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Temperature dependence of turnover in a Sc(OTf)₃-catalyzed intramolecular Schmidt reaction

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Abstract

The intramolecular Schmidt reaction of ketones and tethered azides is an efficient method for the generation of amides and lactams. This reaction is catalyzed by Lewis acids, which tightly bind the strongly basic amide product and result in product inhibition. We report herein conditions to achieve a catalytic Schmidt reaction using substoichiometric amounts of the heat-stable Lewis acid Sc(OTf)₃. This species was shown to effectively release products of the Schmidt reaction in a temperature-dependent fashion. Thus, heat was able to promote catalyst turnover. A brief substrate scope was conducted using these conditions.

Keywords

Intramolecular Schmidt reaction; Turnover; Ring expansion; Polycyclic lactams; Scandium triflate catalysis

The intramolecular Schmidt reaction is a useful tool for the construction of polycyclic lactams¹ as well as their corresponding amines via subsequent reduction.² These cyclic nitrogen-containing species abound in biological systems and the drugs that target them, making the intramolecular Schmidt reaction relevant for the construction of useful molecules.³

Schmidt reactions of ketones require an acid to activate the carbonyl group for azide attack (Fig. 1A).⁴ Since the product amides of this reaction have increased Lewis basicity compared to their starting ketones, product inhibition may occur if the Lewis acid is slow to dissociate from the amide product. In such a case, at least stoichiometric amounts of acid would be required for full conversion, a situation that we observed in our initial studies of this reaction (Fig. 1B). Following an extended search, suitable conditions for a substoichiometric catalytic intramolecular Schmidt reaction were only recently realized, in

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.12.068>.

Dedicated to the memory of Harry Wasserman, an inspirational person and a most elegant scholar

which carrying out the reaction in the strong hydrogen bond donor hexafluoroisopropanol (HFIP) promoted turnover and afforded an attractive alternative to our originally reported conditions (Fig. 1C).⁵

In pursuing these studies, we discovered that 10–25 mol % of Sc(OTf)₃ can effect the intramolecular Schmidt reaction of favorable substrates, although the reactions required undesirably high temperatures for good results. In this Letter, we report these results for the first time. In addition, we studied the role of temperature in these reactions, finding a strong temperature dependence of the turnover of catalyst in the complexed lactam products.

Screening of catalysts was carried out using substrates **1a** or **1b** (Table 1). The phenyl chromophore of **1b** allowed analysis by ultra-high performance liquid chromatography (UPLC). In addition, we used the *cis* isomer of the 4-substituted cyclohexanone **1b** to avoid complicating the analysis by possible *trans*-to-*cis* epimerization⁵ under the reaction conditions. Conversions were estimated using NMR or UPLC.

We quickly identified Sc(OTf)₃ as a useful promoter for the reaction, initially finding that carrying out the reaction in water at high temperatures led to best results (Table 1, entry 3). In some cases, we added phase transfer salts such as *n*-Bu₄NOH to facilitate reactions with more hydrophobic ketones (see Supporting information, Table SI-1), but even here the aqueous mixtures were difficult to purify so alternative conditions were sought. The optimal solvent proved to be acetonitrile, a polar organic solvent able to dissolve all reaction partners (entry 6, optimal conditions in bold). In contrast, nonpolar solvents like xylenes gave unsatisfactory results (e.g., entry 7). The optimized conditions indicated in entry 6 were attempted with alternative catalysts, including Yb(OTf)₃, but lesser conversions were obtained. As a control, we confirmed that performing the reaction in the absence of Lewis acid at 200 °C did not lead to product.

An increase in conversion was observed at higher temperatures, e.g., entry 4 in Table 1, suggesting a possible increase in turnover under these conditions. To study this, we used a variant of the UPLC screen above in which *N*-benzyl-2-pyrrolidinone was chosen as an internal standard due to its similar extinction coefficient to **2b** (see Supplementary material for information on the assay). Using this protocol, we first confirmed that product inhibition was occurring at room temperature by measuring product formation relative to increasing amounts of Sc(OTf)₃ promoter (Fig. 2). These results confirmed that the conversion to product under these conditions required roughly one equivalent of acid for each equivalent of product formed.

