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Rapid Construction of Complex 2-Pyrrolines through Lewis Acid-Catalyzed, Sequential Three-Component Reactions via *in Situ*-Generated 1-Azaallyl Cations

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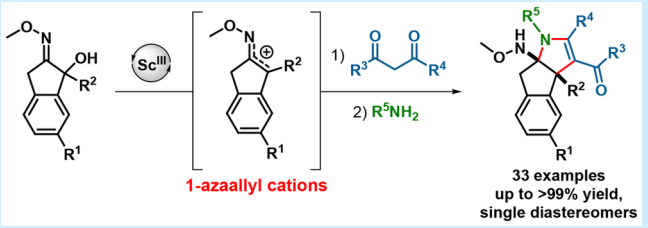
Supporting Information

ABSTRACT: The first $Sc(OTf)_3$-catalyzed dehydration of 2-hydroxy oxime ethers to generate benzylic stabilized 1-azaallyl cations, which are captured by 1,3-carbonyls, is described. A subsequent addition of primary amines in a sequential three-component reaction affords highly substituted and densely functionalized tetrahydroindeno[2,1-*b*]pyrroles as single diastereomers with up to quantitative yield. Thus, three new σ-bonds and two vicinal quaternary stereogenic centers are generated in a one-pot operation.



The rapid generation of complex heterocyclic compounds remains one of the major current challenges of biological and medicinal chemistry and is central to the discovery of novel drug candidates. In light of their straightforward and highly atom- as well as step-economical character, multicomponent reactions (MCRs) have proven powerful for furnishing a wide variety of structurally diverse and biologically active heterocycles,[1] and the development of MCRs that provide pyrroline-derived compounds has garnered growing attention in recent years.[2] This is because they are common structural motifs in natural products such as anthramycine,[3] sibiromycine,[4] myosmine,[5] and spirotryprostatin B,[6] as well as in other pharmaceutically relevant substrates.[7] Consequently, novel and operationally simple strategies and methodologies for the preparation of these *N*-heterocycles are much desired to study their biological activities in more detail.

The use of tertiary alcohols for the construction of all-carbon quaternary stereocenters is a highly attractive process in organic synthesis because water is the sole byproduct. Unfortunately, in many cases, such S_N1-reactions suffer from severe limitations such as unfavorable steric hindrance, the relatively poor leaving group character of the hydroxy group, and competitive elimination pathways.[8] Typically, Lewis or Brønsted acids are used as catalysts, and electron-rich substrates are employed in order to stabilize the resulting carbocations.[9] However, the dehydration of electronically less activated tertiary alcohols, for example, with a carbonyl substituent in the α-position, is only feasible either under harsh reaction conditions[10] or with adjacent, strongly resonance-stabilizing groups.[11]

Imines with a tertiary hydroxy group have thus far never been applied in Lewis acid-catalyzed S_N1-type reactions with carbon nucleophiles to the best of our knowledge. Although the concept of generating α-imino carbocations from hydrazones or oxime ethers was established around 1980,[12,13] the synthetic utility of these intermediates has only been reported for a limited number of noncatalyzed transformations to date.[14,15]

We envisioned tertiary 2-hydroxy oxime ethers potentially serving as suitable substrates for Lewis acid-catalyzed dehydration, as they would generate resonance-stabilized α-methoxyimino carbocations **A**. Based upon their unique electronic character, which resembles resonance-stabilized allyl cations,[15] they can be described as 1-azaallyl cations.[13] As a consequence, we envisaged that 1,3-dicarbonyls could capture them and create a new all-carbon-substituted quaternary stereogenic center. However, in order to induce a cycloannulation process onto the electrophilic oxime ether, primary amines might need to be employed to undergo condensation with the dicarbonyl moiety followed by a 5-*exo*-*trig*-cyclization. This would furnish highly substituted 2-pyrrolines with an aminal moiety ready for further functionalization. Herein, we now report our results in this general direction, which have resulted in the first Lewis acid-catalyzed (2 + 2 + 1)-cycloannulation of *in situ*-generated 1-azaallyl cations (Scheme 1).

We started our investigations with 2-hydroxy oxime ethers **1**, which were synthesized by a three-step procedure from commercially available indanones (see the Supporting Information (SI) for details). Thus, **1a** was treated with methyl acetoacetate under metal triflate catalysis, and the coupling product **2a** was further condensed with benzylamine *in situ* to furnish the desired pyrroline **3a** (Table 1).[16] The optimization studies initially concentrated on the first step of this sequential three-component reaction (3CR) generating intermediate **2a**.

