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FULL PAPER

A Novel $Sc(OTf)_3$-Catalyzed (2+2+1)-Cycloannulation/Aza-Friedel-Crafts Alkylation Sequence toward Multicyclic 2-Pyrrolines

Marcel Schlegel,[a] Peter Coburger,‡[b] and Christoph Schneider*[a]

Abstract: The rapid assembly of molecular complexity continues to be at the forefront of novel reaction development. In the pursuit of that goal, we herein report a novel $Sc(OTf)_3$-catalyzed, one-pot multicomponent reaction, that furnishes complex multicyclic 2-pyrrolines with excellent overall yields and perfect diastereocontrol. This process is based on our previously established (2+2+1)-cycloannulation of *in situ*-generated 1-azaallyl cations, 1,3-dicarbonyls and primary amines. The newly formed and highly reactive aminal moiety is readily substituted with indoles and pyrroles both as external and internal π-nucleophiles to provide densely functionalized *N*-heterocycles with four new σ-bonds and two vicinal quaternary stereogenic centers. In addition, DFT-calculations have been conducted to further characterize the intermediate 1-azaallyl cations.

Introduction

The Lewis acid-catalyzed generation of new C–C-bonds represents one of the most fundamental transformations in modern organic chemistry, because of their broad application in the synthesis of natural products and pharmaceutically interesting compounds.[1] Among the different types of Lewis acids, that have been discovered in the past decades, $Sc(OTf)_3$ stands out as one of the most powerful and useful catalysts to date.[2] In 1993, Kobayashi *et al.* first demonstrated the use of $Sc(OTf)_3$ as a highly reactive and environmentally friendly catalyst in Diels-Alder reactions.[3] As a special bonus, $Sc(OTf)_3$ has been shown to be effective in aqueous medium as well and can be easily recycled after work-up without loss of reactivity.[3,4]

Although the majority of $Sc(OTf)_3$-catalyzed processes concentrate on the activation of C=X π-bonds,[5] significant progress has been made toward the cleavage of C–X σ-bonds in recent years as well.[6] In particular, nucleophilic substitution reactions of alcohols can be efficiently catalyzed by $Sc(OTf)_3$ in the light of the water tolerance of the catalyst. However, these transformations usually require substrates with resonance-stabilizing groups and strong π-nucleophiles, for example in Friedel-Crafts alkylation reactions with (hetero-)arenes.[7]

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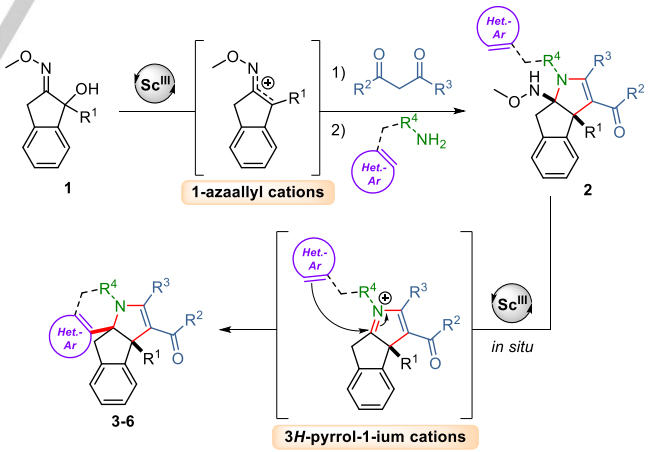
Supporting information for this article can be found under:

The rapid construction of complex, multicyclic scaffolds with full stereochemical control is without doubt of high relevance in the context of the discovery of novel drug candidates. In this respect, the aza-Friedel-Crafts reaction (aza-FCR) and its intramolecular counterpart, the Pictet-Spengler reaction, represent highly important transformations toward the synthesis of nitrogen-containing, biologically active products.[8] For these processes, aldehyde-based imines and iminium ions have been frequently employed as substrates.[9,10] However, the formation of quaternary, α-amino-substituted stereogenic centers from ketone-derived imines with (hetero)arenes have been studied to a far lesser extent, presumably due to the lower reactivity of ketimines which typically require strongly electron-withdrawing adjacent groups.[11] Hemiaminals[12] and enamides[13] have also been reported to generate iminium ions which were captured by heteroarenes *in situ*. Despite the success with some ketone-derived aza-FCR, new preparative approaches are highly desired to form C–C-bonds in electronically and sterically less favorable cases.

