

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/236922287>

ChemInform Abstract: Overcoming Product Inhibition in Catalysis of the Intramolecular Schmidt Reaction.

ARTICLE in JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · MAY 2013

Impact Factor: 12.11 · DOI: 10.1021/ja402848c · Source: PubMed

CITATIONS

13

READS

27

6 AUTHORS, INCLUDING:



Hashim F. Motiwala

University of Michigan

11 PUBLICATIONS 152 CITATIONS

SEE PROFILE



Charlie Fehl

University of Oxford

5 PUBLICATIONS 40 CITATIONS

SEE PROFILE



Patrick R Porubsky

Kansas Bureau of Investigation

28 PUBLICATIONS 409 CITATIONS

SEE PROFILE



Jeffrey Aubé

University of Kansas

272 PUBLICATIONS 4,348 CITATIONS

SEE PROFILE

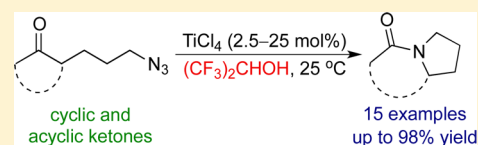
Overcoming Product Inhibition in Catalysis of the Intramolecular Schmidt Reaction

Hashim F. Motiwala, Charlie Fehl, Sze-Wan Li, Erin Hirt, Patrick Porubsky, and Jeffrey Aubé*

Department of Medicinal Chemistry, University of Kansas, Delbert M. Shankel Structural Biology Center, 2034 Becker Drive, West Campus, Lawrence, Kansas 66047, United States

S Supporting Information

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 ranged from 2.5 mol % for favorable substrates to 25 mol % for more difficult cases. Reaction optimization, broad substrate scope, and preliminary mechanistic studies of this improved version of the reaction are 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 its 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 minimizes the generation of metal waste.⁵ Two representative examples are shown in Figure 1a,b. 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 the complex **S–LA** (Figure 1c).⁶ The tethered azide then attacks the activated carbonyl, forming azidohydrin intermediate **A**, which upon antiperiplanar bond migration and nitrogen extrusion results in the formation of product **P**. The lactam produced is strongly Lewis basic and sequesters the catalyst in an unproductive manner. We propose that this unfavorable catalyst–product interaction results in product inhibition, deterring the progress of reaction and necessitating the use of superstoichiometric amounts of catalyst.^{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–hard base interaction. Related reactions that generate amide or lactam products, such as the Beckmann rearrangement and the Ritter reaction, have also suffered in the past from the requirement of a stoichiometric amount of strong acid and harsh reaction conditions.^{8,10} The role of the lactam in product inhibition has been demonstrated for the Beckmann rearrangement using a microchemical system.⁹ However, recent catalytic developments

for these reactions have enabled the use of substoichiometric amounts of Brønsted or Lewis acid, improving the efficiency and expanding the scope of those processes.^{8,10} The use of ionic liquids¹¹ and extensive screening of catalysts and solvents led to the realization of these catalytic reactions. We envisioned that catalysis in the intramolecular Schmidt reaction might be more efficient if conditions could be 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}

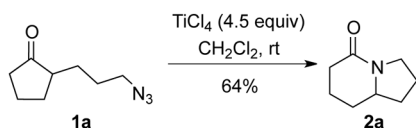
RESULTS AND DISCUSSION

Screening. We sought to replace the stoichiometric Schmidt reaction by identifying conditions that would (1) require low, substoichiometric amounts of catalyst; (2) be mild and efficient, allowing the reaction to proceed at room temperature; and (3) result in a broad substrate scope. We initially focused on catalyst and additive screening. Early on, we found that 10–25 mol % scandium(III) triflate could efficiently promote the reaction of **1c** to **2c**, but only at unacceptably high temperatures (Scheme 1; see the Supporting Information for details of these and all other early attempts). Moreover, these reaction conditions were plagued by 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 H₂O, either alone or with phase-transfer catalysts), and the reaction of **1d** under the same conditions failed (<5% yield). Reactions of substrates such as **1a** and **1d** required longer reaction times than **1c** in the stoichiometric reaction and were often poorer-yielding as well.^{1,12}

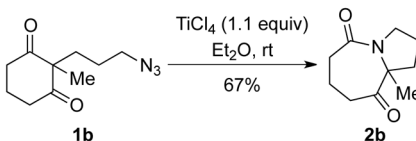
Received: March 20, 2013

Published: May 20, 2013

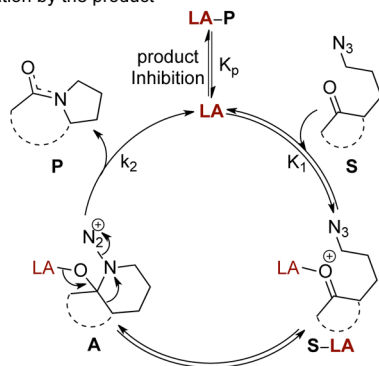
(a) Intramolecular Schmidt reaction of an azidoketone (our lab)^{1b}



(b) Intramolecular Schmidt reaction of an azido 1,3-diketone (Marsden lab)^{4a}



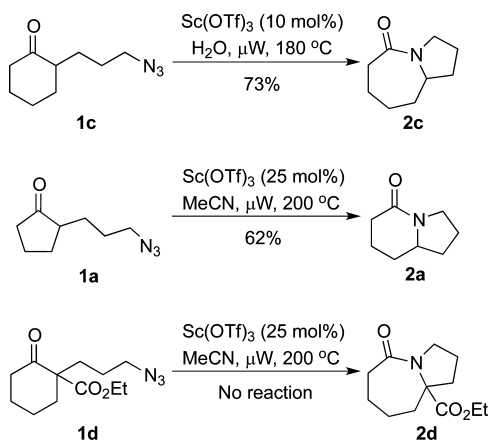
(c) Hypothetical catalytic cycle showing product inhibition through catalyst sequestration by the product



