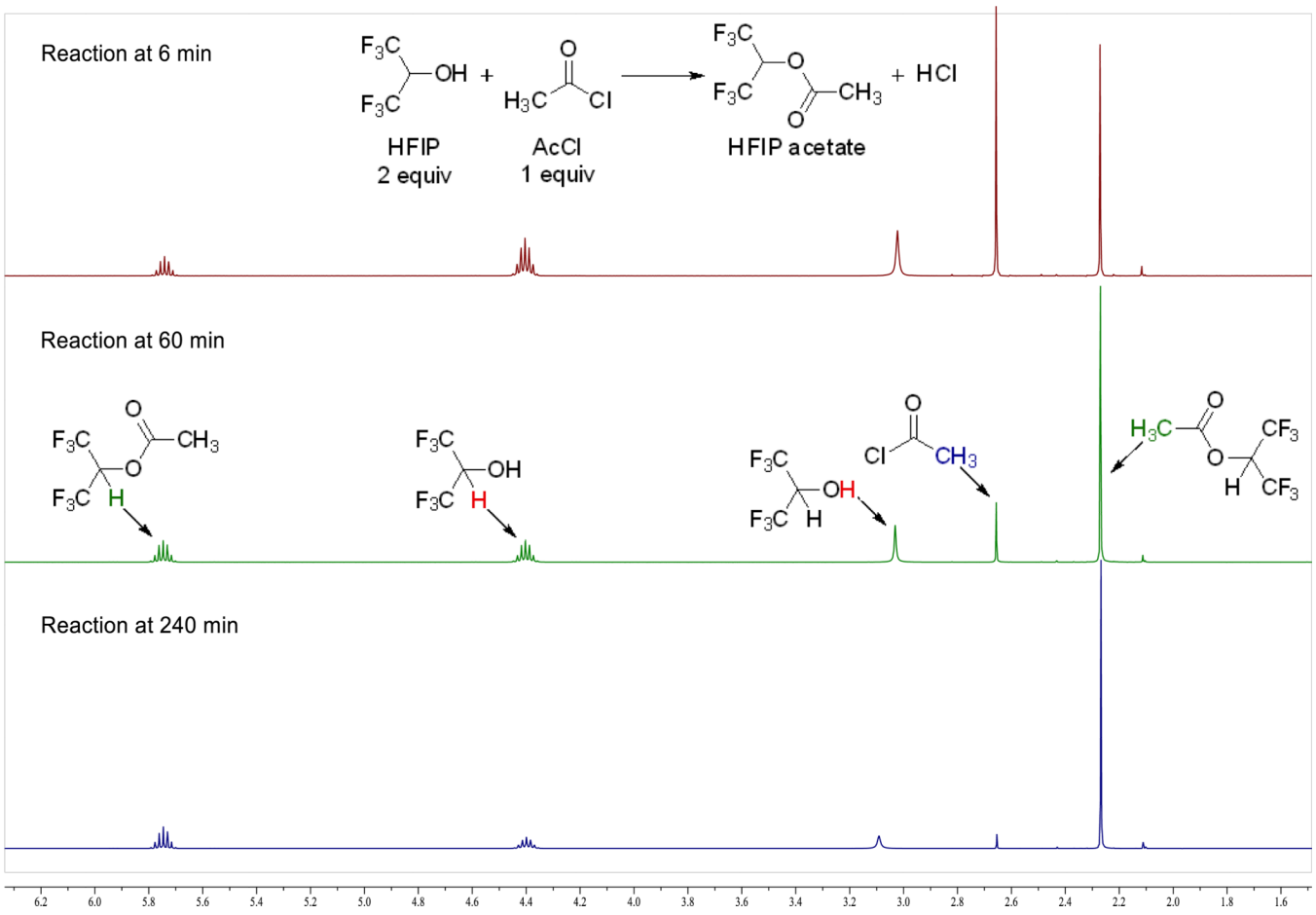


Figure 3.
Reaction monitoring of acetyl chloride with HFIP for the in situ generation of HCl by ^{1}H NMR.