We recently discovered the facile dehydration of tertiary 2-hydroxy oxime ethers **1** with catalytic amounts of $Sc(OTf)_3$ to generate resonance-stabilized 1-azaallyl cations. These highly reactive intermediates were trapped by 1,3-dicarbonyls to form a new all-carbon quaternary stereogenic center. Condensation of the dicarbonyl moiety with primary amines *in situ* furnished highly complex 2-pyrrolines **2** with an aminal group in an overall one-pot transformation.[14]



Scheme 1. Conceptualization of this work.

Based upon this work, we have now developed an extended process, in which electron-rich indoles and pyrroles were added *in situ* as the fourth component to provide densely functionalized and highly substituted 2-pyrrolines **3** with excellent overall yields and perfect diastereoselectivity. The newly formed aminal moiety of **2** was readily cleaved into an iminium ion under Sc(III)-catalysis and underwent an aza-FCR with the electron-rich heteroarene in an overall four-component reaction (4CR). Moreover, the

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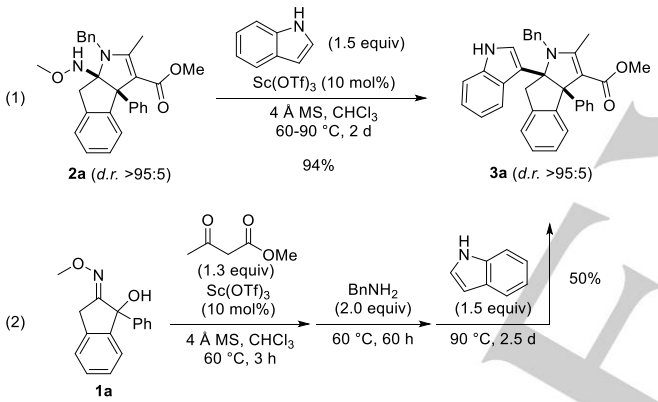
heteroaromatics could be tethered to the amine in the form of tryptamine or other 2-(heteroaryl)ethylamines to generate indolizine-derived multicyclic scaffolds **4**–**6** in a Pictet-Spengler transformation with complete diastereocontrol (Scheme 1).

Results and Discussion

Initial investigations commenced with the aza-FCR between 2-pyrroline **2a** and indole with 10 mol% $Sc(OTf)_3$ at elevated temperature according to our previous report. The indolyl-substituted tetrahydroindeno[2,1-*b*]pyrrole **3a** was isolated as a single diastereomer with excellent yield (Scheme 2, eq. (1)).[14]

Due to the straightforward and high-yielding conversion of the aminal **2a** into the product **3a**, we strove to establish a more challenging 4CR, in which **2a** is formed first from 2-hydroxy oxime ether **1a**, methyl acetoacetate and benzylamine under the reported conditions of the 3CR[14] and then treated with indole *in situ*. To our delight, the formation of 2-pyrroline **3a** was observed but the overall product yield was relatively poor (Scheme 2, eq. (2)).