S = substrate; P = product; LA = Lewis acid/Brønsted acid; S-LA = activation of substrate by Lewis acid; A = azido intermediate; LA-P = Lewis acid-product interaction

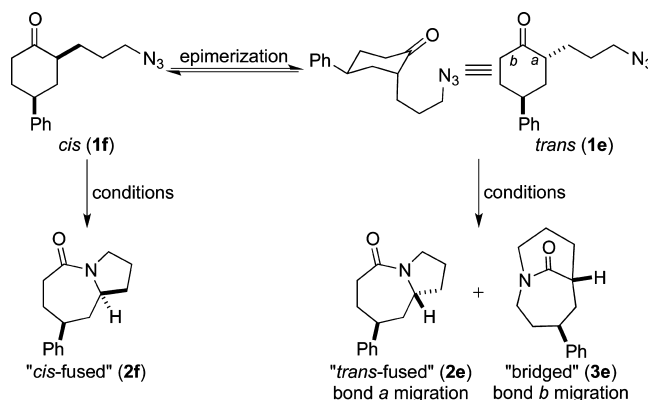
Figure 1. (a, b) Examples of intramolecular Schmidt reactions requiring >1 equiv of catalyst. (c) Hypothetical catalytic cycle displaying product inhibition.

Scheme 1



On the basis of these preliminary results, we decided to expand our search by focusing on three screening parameters: solvent, catalyst, and temperature. *trans*-4-Phenyl-2-(3-azidopropyl)-cyclohexanone (**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 readout for this process would be the detection of lactam **2f** following ring expansion. In addition, the *trans* ketone **1e** is capable of generating either the fused lactam **2e** or the bridged isomer **3e** by migration of one α -carbon or the other.^{1b}

Scheme 2



Finally, the phenyl chromophore in **1e** allowed faster analyses and quantification of reaction mixtures by ultraperformance liquid chromatography (UPLC) (see the Supporting Information).

Figure 2 depicts the results of preliminary screening of reaction conditions (see the Supporting Information for details). Examination of 23 different solvents was first carried out using 20 mol % Sc(OTf)₃ at 150 °C. Only five solvents [nitromethane, benzonitrile, acetic acid, trifluoroethanol (TFE), and the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate] gave the product in high yield. When the Sc(OTf)₃ loading was reduced to 10 mol %, only TFE resulted in complete conversion. We then focused our attention on catalyst screening using 10 mol % catalyst with TFE as the solvent at 80 °C. In total, 51 catalysts were screened, including 44 Lewis acids representing 31 different elements and seven Brønsted acids. Of these, a number of transition-metal salts such as TiCl₄, ZrCl₄, and Fe(OTf)₃, some post-transition-metal salts such as In(OTf)₃ and Bi(OTf)₃, and metalloid-containing compounds such as SiCl₄ and SbCl₅ gave results that were good enough for further screening.

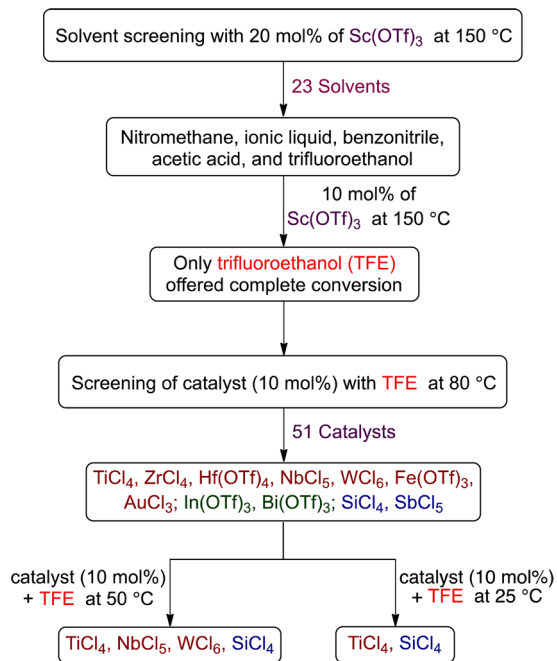
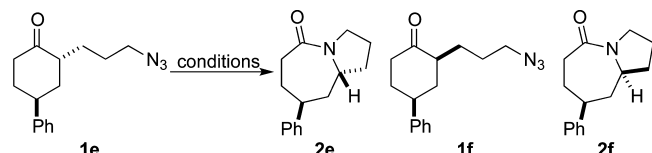


Figure 2. Screening flowchart (see the Supporting Information for details). Transition metals are depicted in deep red, post-transition metals in green, and metalloids in blue.

Table 1. Optimization of Conditions for the Intramolecular Schmidt Reaction of **1e**^{a,b}