With 10 mol % $Zn(OTf)_2$ as catalyst, incomplete conversion of **1a** to **2a** was observed with methyl acetoacetate in different solvents at room temperature (Table 1, entries 1−4). After investigation of further reaction conditions (entries 5−7),

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Scheme 1. Conceptualization of the Three-Component Reaction

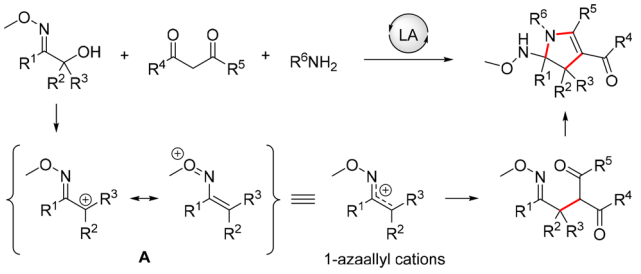
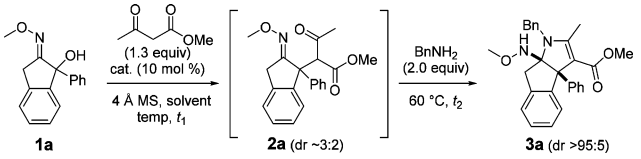


Table 1. Optimization Studies[a]



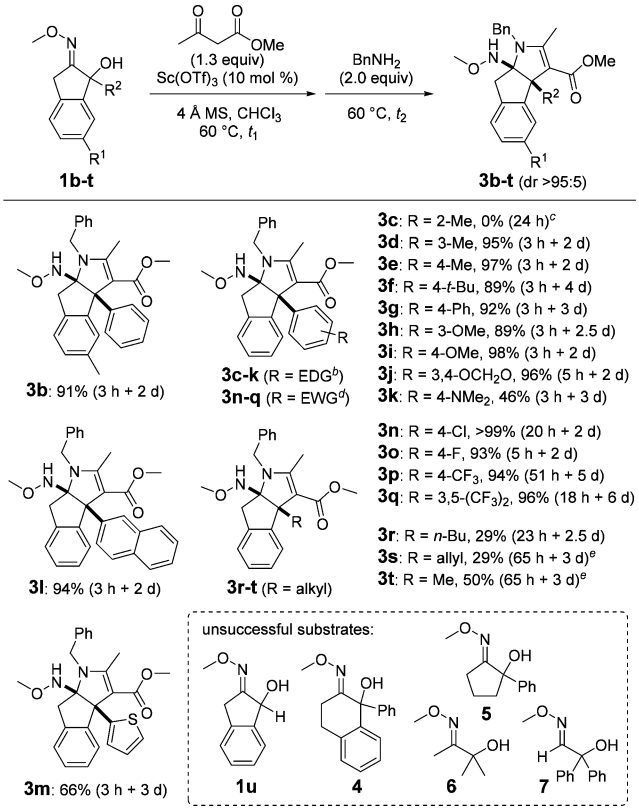
entry	catalyst	solvent	temp (°C)	t_1 (h)	t_2 (d)	yield **2a** (%)[b]	yield **3a** (%)[b]
1–4	$Zn(OTf)_2$	[c]	rt	72	---	5–76[d]	---
5	$Zn(OTf)_2$	$CHCl_3$	60	27	---	92	---
6	$FeCl_3·6H_2O$	CH_3NO_2	60	123	---	61[d]	---
7	$Sc(OTf)_3$	$C_2H_4Cl_2$	80	0.5	---	89	---
8	$Sc(OTf)_3$	$CHCl_3$	60	3	---	97	---
9	$Sc(OTf)_3$[e]	$CHCl_3$	60	3	---	90	---
10	TfOH[e]	$CHCl_3$	60	24	---	n.r.[f]	---
11	TfOH	$CHCl_3$	60	24	---	n.r.[f]	---
12	$Sc(OTf)_3$	$CHCl_3$	60	3	2.5	---	95 (97)[g]
13	$Sc(OTf)_3$	$CHCl_3$	60	3	3[h]	---	65
14	---	$CHCl_3$	---	---	3.5[i]	74	23