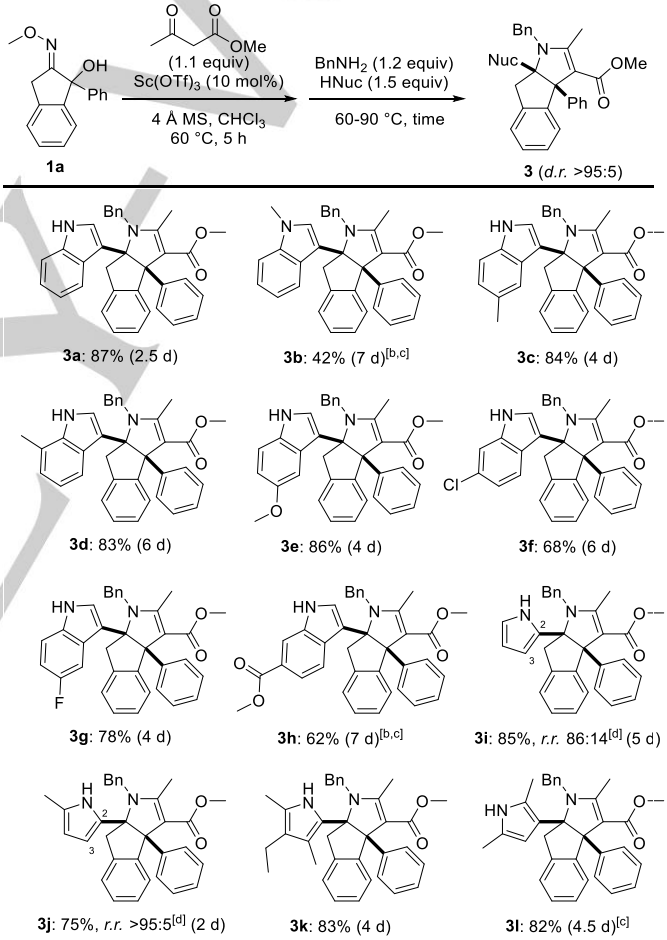


Scheme 2. Aza-FCR of **2a** with indole[14] and first 4CR from **1a**.

After further optimization studies (see Supporting Information (SI)), we found that the amount of the primary amine in the reaction mixture was crucial for the final aza-FCR with indole. A large excess of benzylamine presumably inhibited the catalytic activity of $Sc(OTf)_3$ in this reaction. Therefore, reducing the equivalents of methyl acetoacetate and benzylamine down to 1.1 equiv. and 1.2 equiv., respectively, and adding benzylamine and indole together in the second step resulted in complete conversion of reaction intermediates into the desired product **3a** as monitored by TLC. Thus, the indolyl-substituted 2-pyrroline **3a** was obtained with 87% yield as a single diastereomer using the optimized reaction conditions (Table 1).

The substrate scope of this new sequential 4CR was then studied with further electron-rich heteroaromatics as the fourth component (Table 1). Indoles with electron-donating substituents typically furnished the products **3c**–**e** with very good yields. In contrast, *N*-methyl indole was not sufficiently nucleophilic to drive the reaction to completion, even after heating to 110 °C. Therefore, **3b** was isolated in only 42% yield. Indoles with electron-withdrawing groups, however, were readily tolerated and provided the products **3f**–**h** in acceptable yields. Other heteroaromatic compounds including pyrroles, furans and thiophenes were also tested, but only pyrroles proved to be sufficiently reactive to form the 2-pyrrolines **3i**–**k** with yields up to 85%. As we had shown previously that furans as well as other electronrich π-nucleophiles were readily added to the more reactive hemiaminal with good chemical yields,[14] the rate-determining step of this sequence appears to be the cleavage of the aminal and formation of the iminium ion. Not surprisingly, the regioselectivity of the electrophilic aromatic substitution was always in favor of the 3-position in the indole and the 2-position in the pyrrole series (except for **3l**).

Table 1. Substrate scope of the 4CR.[a]



[a] Reaction conditions: **1a** (0.20 mmol), methyl acetoacetate (0.22 mmol), $Sc(OTf)_3$ (20 μmol), 4 Å MS (50 mg), $CHCl_3$ (1.0 mL), benzylamine (0.24 mmol), nucleophile (0.30 mmol). Isolated yields after column chromatography. [b] Incomplete product formation. [c] Second step occurred at 60–110 °C. [d] Regioisomeric ratio refers to position 2 and 3 of pyrrole.

We next envisioned an intramolecular version of the aza-FCR in which the amine component was tethered to the reactive π-nucleophile in the form of 2-(heteroaryl)ethylamines (Table 2). The 3CR between 2-hydroxy oxime ether **1a**, 1.3 equivalents of