entry	catalyst	catalyst loading (mol %)	solvent	additive	temp (°C)	time (h)	% yield (2e:2f) ^c	% recovery (1e:1f) ^d
1	TiCl ₄	10	CH ₂ Cl ₂	—	25	18	6 (40:60)	84 (10:90)
2	TiCl ₄	10	<i>i</i> -PrOH	—	37	18	trace	86 (3:97)
3	TiCl ₄	10	CH ₃ CN	—	37	18	41 (15:85)	47 (1:99)
4	TiCl ₄	10	CF ₃ CH ₂ OH	—	25	18	79 (82:18) ^d	trace
5	none	—	(CF ₃) ₂ CHOH	—	37	18	ND	93 (98:2)
6	TiCl ₄	10	CH ₃ CN	(CF ₃) ₂ CHOH ^e	25	18	34 (10:90)	61 (5:95)
7	TiCl ₄	10	(CF ₃) ₂ CHOH	—	25	12	91 (98:2) ^f	ND
8	TiCl ₄	5	(CF ₃) ₂ CHOH	—	25	38	89 (99:1) ^f	trace
9	TiCl ₄ ^g	5	(CF ₃) ₂ CHOH	—	25	38	86 (98:2)	trace
10	TiCl ₄ ^h	5	(CF ₃) ₂ CHOH	—	25	38	89 (98:2)	ND
11	TiCl ₄	5	(CF ₃) ₂ CHOH	DTBMP ⁱ	25	38	52 (98:2)	19 (98:2)
12	TiCl ₄	5	(CF ₃) ₂ CHOH	DTBMP ^j	25	38	21 (99:1)	50 (96:4) ^c
13	SiCl ₄	5	(CF ₃) ₂ CHOH	—	25	38	86 (98:2) ^f	ND
14	Sc(OTf) ₃	5	(CF ₃) ₂ CHOH	—	25	38	28 (97:3)	61 (98:2)
15	HCl	10	(CF ₃) ₂ CHOH	—	25	38	40 (96:4) ^f	46 (98:2)
16	HCl	20	(CF ₃) ₂ CHOH	—	25	38	78% (97:3) ^f	trace
17	CF ₃ COOH	10	(CF ₃) ₂ CHOH	—	25	38	62 (97:3)	34 (98:2)
18	(S)-BNDHP	5	(CF ₃) ₂ CHOH	—	25	38	32 (96:4) ^k	62 (98:2)
19	Ti(^{<i>i</i>} OPr) ₄	10	(CF ₃) ₂ CHOH	—	25	38	trace	93 (95:5)

^aTo a solution of substrate **1e** (0.1 mmol) in solvent (0.5 mL) at room temperature was added a catalyst under a nitrogen or argon atmosphere, unless otherwise mentioned (see the Supporting Information for the complete optimization table). For TiCl₄ or SiCl₄, a 1.0 M solution in CH₂Cl₂ was used, unless otherwise mentioned. A 2.0 M solution of HCl in diethyl ether was used. ND = Not detected. ^bConcentration of substrate was ca. 0.2 M, unless otherwise mentioned. ^cIsolated yields after preparative thin-layer chromatography (TLC) purification; ratios were determined by ¹H NMR analysis. ^dIsolated yields after preparative TLC purification; ratios were determined by UPLC of the crude reaction mixtures. ^e1 equiv of (CF₃)₂CHOH was added. ^fBridged lactam **3e** was also isolated in 1–4% yield. ^gConcentration of substrate was ca. 0.4 M. ^hConcentration of substrate was ca. 0.1 M. ⁱ10 mol % 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was used as a Brønsted acid scavenger. ^j20 mol % DTBMP was used. ^k(S)-BNDHP = (S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate. No kinetic resolution was observed.

Further evaluation of these selected catalysts at 10 mol % loading in TFE at lower temperatures (50 and 25 °C) revealed TiCl₄ and SiCl₄ to be the most effective. The identification of TiCl₄ 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 examine more completely the effect of the solvent using **1e** as the substrate and 10 mol % TiCl₄ as the catalyst (Table 1). Again, TFE was observed to give the best results with respect to both conversion and stereochemical retention (cf. entry 4 with entries 1–3). The results with TFE prompted us to consider other fluorinated alcohols, specifically hexafluoro-2-propanol (HFIP). Compared with their non-fluorinated alcohol analogues, TFE and HFIP have low nucleophilicity, low p*K*_a, high ionizing power, high polarity, the ability to solvate anions, and strong hydrogen-bond donor ability.¹⁵ Accordingly, they are often used as a solvent, cosolvent, or Lewis acid substitute^{15e,16} in oxidations¹⁷ and in ring-opening reactions of oxiranes, cycloadditions, and deprotection reactions.^{15b,d,f} 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 Because of the stronger hydrogen-bond donor ability and higher ionizing power of HFIP relative to TFE, HFIP often provides superior

results both in reaction rate enhancement^{15b,e,16,20} and as a helix-inducing cosolvent.^{19a}

Using HFIP as a substitute for TiCl₄ in a control experiment did not afford any product, and substrate **1e** was recovered almost quantitatively (Table 1, entry 5). Using 1 equiv of HFIP as an additive with CH₃CN as a solvent did not improve the yield (entry 6). However, when HFIP was used as the solvent in combination with 10 mol % TiCl₄, complete conversion and negligible epimerization was observed with increased catalyst turnover compared with TFE (cf. entries 7 and 4). Lowering the TiCl₄ catalyst loading to 5 mol % produced similar results as with 10 mol % TiCl₄ but at the expense of a longer reaction time (entry 8). Changing the concentration of the reaction mixture had minimal effect on the yield (entries 9 and 10).

We speculated that reaction of HFIP with TiCl₄ might generate HCl in situ along with Ti[OCH(CF₃)₂]₄. If so, then 5 mol % TiCl₄ should be capable of generating 20 mol % HCl in situ. To test this hypothesis, we ran the reaction in the presence of 10 and 20 mol % 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a proton scavenger (Table 1, entries 11 and 12). Significant catalyst inhibition resulting in lower yields was observed, but reaction to some extent was still observed when 20 mol % DTBMP was used. This could mean that the catalytically active species is HCl generated in situ or that DTBMP, being a base, has some other deleterious effect on the reaction.²¹ The reaction in HFIP with SiCl₄ provided the lactam in good yield (entry 13), but Sc(OTf)₃ provided the product in only 28% yield (entry 14).