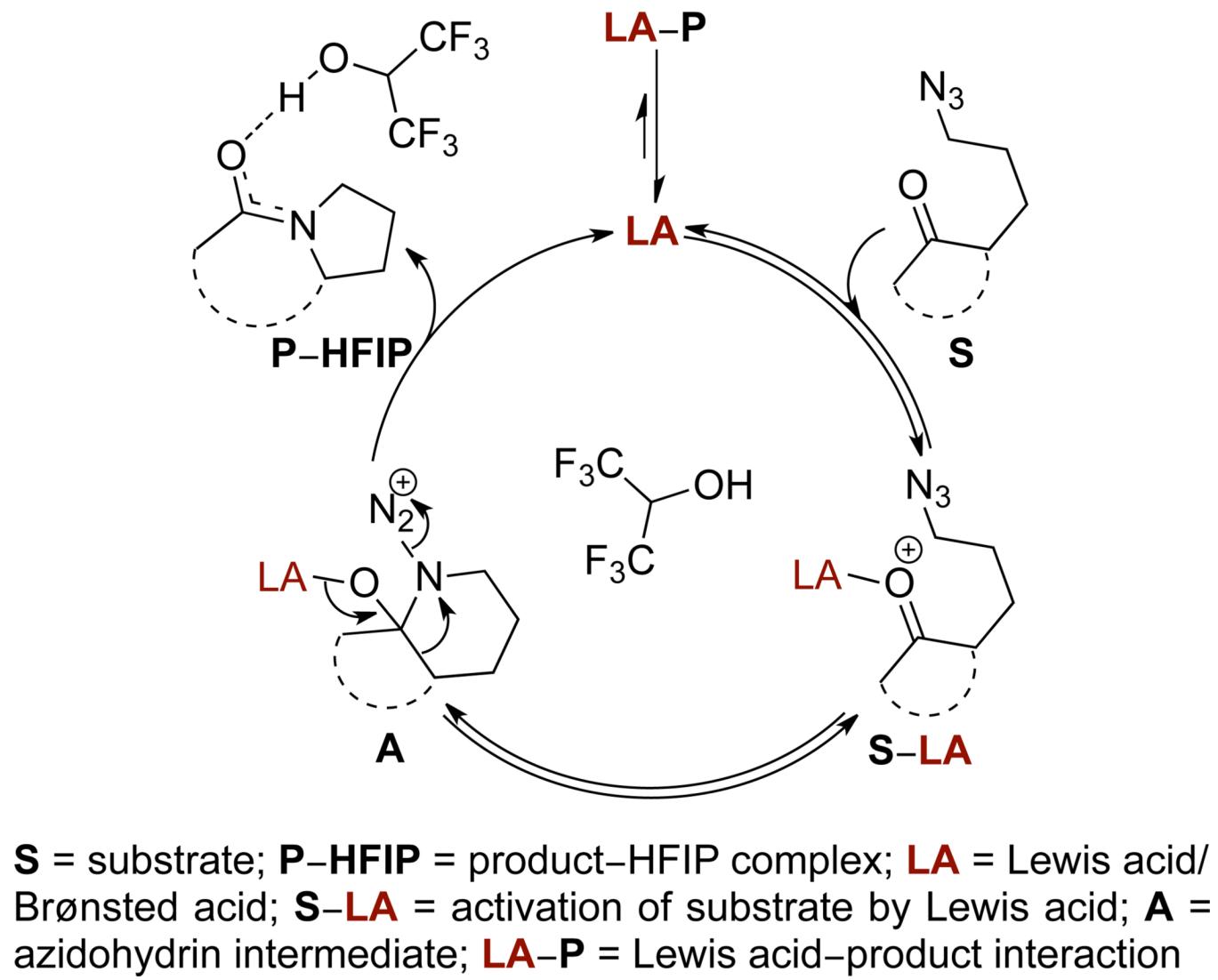


Figure 4.
Proposed catalytic cycle for the intramolecular Schmidt reaction employing HFIP as a solvent.

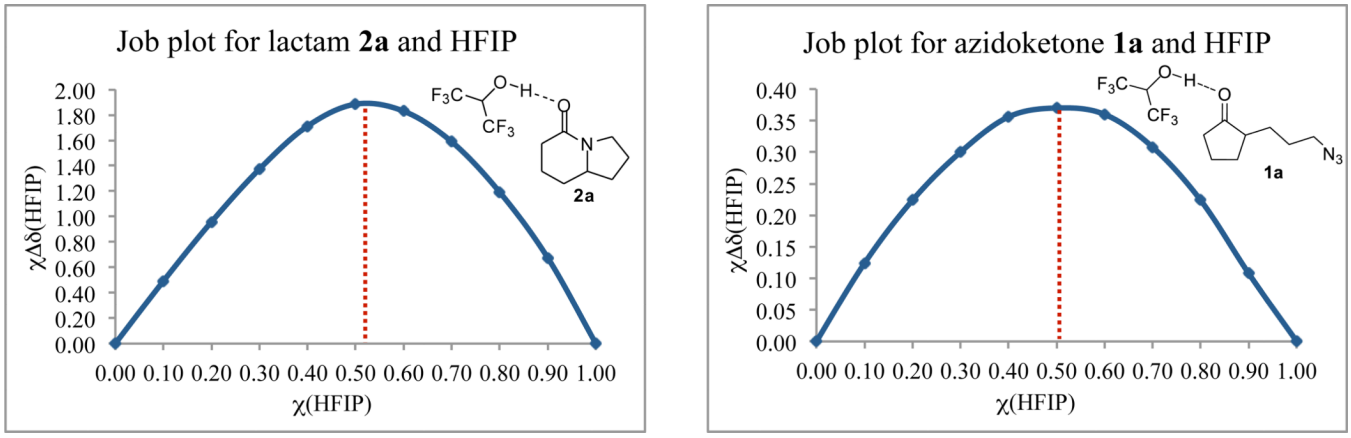


Figure 5.
Job plots for complexation of lactam **2a** and azidoketone **1a** with HFIP.