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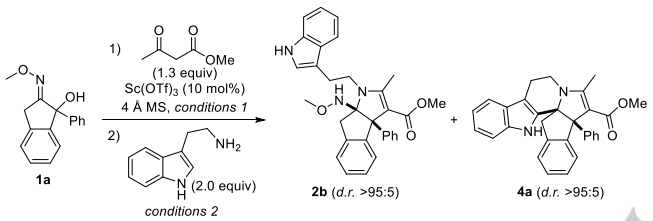
methyl acetoacetate and 2.0 equivalents of tryptamine together with 10 mol% $Sc(OTf)_3$ at 60 °C furnished almost exclusively the aminal **2b** (entry 1). Increasing the temperature to 90 °C in the second step (entry 2) or adding acetic acid at 90 °C (entry 3) resulted in an incomplete cyclization of **2b** into **4a** in both cases. Some high-boiling solvents were also tested for the $Sc(OTf)_3$-catalyzed process. Although full consumption of the intermediate **2b** was observed by TLC, the overall product yields of **4a** obtained after column chromatography remained below our expectations (entries 4–7). The key to the success of this reaction was again the reduction of the amount of the 2-(heteroaryl)ethylamine. Thus, using only 1.2 equiv. of methyl acetoacetate and 1.3 equiv. of tryptamine in chloroform as the solvent gave rise to the desired tetrahydro-β-carboline **4a** with an excellent overall yield of 98% (entry 8). Accordingly, we settled on these optimized reaction conditions for a full study of the substrate scope.

Table 2. Optimization studies.[a]

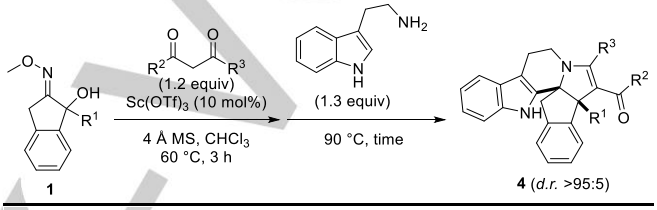


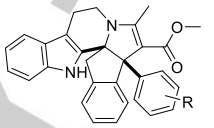
entry	conditions 1	conditions 2	yield 2b [%][b]	yield 4a [%][b]
1	$CHCl_3$, 60 °C, 3 h	60 °C, 44 h	89	traces
2	$CHCl_3$, 60 °C, 3 h	90 °C, 63 h	27	70
3	$CHCl_3$, 60 °C, 3 h	AcOH (2.0 equiv), 90 °C, 78 h	11	83
4	CH_3NO_2, 110 °C, 0.75 h	110 °C, 20 h	0	78
5	$C_2H_4Cl_2$, 110 °C, 0.75 h	110 °C, 20 h	0	80
6	toluene, 110 °C, 0.75 h	110 °C, 20 h	0	88
7[c]	toluene, 110 °C, 3 h	110 °C, 18 h	0	87
8[c]	$CHCl_3$, 60 °C, 3 h	90 °C, 40 h	0	98

[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), tryptamine (0.40 mmol). [b] Isolated yields after column chromatography. [c] 1.2 Equiv. of methyl acetoacetate and 1.3 equiv. of tryptamine used.

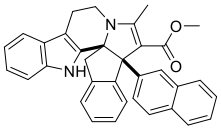
Based on the scope and limitations of our previous work,[14] we screened different indanone-derived 2-hydroxy oxime ethers **1** as well as 1,3-dicarbonyl compounds (Table 3). Substrates **1** with electron-rich aryl groups (R^1) provided the corresponding products **4b**–**h** in good to quantitative yields within two days. The 2-naphthyl substituted *N*-heterocycle **4i** was obtained under identical reaction conditions in 86% overall yield. Electron-withdrawing residues in *para*-position at the phenyl substituent of **1** delivered **4j**–**l** with high yields but required longer reaction times for both steps of the 3CR as well as higher temperatures for completion, presumably through destabilization of the reactive intermediates. Alkyl groups (R^1) were also successfully employed to furnish **4m**–**n**, albeit with slightly reduced overall product yields. The reaction between 2-hydroxy oxime ether **1a** (R^1 = Ph), various 3-oxobutanoic esters and tryptamine gave rise to tetrahydro-β-carbolines **4o**–**s** with yields exceeding 80%. Furthermore, 1,3-diketones like acetylacetone led to the formation of **4t** with 78% yield after 64 h. Although the replacement of the methyl-substituent (R^3) by an ethyl group proved to be almost unreactive for the condensation with benzylamine,[14] the reaction of **1a** with methyl 3-oxopentanoate and tryptamine provided the indolizine-derived product **4u** in acceptable yield.