[a]Reaction conditions: **1a** (0.20 mmol), methyl acetoacetate (0.26 mmol), $Sc(OTf)_3$ (20 μmol), 4 Å MS (50 mg), solvent (1.0 mL), benzylamine (0.40 mmol). [b]Isolated yield after column chromatography. [c]In CH_2Cl_2, THF, toluene, or $CHCl_3$. [d]Incomplete conversion of **1a**. [e]2,6-Di-*tert*-butylpyridine (30 mol %) added. [f]No reaction. [g]Yield of 4.00 mmol scale of **1a** in parentheses. [h]At 80 °C. [i]Reaction of intermediate **2a** (0.20 mmol) with benzylamine (2.0 equiv) and 4 Å MS (50 mg) in $CHCl_3$ (1.0 mL) at 60 °C.

however, 10 mol % $Sc(OTf)_3$ in $CHCl_3$ at 60 °C was found to be the optimal catalytic system to form **2a** in 97% yield within 3 h (entry 8). Treatment of **1a** with a preformed enaminone from methyl acetoacetate and benzylamine in the presence of a Lewis acid led to no reaction. Control experiments in the presence of 2,6-di-*tert*-butylpyridine (DTBP) as a selective proton scavenger were performed to distinguish between Lewis acid and "hidden Brønsted acid" catalysis.[17] When DTBP was added to the $Sc(OTf)_3$-catalyzed reaction, no significant change of the reaction time or the product yield was observed (entry 9). Interestingly, replacement of the Sc(III)-catalyst by TfOH with or without the addition of DTBP resulted in no reaction in both cases (entries 10–11). These experiments excluded a Brønsted acid-catalyzed transformation and supported a Lewis acid-catalyzed pathway.

After complete formation of intermediate **2a** monitored by TLC, excess benzylamine was added at 60 °C. Product **3a** was obtained as a single diastereomer in 95% yield after 2.5 days. This result could be reproduced on gram-scale to obtain 1.71 g (97%) of **3a** under identical reaction conditions (Table 1, entry 12). Its relative configuration was determined by X-ray crystal structure

Scheme 2. Substrate Scope from Various Oxime Ethers 1[a]



[a]Reaction conditions: **1** (0.20 mmol), methyl acetoacetate (0.26 mmol), $Sc(OTf)_3$ (20 μmol), 4 Å MS (50 mg), $CHCl_3$ (1.0 mL), benzylamine (0.40 mmol). Isolated yields after column chromatography. [b]EDG = electron-donating group. [c]Multispot-TLC after first step. [d]EWG = electron-withdrawing group. [e]First step occurred at rt to 60 °C.

analysis (see SI). Further heating to 80 °C in the second step of the 3CR did not result in a shorter reaction time, but in a significantly reduced product yield (entry 13). Finally, condensation of **2a** with benzylamine in the absence of $Sc(OTf)_3$ only provided 23% of product **3a** together with 74% of recovered compound **2a** (entry 14). Based upon this result, we conclude that $Sc(OTf)_3$ is the most likely catalyst for both steps of the 3CR.[18]

The substrate scope of the 3CR was initially studied by the variation of substituents at the 2-hydroxy oxime ether **1**. We picked substituents that would either stabilize or destabilize the putative 1-azaallyl cations (Scheme 2). In the 3CR with methyl acetoacetate and benzylamine, oxime ethers **1** containing 2-aryl groups with electron-donating residues in the *meta*- or *para*-position typically furnished the tetrahydroindeno[2,1-*b*]pyrroles **3b** and **3d–j** in excellent overall yield. The *ortho*-tolyl substituted 2-hydroxy oxime ether **1c** gave rise to a mixture of recovered starting material and decomposition products, which can be explained by steric repulsion of the *ortho*-methyl group with the neighboring substituents in the 1-azaallyl cation intermediate. Introduction of a highly electron-rich *N*,*N*-dimethylamino phenyl substituent (**1k**) delivered **3k** in a moderate yield of 46% due to some decomposition of the corresponding 1-azaallyl cation. 2-Hydroxy oxime ethers with benzannulated (**1l**) or heteroaryl residues (**1m**) were also tolerated in the 3CR providing **3l** and **3m** in 94% and 66% yields, respectively. Despite electron-withdrawing aryl-substituents decreasing the