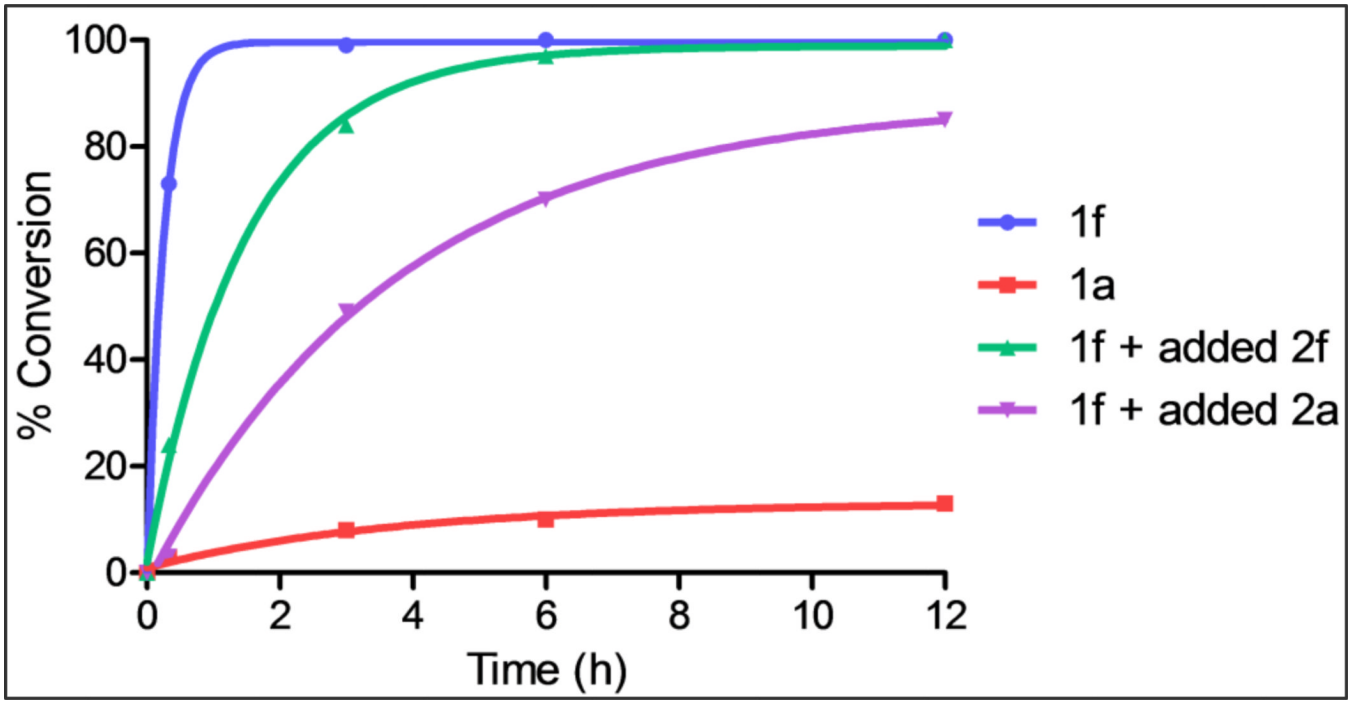
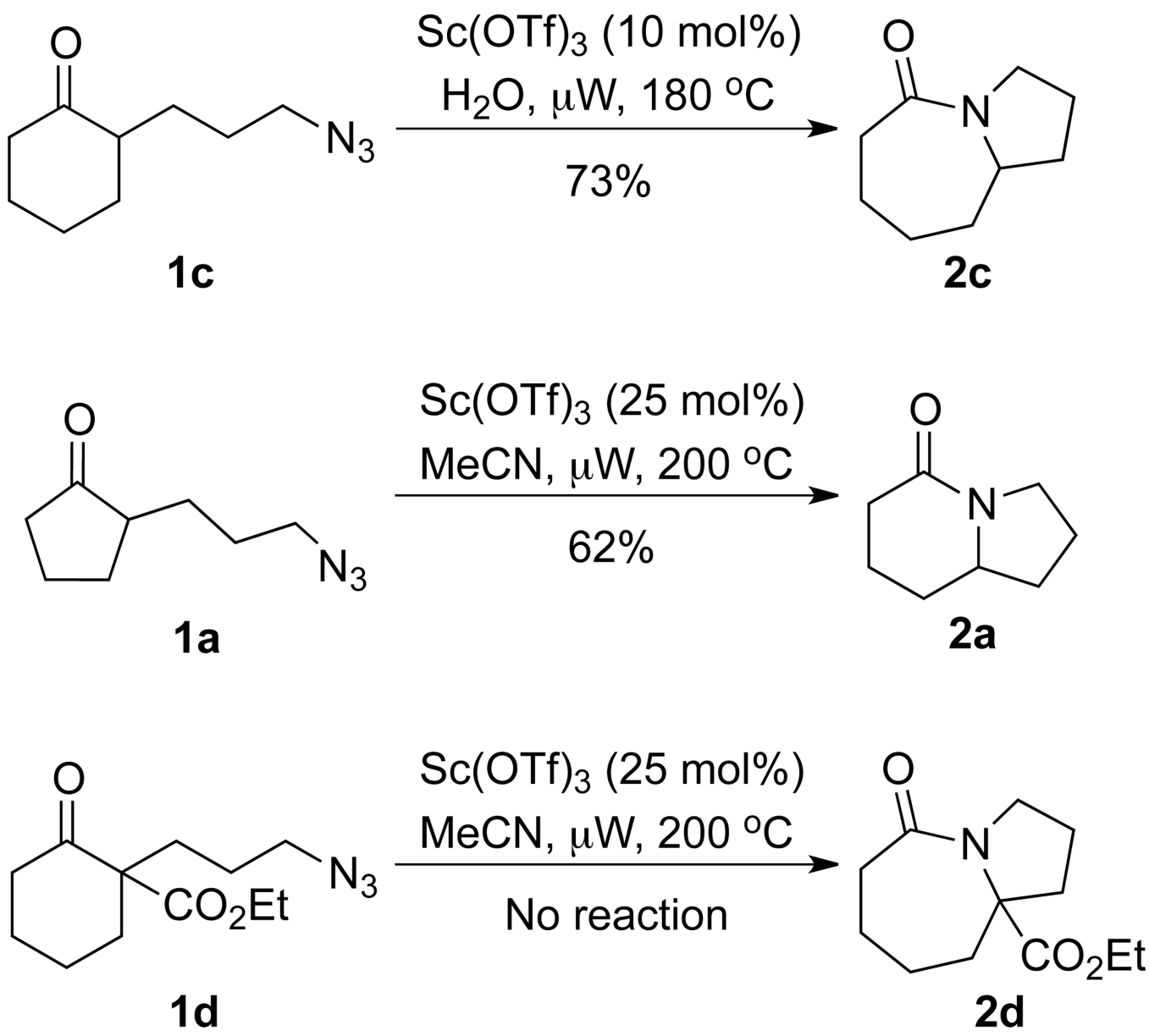
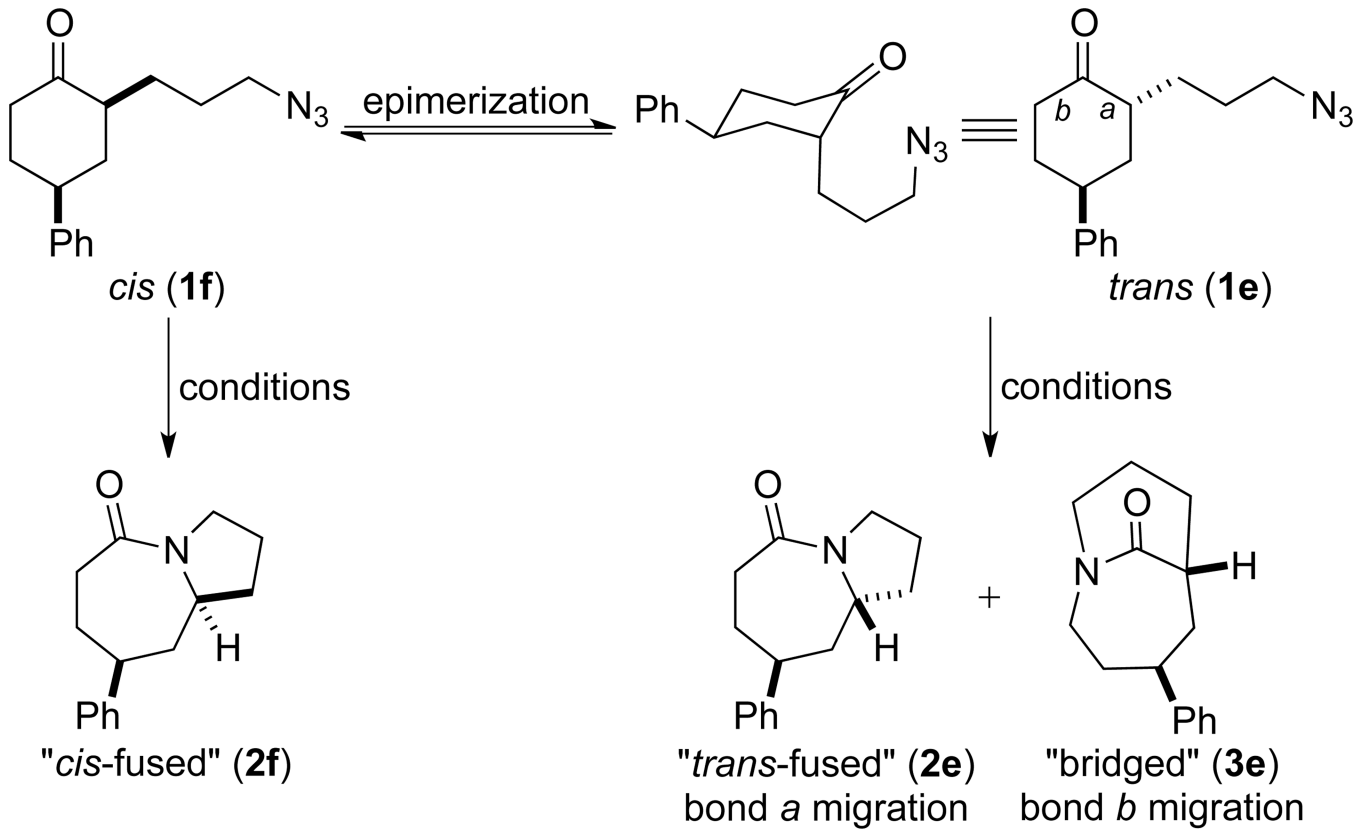