Table 3. Substrate scope of the 3CR with tryptamine.[a]

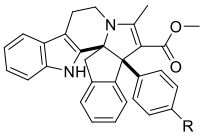




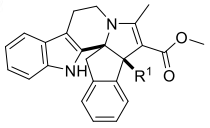
4b: R = 3-Me, >99% (25 h)
4c: R = 4-Me, 97% (25 h)
4d: R = 4-*t*-Bu, 97% (24 h)
4e: R = 3-OMe, 94% (25 h)
4f: R = 4-OMe, 80% (20 h)
4g: R = 3,4-OCH_2O, 75% (43 h)
4h: R = 4-Ph, 60% (25 h)



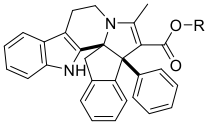
4i: 86% (32 h)



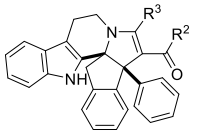
4j: R = Cl, 98% (92 h)[b,c]
4k: R = F, 89% (92 h)[b,c]
4l: R = CF_3, 86% (92 h)[b,c]



4m: R^1 = Me, 75% (21 h)
4n: R^1 = Bu, 56% (45 h)



4o: R = Et, 84% (24 h)
4p: R = *i*-Pr, 92% (23 h)
4q: R = *i*-Bu, 85% (32 h)
4r: R = allyl, 95% (17 h)
4s: R = Bn, 92% (24 h)



4t: R^2 = R^3 = Me, 78% (64 h)[c]
4u: R^2 = OMe, R^3 = Et, 71% (122 h)[c]

[a] Reaction conditions: **1** (0.20 mmol), methyl acetoacetate (0.24 mmol), $Sc(OTf)_3$ (20 μmol), 4 Å MS (50 mg), $CHCl_3$ (1.0 mL), tryptamine (0.26 mmol). Isolated yields after column chromatography. [b] First step required 24 h. [c] Second step occurred at 90–110 °C.

Moreover, the substrate scope was extended to other functionalized amines (Table 4). With 2-(indol-2-yl)ethylamine the tetrahydro-β-carbolines **5a**–**h** were obtained with yields above 90% in almost all cases studied. Also 2-(pyrrol-2-yl) ethylamine could be successfully employed to furnish **6a**–**f** in almost quantitative yields. Finally, 2-(3,4-dimethoxyphenyl) ethylamine was tested for the 3CR, but unfortunately, a complex product mixture was obtained. This result underlines the limitation of our

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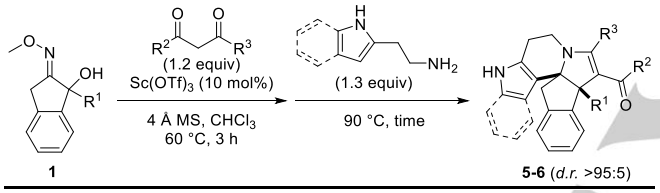
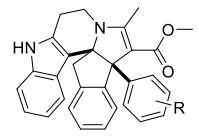
4CR (see Table 1), in which exclusively indoles or pyrroles were sufficiently reactive to undergo inter- or intramolecular aza-FCR.

In order to verify the three-dimensional, complex structure of the multicyclic compounds **4**–**6**, single crystals were obtained from a saturated solution of **4p** in CH_2Cl_2 and analyzed by X-ray crystal structure analysis (Scheme 3, see SI for more details). The phenyl substituent and the indole moiety of **4p** showed a *cis*-configuration. A rational design to explain the diastereo-selective outcome of the reaction is put forth in Scheme 3. After formation of enaminone **8**, the *syn*-addition of the secondary amine onto the electrophilic oxime ether takes place in a 5-*exo*-*trig*-cyclization. This mechanism was supported by X-ray crystal structure analysis of the 2-pyrrolines **2** in our previous work.[14] The resulting aminal **9** undergoes a Sc(III)-catalyzed cleavage of methoxyamine to generate the strained 3*H*-pyrrol-1-ium cation **10**. Due to the curved shape of the tricyclic system, the indole moiety can attack at the convex or the concave side. The Pictet-Spengler reaction occurs exclusively at the convex side since the concave one is sterically not accessible. Consequently, the *cis*-diastereomer of **4p** is the single product formed under these reaction conditions.