A series of experiments specifically measuring the effect of temperature on particular reaction variables were then carried out (Fig. 2). First, holding the catalyst loading level of Sc(OTf)₃ constant at 20% at increasing temperatures revealed a linear relationship until the reaction reached completion (Fig. 3A). Turnover number and frequency are additional parameters that quantify the amount and rate of catalyst turnover.⁶ We also found that both turnover number and frequency increased linearly with temperature (Fig. 3B and C, respectively). The turnover number of this reaction progressed from 0.260 at room temperature to 11.4 at 200 °C, a 43.8-fold increase.

Although it is perhaps intuitive that turnover efficiency might increase along with temperature, this relationship is not regularly reported for synthetic catalysis.⁷ Here we propose that heat assists in the dissociation of the Sc(OTf)₃-lactam product and permits re-entry of the Lewis acid into the catalytic cycle (Fig. 4). In considering other variables, we note that Sc(OTf)₃ has been reported to be thermally stable,⁸ which might contribute to the success of this catalyst under the present set of conditions.

A brief study of reaction scope was undertaken under these conditions (Table 2). Substrates examined included an acyclic ketone, cyclic ketones of various ring sizes, and sterically encumbered ketones. In particular, the cyclopentanone **1e** was used to determine conditions, since this substrate is known to be less facile under other variations of the intramolecular Schmidt reaction,¹ which we have attributed to the increased torsional strain cyclopentanones assume during nucleophilic addition.⁹ The substrate **1e** was indeed recalcitrant to reactivity, but increasing the catalyst loading to 25 mol % led to full conversion. Accordingly, we used this higher catalyst loading for all substrates in Table 2.

The results from the substrate scope indicate moderate to excellent yields for most of the substrates, despite the high temperatures applied to facilitate turnover. Notably, representatives of another class of ketones known to be problematic, electron-poor ketones **1l** and **1m**, failed to react under these conditions. They do react, albeit slowly, under other super-stoichiometric sets of conditions.⁴

Caution: Despite the theoretical interest of these observations, we do not recommend adoption of these conditions for many azides, especially those of relatively low molecular weight. Any reactions using alkyl azides at high temperatures should be carried out with extreme caution (e.g. using small scale, proper protection with shields).

In conclusion, we have investigated Sc(OTf)₃ promotion of the intramolecular Schmidt reaction of ketones with alkyl azides.

Although Sc(OTf)₃ was found to be a suitable catalyst, the requirement for carrying out the reaction at high temperatures and limited scope render these conditions less attractive than alternatives.^{1,5} However, the observation that turnover frequency and number were strongly correlated with temperature supports the idea that heat may be underexplored in overcoming product inhibition in catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

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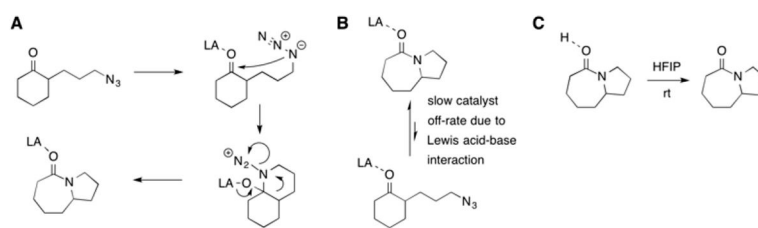


Figure 1. The intramolecular Schmidt reaction. (A) Mechanism of Lewis acid (L.A.) activation. (B) Proposed rationale for product inhibition. (C) Overcoming product inhibition through proton shuffling with hexafluoroisopropanol (HFIP) solvent.⁵