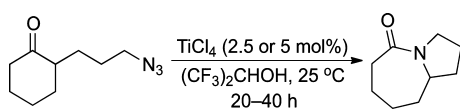
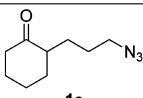
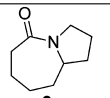
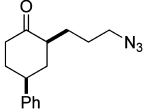
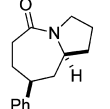
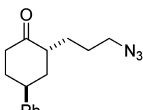
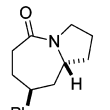
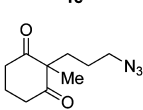
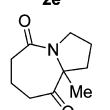
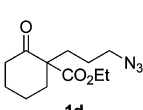
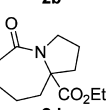
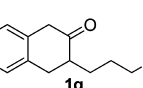
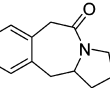
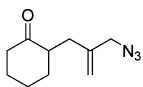
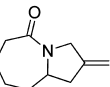
The reactions with Brønsted acids (5–20 mol %) delivered comparatively lower yields of the product than the reaction with 5 mol % TiCl_4 (entries 15–18). Interestingly, reaction with 20 mol % HCl in ether (entry 16) gave a lower yield than that with 5 mol % TiCl_4 (entry 8). The use of a chiral phosphoric acid^{4b} neither provided good yield nor led to any degree of kinetic resolution (entry 18). The reaction with $\text{Ti}(\text{iOPr})_4$ 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 when HCl in ether solution was added, possibly as a result of 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 azido ketones, as previous experience had 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, the transformations of **1c** and cis ketone **1f** required only 2.5 mol % TiCl_4 (entries 1 and 2), whereas trans ketone **1e** required 5 mol % TiCl_4 and a longer reaction time to obtain a slightly lower yield of the product (entry 3). The reaction of 1,3-diketone **1b** proceeded in higher yield than reported in the literature (entry 4; cf. Figure 1b),⁴ while 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** (entry 6) and allylic azide **1h** (entry 7) also provided good yields of the corresponding lactams **2g** and **2h**.

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

Substrate **1o** containing a tertiary amine (a possible additional source of catalyst inactivation) required 35 mol % TiCl_4 to provide pyrrolidiazepinone **2o** (Table 3, 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 commencing only upon the addition of 25 mol % TiCl_4 .²³ This observation suggests that the initial 25 mol % TiCl_4 , which was capable of generating 100 mol % HCl, formed a salt with the basic amine, with the remaining 10 mol % TiCl_4 being responsible for the desired transformation into lactam **2o**. Azido aldehyde **1p** required only 5 mol % TiCl_4 to provide 3-benzylpyrrolidinone (**2p**) in good yield (entry 9). Unfortunately, extending the tether length between the carbonyl and the

Table 2. Initial Substrate Scope for the Catalytic Intramolecular Schmidt Reaction of Cyclohexanone-Derived Azido Ketones^{a,b}

					
entry	substrate	catalyst loading (mol%)	time (h)	product	yield ^c (%)
1		2.5	20		94
2		2.5	20		98
3		5	38		87 ^d
4		5	24		94
5		5 10	40 18		94 95
6		5	24		89
7		5	24		84

^aTo a solution of a substrate (0.4 mmol) in hexafluoro-2-propanol (2.0 mL) at room temperature was added a 1.0 M solution of TiCl_4 in CH_2Cl_2 under a nitrogen atmosphere, and the reaction mixture was stirred at 25 °C for the designated period, unless otherwise mentioned. ^bConcentration of substrate was ca. 0.2 M. ^cIsolated yields. ^dBridged lactam **3e** was also isolated in ca. 2% yield.

azide moiety from the usual four to five carbons resulted in a sluggish reaction that afforded only an 11% yield of lactam **2q**, even when 20 mol % 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 optimize our reaction conditions further 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 , AcCl) as an effective promoter of this reaction even in the absence of TiCl_4 (entries 21–25). Thus, the reaction with 80 mol % AcCl (entry 25) gave results comparable to those with 20 mol % TiCl_4 (entry 1).

Table 3. Additional Evaluation of the Reaction Scope^{a,b}

<div><div><div><div><div><div></div><div>O</div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div></div></div></div></div>					
--	--	--	--	--	--

^aTo a solution of substrate (0.4 mmol) in hexafluoro-2-propanol (2.0 mL) at room temperature was added a 1.0 M solution of TiCl₄ in CH₂Cl₂ under a nitrogen atmosphere, and the reaction mixture was stirred at 25 °C for the designated period, unless otherwise noted. ^bConcentration of substrate was ca. 0.2 M. ^cIsolated yields. ^dYields in parentheses are based on recovered starting material. ^eBridged lactam 3i was also isolated in 2% yield (see the Supporting Information). ^fThe product contained 7% 1-phenethylpiperidin-2-one (3l) (see the Supporting Information). ^gThe product contained 3% N-methyl-2-piperidone (3m) (see the Supporting Information).

We realized that this would support the case that HCl is the active catalytic species, provided that we could show HFIP to be capable of generating HCl from AcCl (an ironic notion in view of the low nucleophilicity of HFIP^{15b}). To address this, we combined 1 equiv of AcCl and 2 equiv of HFIP in CDCl₃ and monitored the reaction

by ¹H NMR spectroscopy (Figure 3; see the Supporting Information for details). Within 6 min, ca. 50% conversion to HFIP acetate was observed. The rate decreased after 20 min, and the reaction took 4 h to reach >95% conversion. Conversely, we were not able to obtain any evidence for the in situ generation of HCl from TiCl₄.