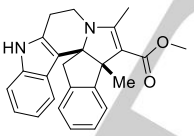
Table 4. Substrate scope of the 3CR with other 2-(heteroaryl)ethylamines.[a]



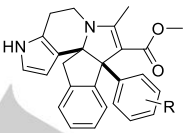
1 → **5-6** (*d.r.* >95:5)



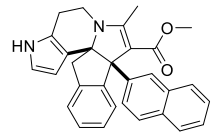
5a: R = H, 94% (24 h)
5b: R = 3-Me, >99% (43 h)[b]
5c: R = 4-Me, 95% (43 h)
5d: R = 4-*t*-Bu, 96% (25 h)
5e: R = 3-OMe, >99% (43 h)
5f: R = 4-Cl, 95% (70 h)[b,c]
5g: R = 4-CF_3, 93% (70 h)[b,c]



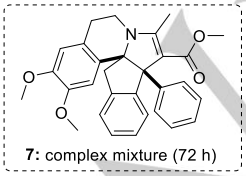
5h: 87% (19 h)



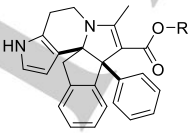
6a: R = H, >99% (24 h)
6b: R = 3-Me, 94% (20 h)
6c: R = 4-F, >99% (20 h)



6d: >99% (20 h)



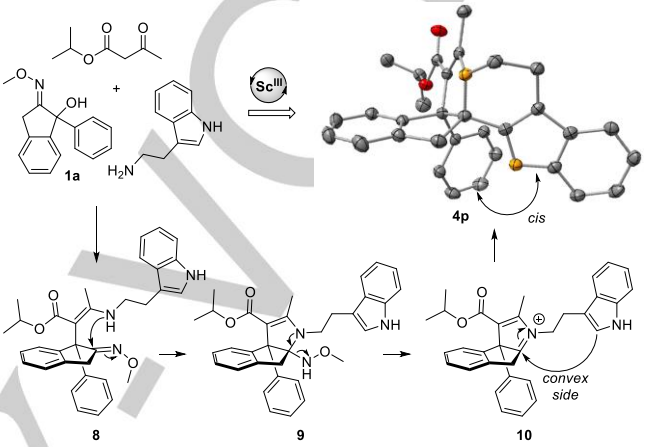
7: complex mixture (72 h)



6e: R = *i*-Pr, 91% (24 h)
6f: R = allyl, 90% (24 h)

[a] Reaction conditions: **1** (0.20 mmol), methyl acetoacetate (0.24 mmol), $Sc(OTf)_3$ (20 μmol), 4 Å MS (50 mg), $CHCl_3$ (1.0 mL), 2-(heteroaryl)ethylamine (0.26 mmol). Isolated yields after column chromatography. [b] Second step occurred at 90–110 °C. [c] First step required 24 h.

The key intermediates in our previous[14] as well as in the present work were considered to be 1-azaallyl cations. DFT-calculations were carried out to characterize these reactive species. The electronic structures of allyl cation **11**, α-(*N*-methoxy)imino carbocation **12**, α-(*N*-methyl)imino carbocation **13** and α-oxy carbocation **14** in the parent simple allylic systems (Table 5), as well as in the indanone-based systems (see SI) were calculated at the M06-2X/def2-TZVP level.

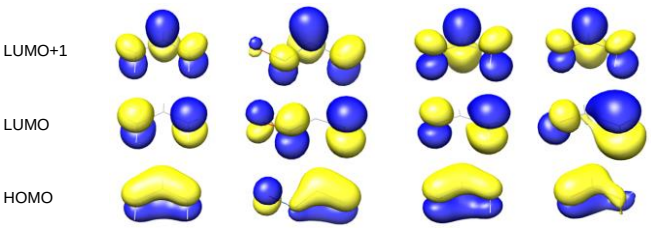


Scheme 3. Stereochemical model for the *cis*-diastereoselectivity of **4**.