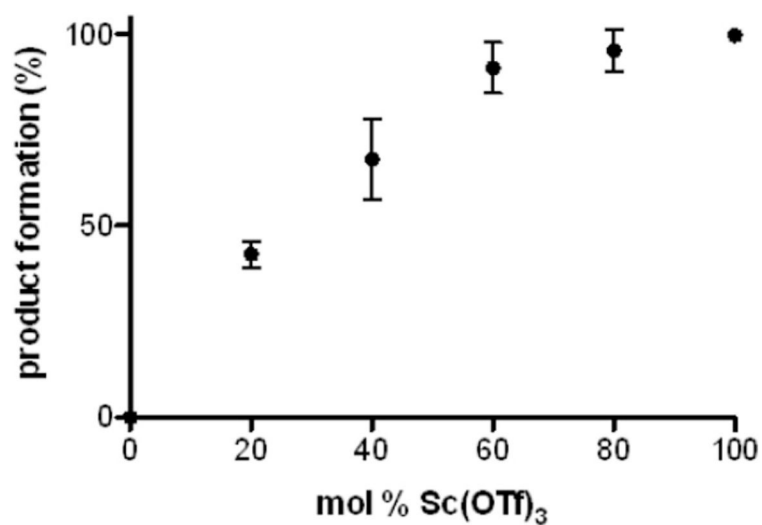


Figure 2.
Dependence of conversion of **1b** to **2b** on Lewis acid equivalents at room temperature after 24 h.

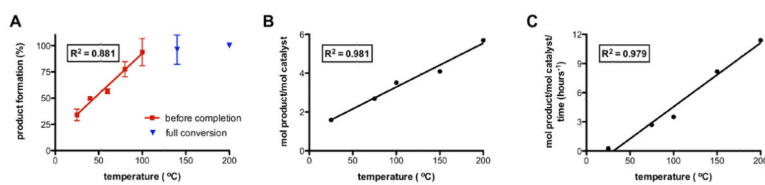


Figure 3. Temperature dependence of various variables for the conversion of **1b** to **2b** promoted by 20 mol % Sc(OTf)₃. (A) Conversion to product. (B) Catalyst turnover number. (C) Catalyst turnover frequency.

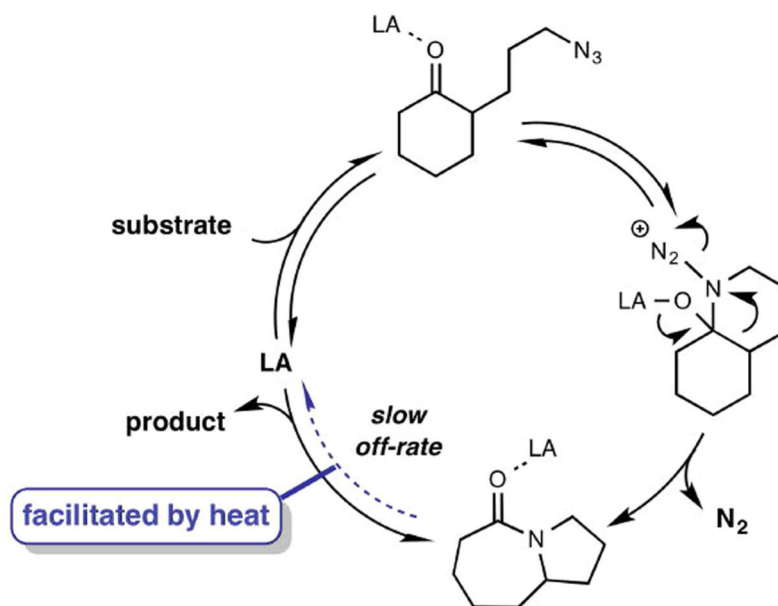
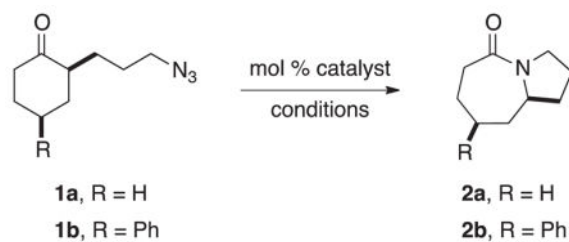


Figure 4.
Proposed catalytic cycle.