Table 4. Further Optimization of the Reaction Conditions for 1a^{a,b}

Reaction scheme: 1a (2-azidoethyl cyclopentanone) $\xrightarrow[\text{25 } ^\circ\text{C, 24 h}]{\text{catalyst, additive (CF}_3)_2\text{CHOH}}$ 2a (2,3-dihydro-1H-indolizin[5,1-b]pyridine-1-one)

entry	catalyst	catalyst loading (mol %)	additive	additive loading (mol %)	2a:1a ^c
1	TiCl ₄	20	—	—	95:5
2	TiCl ₄	10	—	—	59:41
3	TiF ₄	10	—	—	26:74
4	TiBr ₄	10	—	—	46:54
5	Ti(ⁱ OPr) ₄	10	—	—	0:100
6	SiCl ₄	10	—	—	58:42
7	SbCl ₅	10	—	—	45:55
8	NbCl ₅	10	—	—	44:56
9	WCl ₆	10	—	—	54:46
10	HCl in ether ^d	40	—	—	45:55
11	aqueous HCl ^e	40	—	—	59:41
12	HCl in HFIP ^f	40	—	—	57:43–75:25
13	H ₂ SO ₄	40	—	—	76:24
14	—	—	CF ₃ SO ₃ H	20	49:51
15	TiCl ₄	5	CF ₃ SO ₃ H	5	42:58
16	TiCl ₄	5	ClSO ₃ H	5	49:51
17	TiCl ₄	10	AgOTf ^g	20	56:44
18	TiCl ₄	10	Al(ⁱ OPr) ₃	20	50:50
19	TiCl ₄	10	silica gel ^h	—	47:53
20	TiCl ₄	10	CH ₃ COCl ⁱ	40	95:5
21	—	—	CH ₃ COCl ⁱ	40	58:42
22	—	—	CH ₃ COCl ^j	40	70:30
23	—	—	CH ₃ COCl ^j	70	90:10
24	—	—	CH ₃ COCl ^j	80	94:6
25	—	—	CH ₃ COCl ^j	80	97:3 ^k
26	—	—	CH ₃ COBr ^l	40	72:28
27	—	—	CH ₃ COBr ^l	80	98:2 ^m
28	TiCl ₄	10	(CH ₃) ₃ SiCl	40	89:11
29	—	—	(CH ₃) ₃ SiCl	80	92:8
30	—	—	(CH ₃) ₃ SiI	80	13:87 ⁿ

^aTo a solution of substrate 1a (0.1 mmol) in (CF₃)₂CHOH (0.5 mL) at room temperature was added a catalyst and/or an additive under a nitrogen atmosphere, unless otherwise mentioned. For TiCl₄, SiCl₄, and SbCl₅, a 1.0 M solution in CH₂Cl₂ was used. ^bConcentration of substrate was ca. 0.2 M. ^c¹H NMR ratios determined after a brief workup (see the Supporting Information for details). ^dA 1.0 M solution of HCl in ether (commercial) was used. ^eAqueous HCl (37%) was used. ^fA 0.105–0.116 M solution of HCl in hexafluoro-2-propanol was prepared and used immediately. ^gTiCl₂(OTf)₂ was generated in situ from TiCl₄ and AgOTf.²⁴ ^hSilica gel (50 mg) was added. ⁱAn old container of acetyl chloride (>5 years since initial opening) was used. ^jA new container of acetyl chloride was used. ^kThe 2a:1a ratio did not change between 18 and 24 h. ^lA new container of acetyl bromide was used. ^mThe 2a:1a ratio did not change between 18 and 24 h. ⁿSeveral other unidentified byproducts/impurities were also observed.

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 the addition of 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 nonreproducibility of these experiments can be blamed on the ease with which the HCl gas escaped the solution, making it difficult to gauge accurately the amount of acid present in a particular experiment. For example, markedly reduced yields (on the low end noted in entry 12) were obtained when HCl/HFIP solutions were aged for even a few minutes. We also examined whether HBr generated by the addition of AcBr to HFIP was a suitable substitute for HCl, and the initial evidence suggested that it is (cf. entries 26 and 27 with 22 and 25). We still prefer to use AcCl-generated HCl because AcCl is generally

easier to handle and more resistant to hydrolysis in air. Moreover, we observed very little difference when different sources of AcCl were used in the reaction (i.e., freshly opened vs older bottles of reagent; cf. entries 25 and 24). Taking into account both efficiency and practicality, we prefer using TiCl₄ or AcCl as the HCl source among all of the methods tested to date.

We decided to explore the substrate scope further under these new reaction conditions utilizing AcCl as a procatalyst. The substrate scope was comparable to that described for TiCl₄, and lactams were obtained in good to excellent yields (Table 5). Although higher amounts of AcCl than TiCl₄ were required to achieve complete conversion, the use of AcCl was convenient. In addition, both HFIP and its acetate ester byproduct are volatile, easing the workup. Finally, no metal waste was produced.

Mechanism. On the basis of precedent,^{15b–e,18} we propose the involvement of HFIP as a strong hydrogen-bond donor to the