Figure 6.
Relative reaction rates for **1f** and **1a** (see Scheme 3a, below), **1f** with 1 equiv of **2f** added at the outset of the reaction (Scheme 3b), and **1f** with 1 equiv of **2a** added at the outset of the reaction (Scheme 3c).

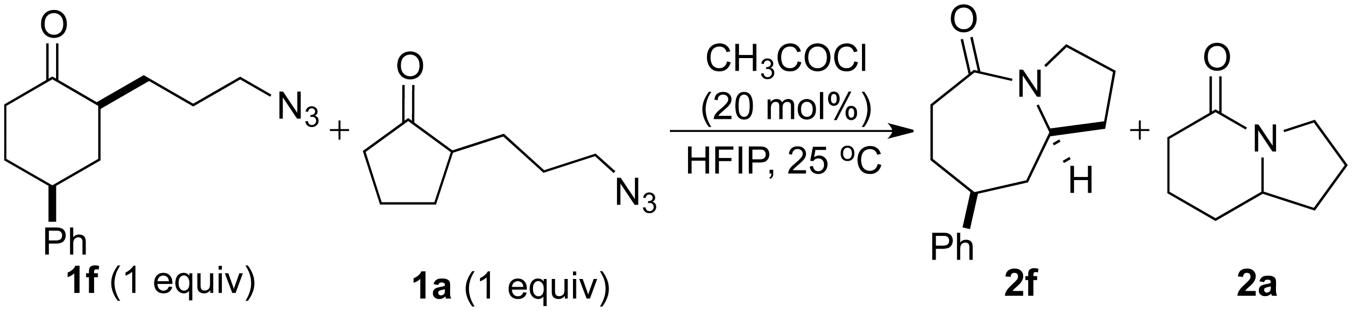


Scheme 1.

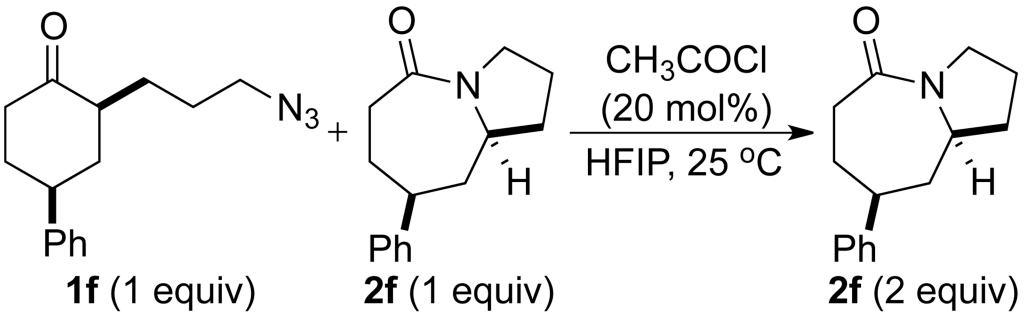


Scheme 2.