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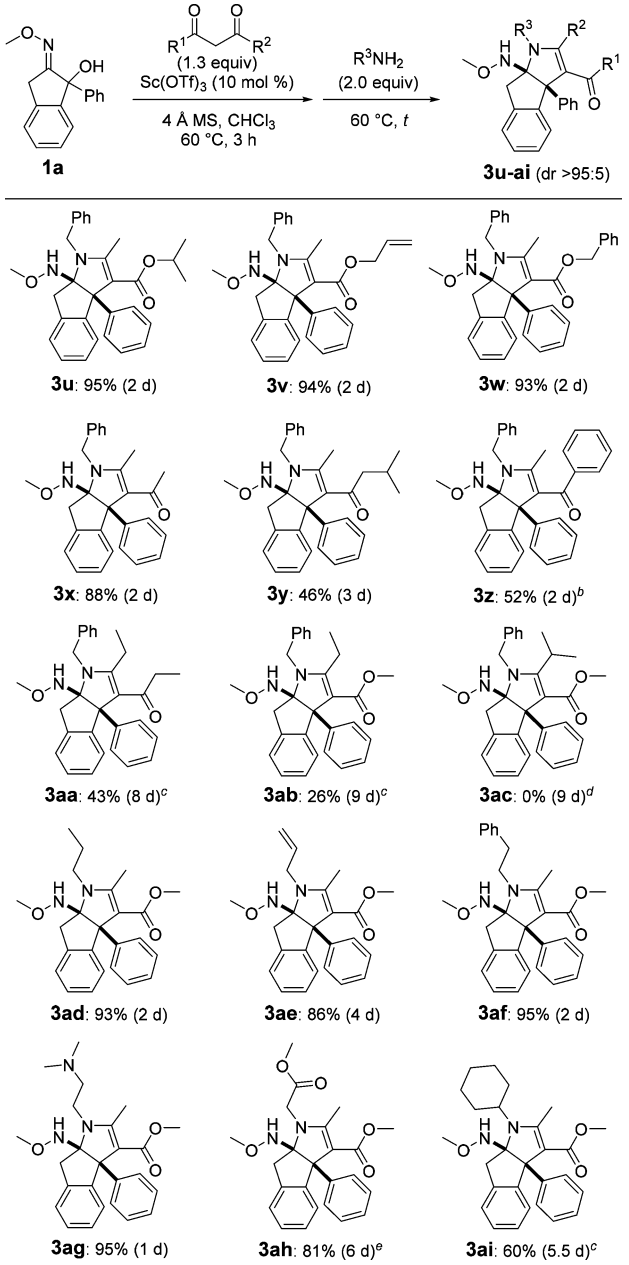
Scheme 3. Substrate Scope from Various Dicarbonyl Compounds and Amines[a]

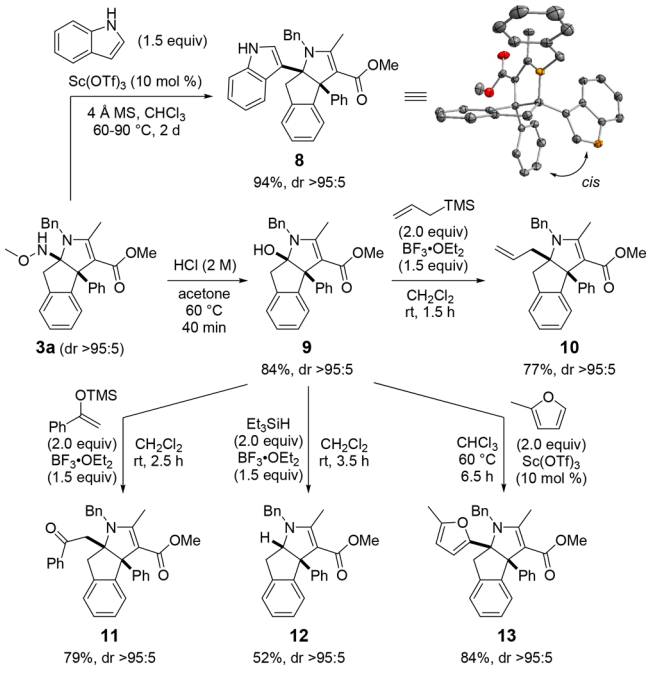


[a]Reaction conditions: **1a** (0.20 mmol), 1,3-dicarbonyl (0.26 mmol), $Sc(OTf)_3$ (20 μmol), 4 Å MS (50 mg), $CHCl_3$ (1.0 mL), amine (0.40 mmol). Isolated yields after column chromatography. [b]First step required 5 h. [c]Incomplete product formation. [d]No reaction in the second step at 60–90 °C. [e]4.0 equiv of amine used.