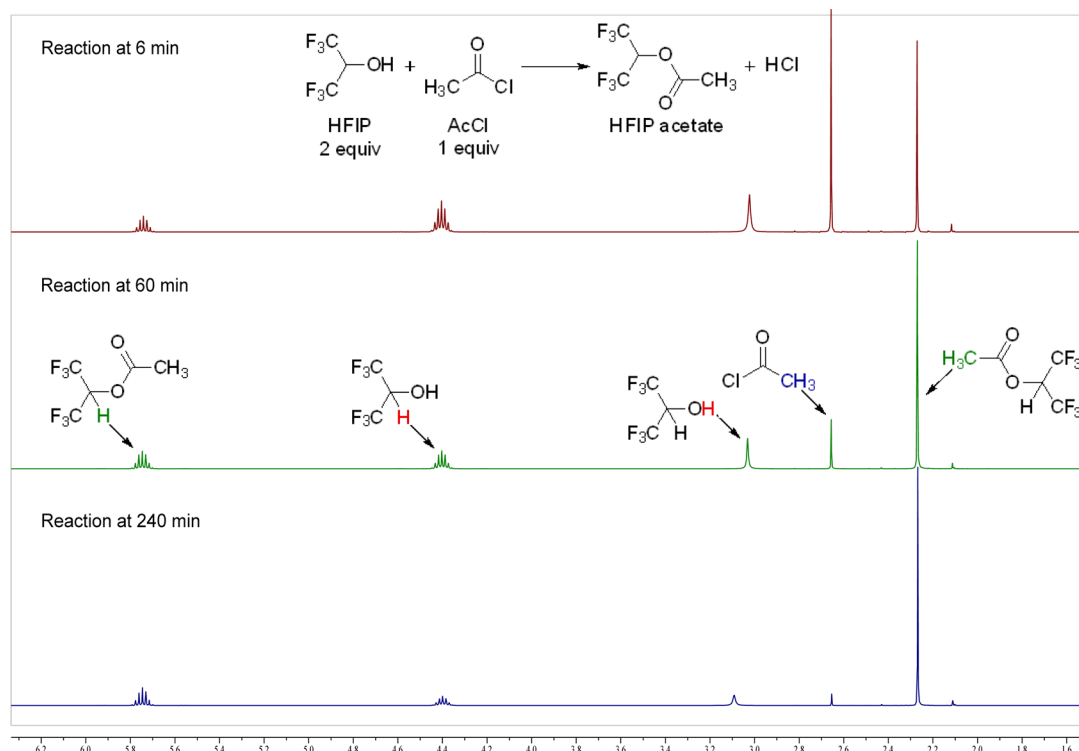


Figure 3. Results of ^1H NMR monitoring of the reaction of acetyl chloride with HFIP to generate HCl in situ.

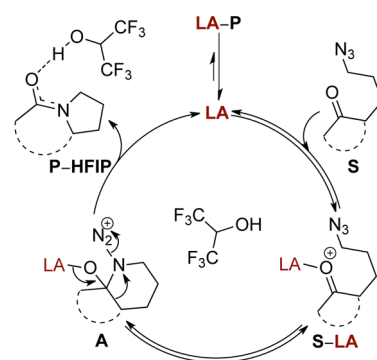


Figure 4. Proposed catalytic cycle for the intramolecular Schmidt reaction employing HFIP as the solvent.

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 as the solvent can potentially form complexes with the substrate, intermediates, and product. Critically, hydrogen bonding of HFIP with the lactam carbonyl by displacement of the Lewis or Brønsted acid allows for regeneration of the catalyst (most likely a proton). In addition, one cannot rule out coordination between HFIP and the catalyst to produce a catalytically more reactive species such as $[\text{HFIP}\cdot\text{H}]^+$.²⁵ We note that a cursory measurement of the pH of the reaction mixture using pH indicator strips (nonbleeding) 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_2Cl_2 (the pH of pure HFIP was measured to be 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 with strengths comparable to those of covalent linkages.^{15c} Such 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 the HFIP–substrate and HFIP–product complexes (Figure 5). The Job plots based on the ^1H NMR data provide good evidence that HFIP forms a 1:1 complex with both substrate **1a** and product **2a**. Although the stoichiometries of binding were similar, the complexation shift ($\Delta\delta$) of the HFIP hydroxyl resonance upon complexation of lactam **2a** was significantly higher than for azido ketone **1a**, consistent with the expected stronger complexation of HFIP with the lactam than with the ketone.

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

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 a higher catalyst loading.²⁷ To demonstrate different degrees of product inhibition with different lactams, ^1H NMR experiments were carried out to determine the effect of adding two different product lactams at the outset of a single relatively fast reaction. For this, we chose the product of the quicker reaction leading to **2f** (and a case that succeeds with 10 mol % AcCl procatalyst) and

Table 5. Scope under 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}
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
8	 1i	80	48	 2i	87 ^f
9	 1k	100	62	 2k	92
10	 1l	100	32	 2l	96 ^g

^aTo a solution of a substrate (0.4 mmol) in HFIP (2.0 mL) at room temperature was added CH₃COCl under a nitrogen atmosphere, and the reaction mixture was stirred at 25 °C for the designated period, unless otherwise noted. ^bConcentration of substrate was ca. 0.2 M. ^cIsolated yields. ^dBridged lactam **3e** was also isolated in ca. 3% yield. ^eThe reaction was run on a 0.1 mmol scale. ^fBridged lactam **3i** was also isolated in 3% yield (see the Supporting Information). ^gThe product contained 7% 1-phenethylpiperidin-2-one (**3l**) (see the Supporting Information).

2a, the product of a much slower reaction (and one that requires 80 mol % AcCl to reach completion). In the first case, the facile azido ketone substrate **1f** was combined with an equimolar amount of its lactam product **2f** and then treated with 20 mol % AcCl in HFIP (Figure 6 and Scheme 3b). The time needed 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 % AcCl 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} A more detailed series of kinetic studies is necessary

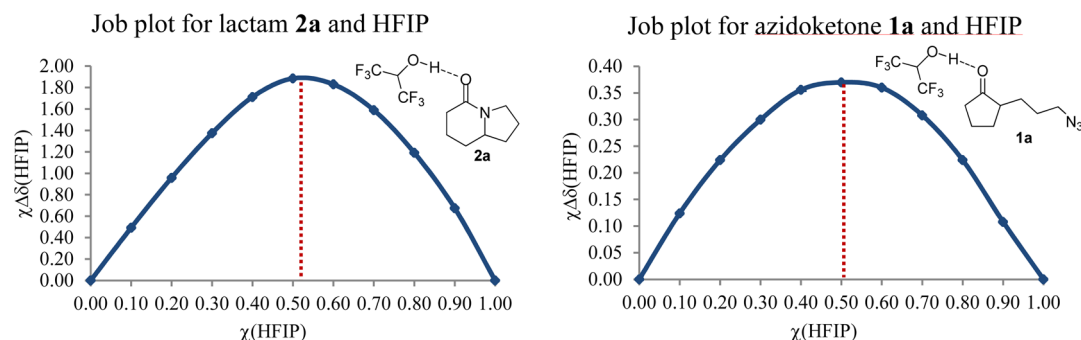


Figure 5. Job plots for complexation of lactam **2a** and azido ketone **1a** with HFIP.