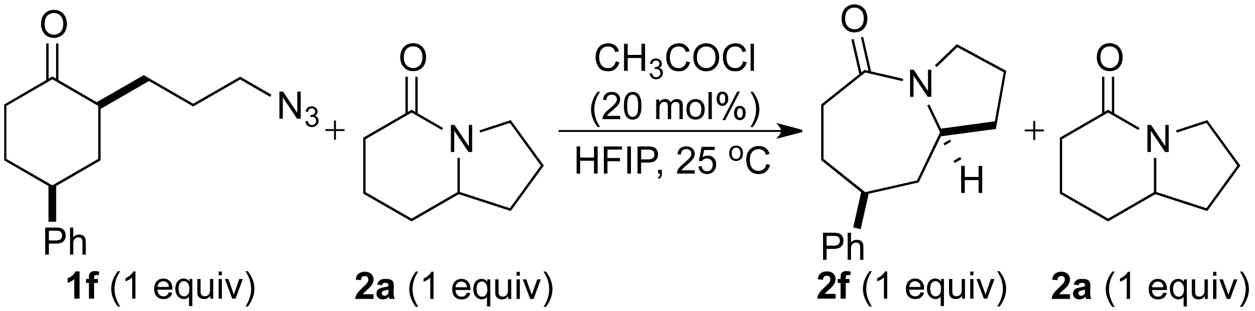
(a) Competition experiment between azidoketones **1f** and **1a**



(b) Product inhibition experiment of **1f** in the presence of added **2f**



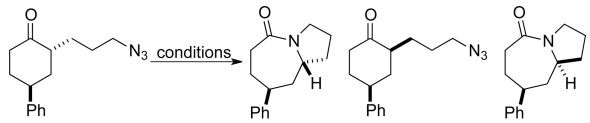
(c) Product inhibition experiment of **1f** in the presence of added **2a**



Scheme 3.

Table 1

Optimization of conditions for intramolecular Schmidt reaction of **1e**[a,b]



entry	catalyst	catalyst loading (mol%)	solvents	additives	temp (°C)	time (h)	% yield (2e:2f)[c]	% recovery (1e:1f)[d]
1	$TiCl_4$	10	CH_2Cl_2	-	25	18	6% (40:60)	84% (10:90)
2	$TiCl_4$	10	*i*-PrOH	-	37	18	trace	86% (3:97)
3	$TiCl_4$	10	CH_3CN	-	37	18	41% (15:85)	47% (1:99)
4	$TiCl_4$	10	CF_3CH_2OH	-	25	18	79% (82:18)[d]	trace
5	none	-	$(CF_3)_2CHOH$	-	37	18	ND	93% (98:2)
6	$TiCl_4$	10	CH_3CN	$(CF_3)_2CHOH$[e]	25	18	34% (10:90)	61% (5:95)
7	$TiCl_4$	10	$(CF_3)_2CHOH$	-	25	12	91% (98:2)[f]	ND
8	**$TiCl_4$**	**5**	**$(CF_3)_2CHOH$**	-	**25**	**38**	**89% (99:1)**[f]	**trace**
9	$TiCl_4$[g]	5	$(CF_3)_2CHOH$	-	25	38	86% (98:2)	trace
10	$TiCl_4$[h]	5	$(CF_3)_2CHOH$	-	25	38	89% (98:2)	ND
11	$TiCl_4$	5	$(CF_3)_2CHOH$	DTBMP[i]	25	38	52% (98:2)	19% (98:2)
12	$TiCl_4$	5	$(CF_3)_2CHOH$	DTBMP[j]	25	38	21% (99:1)	50% (96:4)[b]
13	$SiCl_4$	5	$(CF_3)_2CHOH$	-	25	38	86% (98:2)[f]	ND
14	$Sc(OTf)_3$	5	$(CF_3)_2CHOH$	-	25	38	28% (97:3)	61% (98:2)
15	HCl	10	$(CF_3)_2CHOH$	-	25	38	40% (96:4)[f]	46% (98:2)
16	HCl	20	$(CF_3)_2CHOH$	-	25	38	78% (97:3)[f]	trace
17	CF_3COOH	10	$(CF_3)_2CHOH$	-	25	38	62% (97:3)	34% (98:2)
18	(*S*)-BNDHP	5	$(CF_3)_2CHOH$	-	25	38	32% (96:4)[k]	62% (98:2)
19	$Ti(^iOPr)_4$	10	$(CF_3)_2CHOH$	-	25	38	trace	93% (95:5)

[a] To a solution of substrate **1e** (0.1 mmol) in solvent (0.5 mL) at room temperature was added a catalyst under nitrogen or argon atmosphere unless otherwise mentioned (see Supporting Information for the complete optimization table). Throughout, 1.0 M solutions of $TiCl_4$ or $SiCl_4$ in CH_2Cl_2 were used. 2.0 M solution of HCl in diethyl ether was used. ND = Not detected.

[b] Concentration ca. 0.2 M unless otherwise mentioned.

[c] Isolated yield after preparative TLC purification; ratio determined by ^{1}H NMR.

[d] Isolated yield after preparative TLC purification; ratio determined by UPLC of the crude reaction mixture.

[e] 1 equiv of $(CF_3)_2CHOH$ was added.

[f] Bridged lactam **3e** was also isolated in ca. 1–4% yield.

[g] Concentration ca. 0.4 M.

[h] Concentration ca. 0.1 M.

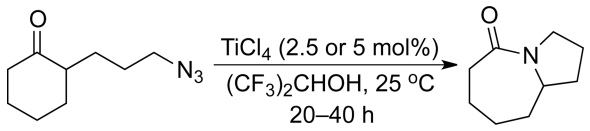
[i] 10 mol% of 2,6-di-tert-butyl-4-methylpyridine (DTBMP) was used as a Brønsted acid scavenger.