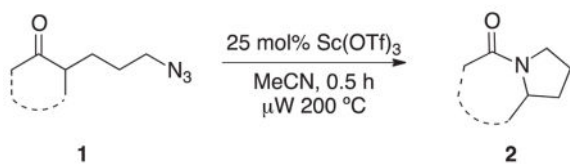
Table 1Screening of intramolecular Schmidt reaction conditions^a

Entry	R	Mol % catalyst	Conditions	% conv. (% yield)
1	H	5% TiCl ₄	CH ₂ Cl ₂ , rt, 16 h	8 ^b
2	H	10% Sc(OTf) ₃	MeCN, 80 °C, 16 h	47 ^b
3	H	10% Sc(OTf) ₃	H ₂ O, 180 °C, 16 h	>95 ^b (73)
4	Ph	10% Sc(OTf) ₃	MeCN, 180 °C, 5 h ^c	>95 ^d (72)
5	Ph	10% Sc(OTf) ₃	MeCN, 180 °C, 1 h ^c	>95 ^d (83)
6	Ph	10% Sc(OTf)₃	MeCN, 200 °C, 0.5 h^c	>95^d (92)
7	Ph	10% Sc(OTf) ₃	xylenes, 180 °C, 1 h ^c	10 ^d
8	Ph	25% TFA	MeCN, 200 °C, 0.5 h ^c	25 ^d
9	Ph	25% BF ₃ ·OEt ₂	MeCN, 200 °C, 0.5 h ^c	70 ^d
10	Ph	25% TiCl ₄	MeCN, 200 °C, 0.5 h ^c	60 ^d
11	Ph	25% Yb(OTf) ₃	MeCN, 200 °C, 0.5 h ^c	80 ^d
12	Ph	None	MeCN, 200 °C, 0.5 h ^c	0 ^c

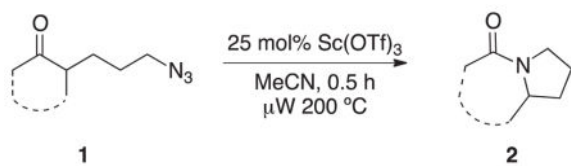
^a Most examples taken from Ref. 5 (Supporting information).^b Conversion was determined by NMR. Isolated yield is shown in parentheses.^c Microwave heating conditions were applied.^d Conversion was determined by UPLC. Isolated yield is shown in parentheses.

Table 2

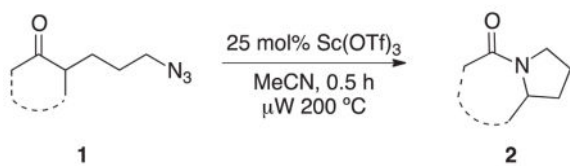
Exploration of reaction scope



Entry	Substrate	Product	% yield ^a
1			89
	1a	2a	
2			92
	1b	2b	
3			83
	1c	2c	
4			75
	1d	2d	
5			62
	1e	2e	



Entry	Substrate	Product	% yield ^d
6	<p>1f</p>	<p>2f</p>	62
7	<p>1g</p>	<p>2g</p>	80
8	<p>1h</p>	<p>2h</p>	92
9	<p>1i</p>	<p>2i</p>	76
10	<p>1j</p>	<p>2j</p>	46
11	<p>1k</p>	<p>2k</p>	77



Entry	Substrate	Product	% yield ^a
12	<p>1l</p>	<p>2l</p>	No reaction
13	<p>1m</p>	<p>2m</p>	No reaction

^a Isolated yield, averaged from three experiments.