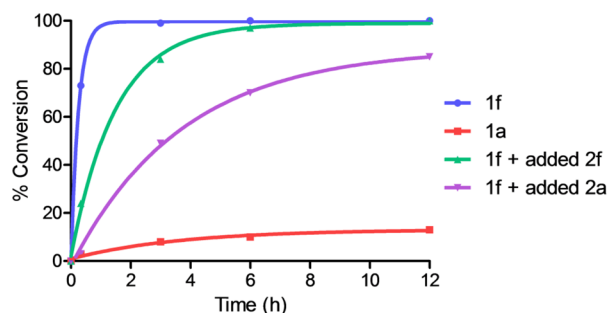
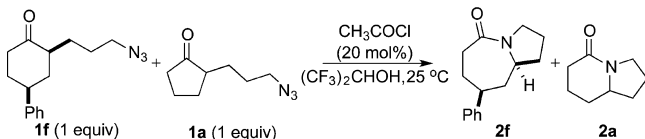


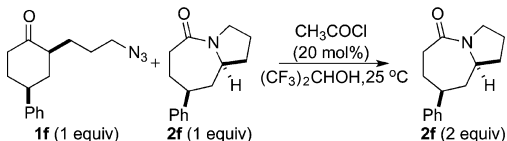
Figure 6. Relative reaction rates for **1f** and **1a** (see Scheme 3a), **1f** with 1 equiv of **2f** added at the outset of the reaction (Scheme 3b), and **1f** with 1 equiv of **2a** added at the outset of the reaction (Scheme 3c).

Scheme 3

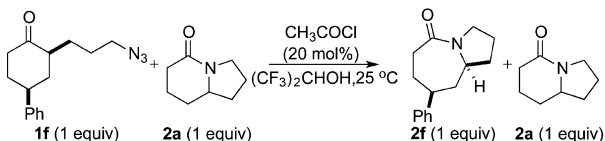
(a) Competition experiment between azidoketones **1f** and **1a**



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



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



to address fully the relative roles of kinetics versus product inhibition and will be reported in due course.

CONCLUSIONS

We have demonstrated a catalytic intramolecular Schmidt reaction with broad substrate scope and utility. Two versions of the reaction, one using TiCl_4 and the other with AcCl , have been identified as having strong synthetic utility that is as good or better than all previous versions of this process. In either case, the strong hydrogen-bonding ability of hexafluoro-2-propanol was critical to the development of these substoichiometric reactions. The discovery of conditions employing AcCl as a procatalyst in

the presence of hexafluoro-2-propanol provided evidence that HCl is an active catalytic species as well as providing a metal-free catalytic reaction. Prior to this discovery, the primary metal-free variations of the intramolecular Schmidt reaction used either trifluoroacetic acid as the solvent or TfOH or ClSO_3H as a stoichiometric reagent.

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

In addition, ^1H NMR experiments were performed to exhibit different degrees of product inhibition with different lactams. That such structurally similar lactams have substantially different effects on the rate of a given reaction is at minimum provocative and might lead to increased understanding of the role of product inhibition in this and other reactions that afford lactam or amide products. Future efforts will be directed to extending the scope of this reaction and elucidating 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.

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 ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

jaube@ku.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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