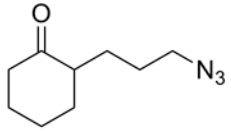
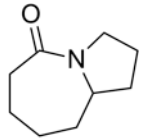
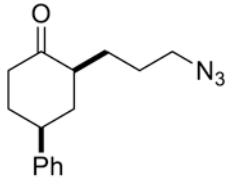
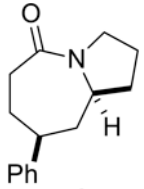
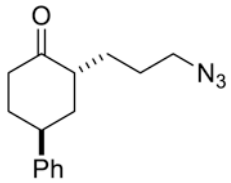
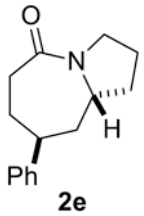
[j] 20 mol% of DTBMP was used.

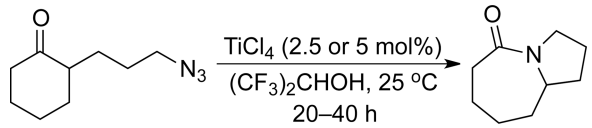
[k] (*S*)-BNDHP = (*S*)- (+)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate. No kinetic resolution was observed.

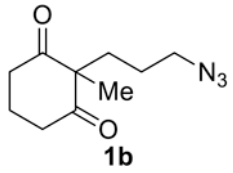
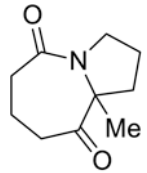
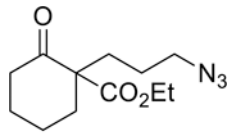
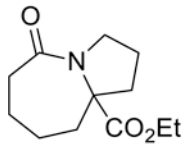
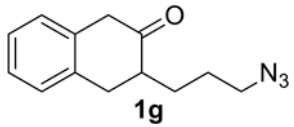
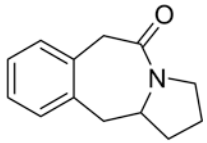
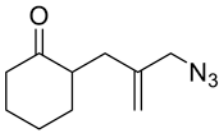
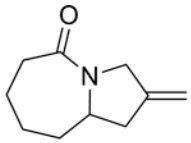
Table 2

Initial Substrate Scope for the catalytic intramolecular Schmidt reaction on cyclohexanone-derived azidoketones.[a,b]



entry	substrate	catalyst loading (mol%)	time (h)	product	yield[c] (%)
1	 **1c**	2.5	20	 **2c**	94
2	 **1f**	2.5	20	 **2f**	98
3	 **1e**	5	38	 **2e**	87[d]



entry	substrate	catalyst loading (mol%)	time (h)	product	yield[c] (%)
4	 **1b**	5	24	 **2b**	94
5	 **1d**	5 10	40 18	 **2d**	94 95
6	 **1g**	5	24	 **2g**	89
7	 **1h**	5	24	 **2h**	84

[a] To a solution of a substrate (0.4 mmol) in hexafluoro-2-propanol (2.0 mL) at room temperature was added $TiCl_4$ under nitrogen atmosphere and reaction was allowed to stirred at 25 °C for a designated period unless otherwise mentioned.

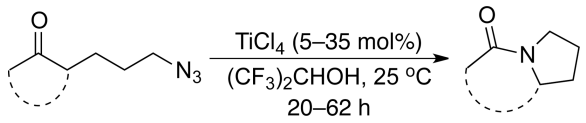
[b] Concentration ca. 0.2 M.

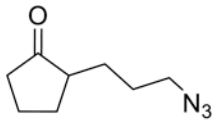
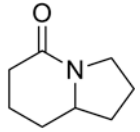
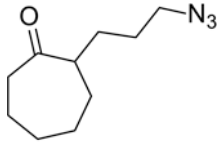
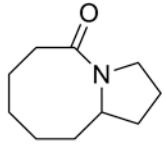
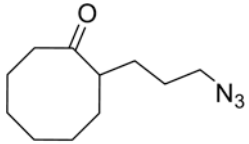
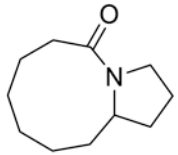
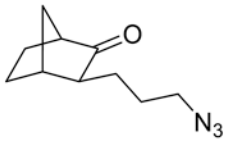
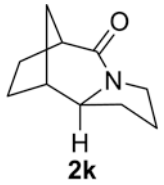
[c] Isolated yield.

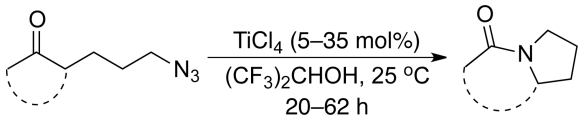
[d] Bridged lactam **3e** was also isolated in ca. 2% yield.

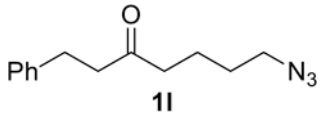
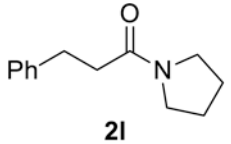
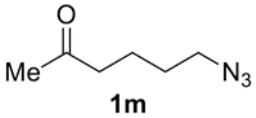
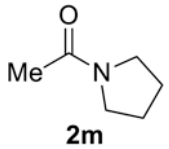
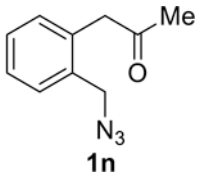
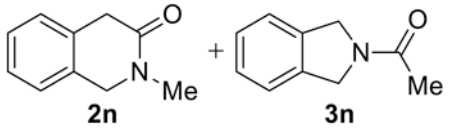
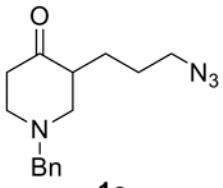
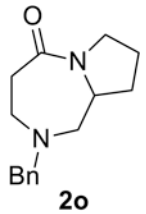
Table 3