reactivity of the 2-hydroxy oxime ethers **1**, the products **3n–q** were isolated in excellent yields, but required longer reaction times for the first step. Aryl groups (R^2) could also be replaced by alkyl groups to furnish the tetrahydroindeno[2,1-*b*]pyrroles **3r–t** in moderate yield. The secondary alcohol **1u**, as well as other 2-hydroxy oxime ethers (**4–7**) proved to be unreactive under these reaction conditions or gave rise to decomposition products.

Different 3-oxobutanoic esters were investigated in the reaction with **1a** followed by condensation with benzylamine to furnish **3u–w** in excellent yields (Scheme 3). In addition, 1,3-diketones provided the tetrahydroindeno[2,1-*b*]pyrroles **3x–z** regioselectively in moderate to good yields. Increasing the steric hindrance of the substituent R^2 from methyl to ethyl or *iso*-propyl resulted either in incomplete conversion of the respective intermediates **2** into the products **3aa** and **3ab** or in no reaction with benzylamine (for **3ac**). In the latter case, only the corresponding intermediate **2** was isolated in 81% yield (dr ≈ 1:1). Increasing the temperature of the second step to 90 °C did not improve the outcome of the 3CR in these cases. Also, tetrahydroindeno[2,1-*b*]pyrrole products **3ad–ah** were synthesized from **1a**, methyl acetoacetate, and functionalized amines with more than 80% overall yields. With cyclohexylamine, **3ai** was isolated in 60% yield along with 28% of **2a**.

Scheme 4. Derivatization of 3a



Tetrahydroindeno[2,1-*b*]pyrroles **3** contain an aminal moiety that is ideally suited for further manipulation. Along these lines, **3a** was reacted with indole as a π-nucleophile in the presence of 10 mol % $Sc(OTf)_3$ at 60–90 °C. The methoxyamino group was cleaved under these conditions to form an iminium ion, which was attacked by indole. Thus, 2-hydroxy oxime ethers **1** can be regarded as latent tris-electrophiles. The substitution product **8** was formed in 94% yield with complete retention of the relative configuration as proven by the crystal structure (see SI for more details).[19] As the aminal **3a** could not be directly substituted by other nucleophiles under Lewis acidic conditions, it was converted into the more reactive hemiaminal **9** by hydrolysis. The $BF_3{\cdot}OEt_2$-promoted Hosomi–Sakurai reaction of **9** with allyltrimethylsilane delivered compound **10** in 77% yield and as a single diastereomer. These reaction conditions were also applied in a Mannich reaction with a silyl enol ether, as well as a reduction with triethylsilane to furnish **11** and **12**, respectively, with good yields. Finally, the $Sc(OTf)_3$-catalyzed aza-Friedel–Crafts alkylation of **9** with 2-methylfuran provided **13** in 84% yield (Scheme 4).

In summary, we have developed a highly efficient, chemo- and diastereoselective synthesis of tetrahydroindeno[2,1-*b*]pyrroles **3** via (2 + 2 + 1)-cycloannulation of 2-hydroxy oxime ethers **1**, 1,3-dicarbonyl compounds, and primary amines through a putative 1-azaallyl cation as the key intermediate. The optimal

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protocol for this sequential three-component reaction features a catalytic and easily scalable process, readily accessible starting materials, operational simplicity with no necessity for an inert atmosphere, high functional group tolerance, typically excellent yields, and complete diastereoselectivity. Moreover, manipulation of the obtained products by substitution of the aminal with different π-nucleophiles reveals the broad utility of the present methodology to form complex nitrogen heterocycles. Current investigations are being directed toward detailed mechanistic insights into the generation of 1-azaallyl cations and their full exploitation in novel and stereoselective C−C-bond forming events.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01205.

Experimental procedures, characterization data, and X-ray structures of **3a** and **9** (PDF)

Accession Codes

CCDC 1817406−1817407 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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