■ REFERENCES

- (1) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966. (b) Milligan, G. L.; Mossman, C. J.; Aube, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459.
- (2) For reviews, see: (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240. (b) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146–156. (c) Grecian, S.; Aube, J. In *Organic Azides: Syntheses and Applications*; Bräse, S.; Banert, K., Eds.; Wiley: Chichester, U.K., 2010; pp 191–237. (d) Wroblewski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aube, J. *Org. React.* **2012**, *78*, 1–320.
- (3) For selected examples, see: (a) Wendt, J. A.; Aubé, J. *Tetrahedron Lett.* **1996**, *37*, 1531–1534. (b) Iyengar, R.; Schildknecht, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625–1627. (c) Wroblewski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475–5481. (d) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018–6024. (e) Frankowski, K. J.; Neuenswander, B.; Aubé, J. *J. Comb. Chem.* **2008**, *10*, 721–725. (f) Zhao, Y.-M.; Gu, P.; Zhang, H.-J.; Zhang, Q.-W.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M. *J. Org. Chem.* **2009**, *74*, 3211–3213. (g) Ghosh, P.; Judd, W. R.; Ribelin, T.; Aubé, J. *Org. Lett.* **2009**, *11*, 4140–4142. (h) Kapat, A.; Nyfeler, E.; Giuffredì, G. T.; Renaud, P. *J. Am. Chem. Soc.* **2009**, *131*, 17746–17747. (i) Chen, Z.-H.; Chen, Z.-M.; Zhang, Y.-Q.; Tu, Y.-Q.; Zhang, F.-M. *J. Org. Chem.* **2011**, *76*, 10173–10186. (j) Ma, A.-J.; Tu, Y.-Q.; Peng, J.-B.; Dou, Q.-Y.; Hou, S.-H.; Zhang, F.-M.; Wang, S.-H. *Org. Lett.* **2012**, *14*, 3604–3607.
- (4) (a) Lertpibulpanya, D.; Marsden, S. P. *Org. Biomol. Chem.* **2006**, *4*, 3498–3504. (b) Yang, M.; Zhao, Y.-M.; Zhang, S.-Y.; Tu, Y.-Q.; Zhang, F.-M. *Chem.—Asian J.* **2011**, *6*, 1344–1347.
- (5) (a) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246. (b) Bolm, C.; Legros, J.; Le Pailh, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254.
- (6) Gutierrez, O.; Aubé, J.; Tantillo, D. J. *J. Org. Chem.* **2012**, *77*, 640–647.
- (7) For reviews of reaction kinetics involving product inhibition, see: (a) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302–4320. (b) Mathew, J. S.; Klusmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E. A. C.; Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711–4722. For a selected example of product inhibition in a catalytic Diels–Alder reaction, see: (c) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573.
- (8) For catalytic Ritter reactions, see: (a) Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2007**, 4642–4645. (b) Guérinot, A.; Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 19–28.
- (9) Zhang, J. S.; Wang, K.; Lu, Y. C.; Luo, G. S. *AIChE J.* **2012**, *58*, 3156–3160.
- (10) For examples of catalytic Beckmann rearrangements, see: (a) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1991**, 1653–1656. (b) Lee, J. K.; Kim, D.-C.; Eui Song, C.; Lee, S.-g. *Synth. Commun.* **2003**, *33*, 2301–2307. (c) Sato, S.; Hoshino, H.; Sugimoto, T.; Kashiwagi, K. *Chem. Lett.* **2010**, *39*, 1319–1320. (d) Liu, L.-F.; Liu, H.; Pi, H.-J.; Yang, S.; Yao, M.; Du, W.; Deng, W.-P. *Synth. Commun.* **2011**, *41*, 553–560.
- (11) Zicmanis, A.; Katkevica, S.; Mekss, P. *Catal. Commun.* **2009**, *10*, 614–619.
- (12) Nucleophilic addition reactions to cyclopentanones are generally slower than those to cyclohexanones. See: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 762 and 769–771.
- (13) Gracias, V.; Zeng, Y.; Desai, P.; Aubé, J. *Org. Lett.* **2003**, *5*, 4999–5001.
- (14) Gu, P.; Zhao, Y.-M.; Tu, Y. Q.; Ma, Y.; Zhang, F. *Org. Lett.* **2006**, *8*, 5271–5273.
- (15) (a) Catalán, J.; Palomar, J.; Díaz, C.; de Paz, J. L. G. *J. Phys. Chem. A* **1997**, *101*, 5183–5189. (b) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18–29. (c) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 8421–8426. (d) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, 2925–2943. (e) Ratnikov, M. O.; Tumanov, V. V.; Smit, W. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9739–9742. (f) Palladino, P.; Stetsenko, D. A. *Org. Lett.* **2012**, *14*, 6346–6349.
- (16) Khaksar, S.; Heydari, A.; Tajbakhsh, M.; Vahdat, S. M. *J. Fluorine Chem.* **2010**, *131*, 1377–1381.
- (17) (a) Neimann, K.; Neumann, R. *Org. Lett.* **2000**, *2*, 2861–2863. (b) Iskra, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2002**, *43*, 1001–1003.
- (18) Shuklov, I. A.; Dubrovina, N. V.; Barsch, E.; Ludwig, R.; Michalik, D.; Börner, A. *Chem. Commun.* **2009**, 1535–1537.
- (19) (a) Hong, D.-P.; Hoshino, M.; Kuboi, R.; Goto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8427–8433. (b) Konno, T.; Iwashita, J.; Nagayama, K. *Protein Sci.* **2000**, *9*, 564–569. (c) Roccatano, D.; Fioroni, M.; Zacharias, M.; Colombo, G. *Protein Sci.* **2005**, *14*, 2582–2589.
- (20) Cativiela, C.; García, J. I.; Mayoral, J. A.; Salvatella, L. *Can. J. Chem.* **1994**, *72*, 308–311.
- (21) During screening of the reaction conditions, the use of an amine base as an additive had a deleterious effect on the reaction outcome (see the Supporting Information for details).
- (22) Iden, H. S.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 3425–3428.
- (23) The reaction mixture was monitored by TLC, and no product spot was observed until after the addition of 25 mol % TiCl₄.
- (24) Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141–142.
- (25) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134–9142.
- (26) Jiang, J.; MacLachlan, M. J. *Chem. Commun.* **2009**, 5695–5697.
- (27) (a) Gorshkova, G. N.; Kolodkin, F. L.; Polishchuk, V. V.; Ponomarenko, V. A.; Sidel'kovskaya, F. P. *Russ. Chem. Bull.* **1970**, *19*, 506–509. (b) Filgueiras, C. A. L.; Huheey, J. E. *J. Org. Chem.* **1976**, *41*, 49–53. (c) Wan, P.; Modro, T. A.; Yates, K. *Can. J. Chem.* **1980**, *58*, 2423–2432. (d) Cox, R. A.; Druet, L. M.; Klausner, A. E.; Modro, T. A.; Wan, P.; Yates, K. *Can. J. Chem.* **1981**, *59*, 1568–1573. (e) Puffr, R.; Kubanek, V. *Lactam Based Polyamides, Volume I: Polymerization, Structure and Properties*; CRC Press: Boca Raton, FL, 1991. (f) Le Questel, J.-Y.; Laurence, C.; Lachkar, A.; Helbert, M.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2091–2094. (g) El Firdoussi, A.; Esseffar, M.; Bouab, W.; Abboud, J. L. M.; Mò, O.; Yáñez, M. *J. Phys. Chem. A* **2004**, *108*, 10568–10577. (h) Glover, S. A.; Rosser, A. A. *J. Org. Chem.* **2012**, *77*, 5492–5502.