Additional evaluation of reaction scope[a,b]



entry	substrate	catalyst loading (mol%)	time (h)	product	yield (%)[c]
1	 **1a**	10	44	 **2a**	60 (78)[d]
		15	44		79
		20	24		87
2	 **1i**	5	62	 **2i**	34 (85)[d]
		20	48		86[e]
3	 **1j**	25	62	 **2j**	90
4	 **1k**	10	62	 **2k**	43 (78)[d]
		25	62		87 (90)[d]



entry	substrate	catalyst loading (mol%)	time (h)	product	yield (%)[c]
5	 **1l**	20	24	 **2l**	79 (96)[d,f]
		25	32		94[f]
6	 **1m**	10	36	 **2m**	73[g]
		15	24		77(81)[d,g]
		20	24		86[g]
7	 **1n**	15	24	 **2n**:**3n** = 4:1	64
8	 **1o**	35	20	 **2o**	90

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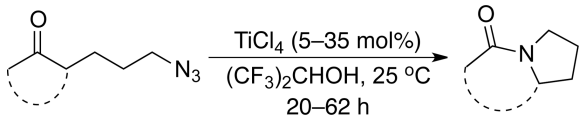
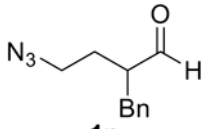
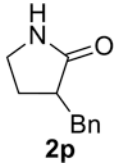
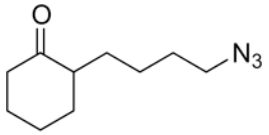
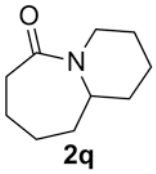


entry	substrate	catalyst loading (mol%)	time (h)	product	yield (%)[c]
9	 **1p**	5	24	 **2p**	86
10	 **1q**	20	60	 **2q**	11 (20)[d]

[a] To a solution of a substrate (0.4 mmol) in hexafluoro-2-propanol (2.0 mL) at room temperature was added $TiCl_4$ under nitrogen atmosphere and reaction was allowed to stir at 25 °C for the designated period unless otherwise noted.

[b] Concentration ca. 0.2 M.

[c] Isolated yield.

[d] Yields in parentheses are based on recovered starting material.

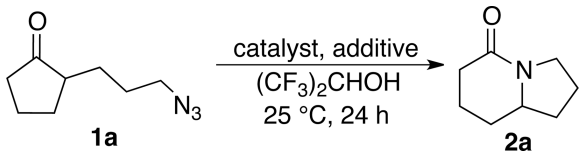
[e] Bridged lactam **3i** was also isolated in 2% yield (see Supporting Information).

[f] Contains 7% of 1-phenethylpiperidin-2-one **3l** (see Supporting Information).

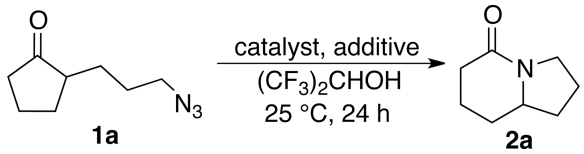
[g] Contains 3% of *N*-methyl-2-piperidone **3m** (see Supporting Information).

Table 4

Further optimization of reaction conditions for **1a**[a,b]



entry	Catalysts	catalyst (mol%)	additive	additive (mol%)	NMR ratio of 2a:1a[c]
1	**$TiCl_4$**	**20**	-	-	**95:5**
2	$TiCl_4$	10	-	-	59:41
3	TiF_4	10	-	-	26:74
4	$TiBr_4$	10	-	-	46:54
5	$Ti(^iOPr)_4$	10	-	-	0:100
6	$SiCl_4$	10	-	-	58:42
7	$SbCl_5$	10	-	-	45:55
8	$NbCl_5$	10	-	-	44:56
9	$WC1_6$	10	-	-	54:46
10	HC1 in ether[d]	40	-	-	45:55
11	Aqueous HCl[e]	40	-	-	59:41
12	HC1 in HFIP[f]	40	-	-	57:43–75:25 (variable)
13	H_2SO_4	40	-	-	76:24
14	-	-	CF_3SO_3H	20	49:51
15	$TiCl_4$	5	CF_3SO_3H	5	42:58
16	$TiCl_4$	5	$CISO_3H$	5	49:51
17	$TiCl_4$	10	AgOTf[g]	20	56:44
18	$TiCl_4$	10	$Al(^iOPr)_3$	20	50:50
19	$TiCl_4$	10	Silica gel[h]	-	47:53



1a **2a**

entry	Catalysts	catalyst (mol%)	additive	additive (mol%)	NMR ratio of 2a:1a[c]
20	**$TiCl_4$**	**10**	**CH_3COCl**[i]	**40**	**95:5**
21	-	-	CH_3COCl[i]	40	58:42
22	-	-	CH_3COCl[i]	40	70:30
23	-	-	CH_3COCl[i]	70	90:10
24	-	-	CH_3COCl[i]	80	94:6
25	-	-	**CH_3COCl**[j]	**80**	**97:3**[k]
26	-	-	CH_3COBr[l]	40	72:28
27	-	-	**CH_3COBr**[l]	**80**	**98:2**[m]
28	$TiCl_4$	10	$(CH_3)_3SiCl$	40	89:11
29	-	-	$(CH_3)_3SiCl$	80	92:8
30	-	-	$(CH_3)_3SiI$	80	13:87[n]

[a] To a solution of substrate **1a** (0.1 mmol) in $(CF_3)_2CHOH$ (0.5 mL) at room temperature was added a catalyst and/or an additive under nitrogen atmosphere unless otherwise mentioned. Throughout, 1.0 M solutions of $TiCl_4$, $SiCl_4$, or $SbCl_5$ in CH_2Cl_2 were used.

[b] Concentration ca. 0.2 M.

[c] ^{1}H NMR ratio determined after a brief work-up (see Supporting Information for details).

[d] A 1.0 M solution of HCl in ether (commercial) was used.

[e] Aqueous HCl (37%) was used.

[f] A ca. 0.105–0.116 M solution of HCl in hexafluoro-2-propanol was prepared and used immediately.

[g] $TiCl_2(OTf)_2$ was generated in situ from TiCl4 and AgOTf.[24]

[h] Silica gel (50 mg) was added.

[i] An old (> 5 years since being opened) container of acetyl chloride was used.

[j] A new container of acetyl chloride was used.

[k] The ratio of **2a:1a** did not change between 18–24 h.

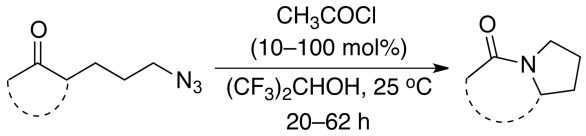
[l] A new container of acetyl bromide was used.

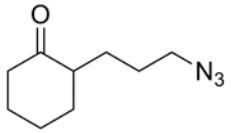
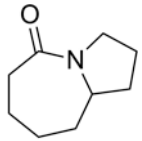
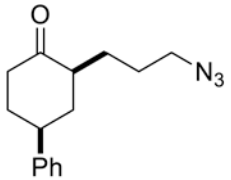
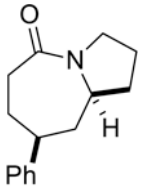
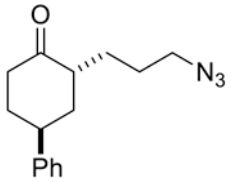
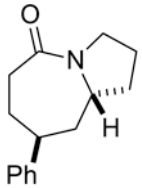
[m] The ratio of **2a:1a** did not change between 18–24 h.

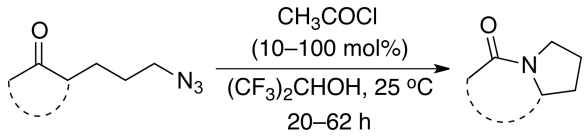
[n] Several other unidentified byproducts/impurities were also observed.

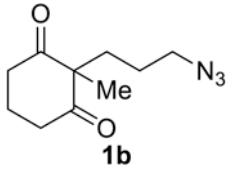
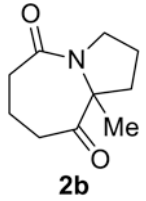
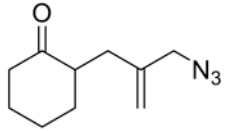
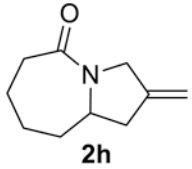
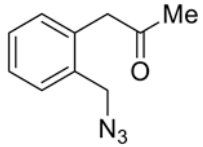
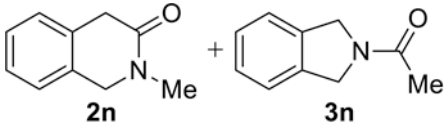
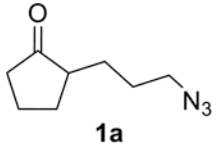
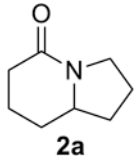
Table 5

Scope for the conditions employing acetyl chloride.[a,b]



entry	Substrate	catalyst loading (mol%)	time (h)	product	yield (%)[c]
1	 **1c**	10	20	 **2c**	95
2	 **1f**	10	20	 **2f**	98
3	 **1e**	20	38	 **2e**	90[d,e]



entry	Substrate	catalyst loading (mol%)	time (h)	product	yield (%)[c]
4	 **1b**	20	24	 **2b**	95
5	 **1h**	20	24	 **2h**	77
6	 **1n**	60	24	 **2n** + **3n** **2n**:**3n** = 65:35	68
7	 **1a**	80	24	 **2a**	90

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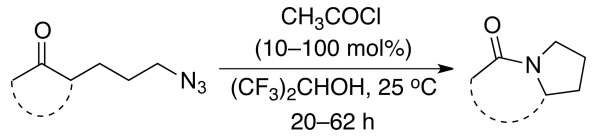
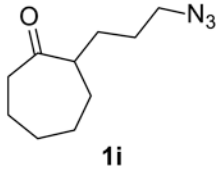
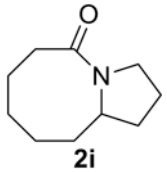
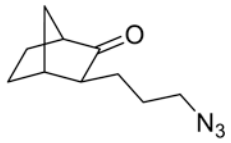
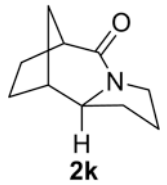
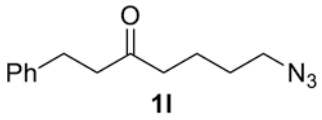
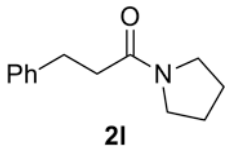


entry	Substrate	catalyst loading (mol%)	time (h)	product	yield (%)[c]
8	 **1i**	80	48	 **2i**	87[f]
9	 **1k**	100	62	 **2k**	92
10	 **1l**	100	32	 **2l**	96[g]

[a] To a solution of a substrate (0.4 mmol) in HFIP (2.0 mL) at room temperature was added CH3COCl under nitrogen atmosphere and reaction stirred at 25 °C for a designated period unless otherwise noted.

[b] Concentration ca. 0.2 M.

[c] Isolated yield.

[d] Bridged lactam **3e** was also isolated in ca. 3% yield.

[e] Reaction was ran on 0.1 mmol scale.

[f] Bridged lactam **3i** was also isolated in 3% yield (see Supporting Information).

[g] Contains 7% of 1-phenethylpiperidin-2-one **3l** (see Supporting Information).