Table 5. Comparison of allylic carbocations at the M06-2X/def2-TZVP level.[a]

M06-2X/def2-TZVP	**11**	**12**	**13**	**14**
Mayer bond order	1.4 (C=C) 1.4 (C–C)	1.5 (C=N) 1.3 (C–C) 1.3 (O–N)	1.7 (C=N) 1.2 (C–C)	2.0 (C=O) 1.0 (C–C)
Allylic LUMO+1	–4.5 eV	–4.6 eV	–5.1 eV	–5.8 eV
LUMO+1 comp.	31/39/31	3(O)/18(N)/43/29	26/47/23	24/52/20
Allylic LUMO	–9.3 eV	–9.2 eV	–10.4 eV	–11.5 eV
LUMO comp.	42/12/42	16(O)/35(N)/9/39	30/10/56	17/8/68
Allylic HOMO	–17.1 eV	–16.6 eV	–18.6 eV	–20.3 eV
HOMO comp.	24/44/26	22(O)/10(N)/38/28	37/43/16	49/40/9

Kohn-Sham orbitals (surface isovalue = 0.06)



[a] The allylic HOMO corresponds to the HOMO−1 for the α-(*N*-methyl)imino carbocation **13** and the α-oxy carbocation **14**, respectively. Orbital compositions are derived from Loewdin population analysis. Note that the cyclic form ($\oplus$○△) is preferred for the α-oxy carbocation **14** ($\Delta G°$ = 26.6 kcal/mol).

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The comparison of the Mayer bond orders of the four allylic systems implies that the electronic structure of the α-(*N*-methoxy)imino carbocation **12** resembles the allyl cation **11** more closely than **13** or **14**. It is noteworthy that replacing the methoxy group of **12** by a methyl group (**13**) results in an electronic structure that is intermediate between a 1-azaallyl cation and a α-imino carbocation. These interpretations are supported by the energies and compositions of the Kohn-Sham orbitals, which represent the allylic systems of these cations and display the same trends. Our results are in agreement with previous wavefunction theory calculations by Creary *et al.* who have already mentioned the almost identical electronic nature of the allyl cation **11** and the α-(*N*-methoxy)imino carbocation **12**.[15] The exact same trends can be derived for the indanone-based systems (see SI for more details). These results indicate that the reactive intermediates in the present work can be considered as 1-azaallyl cations rather than simple α-(*N*-methoxy)imino benzylic carbocations.

Conclusions

In summary, we have developed a highly efficient, chemo- and diastereoselective synthesis of complex 2-pyrrolines by virtue of three- and four-component reactions. The Lewis acid-catalyzed (2+2+1)-cycloannulation of 2-hydroxy oxime ethers **1**, 1,3-dicarbonyl compounds and primary amines followed by an inter- or intramolecular aza-FCR with indoles or pyrroles *in situ* furnished densely functionalized *N*-heterocycles **3**–**6** with typically excellent yields. Furthermore, the present methodology benefits from easily accessible starting materials, the operational simplicity with no necessity for an inert atmosphere, the multi-catalytic role of $Sc(OTf)_3$ and the broad substrate scope. In addition, DFT-calculations at the M06-2X/def2-TZVP level revealed the electronic structure of 1-azaallyl cations which were considered to be the key intermediates in this work. Current investigations are being directed at the full application of these reactive electrophilic species in novel, stereoselective C─C-bond forming processes.

Experimental Section

General procedure for compounds **4**: 2-Hydroxy oxime ether **1** (0.20 mmol, 1.0 equiv), a 1,3-dicarbonyl compound (0.24 mmol, 1.2 equiv), $Sc(OTf)_3$ (20 μmol, 0.10 equiv) and 4 Å molecular sieves (50 mg) were placed in an oven dried and sealable DURAN® test tube. Absolute $CHCl_3$ (1 mL) was added and the reaction mixture was heated to 60 °C while stirring. After complete consumption of **1**, tryptamine (0.26 mmol, 1.30 equiv) was added and it was stirred for the indicated time at 90 °C. The reaction mixture was quenched with sat. $NaHCO_3$-solution and extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude products were purified by flash column chromatography (MTBE/hexane). Compounds **4** were dried *in vacuo* (~0.1 mbar) at 60 °C overnight.

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Keywords: tertiary alcohols • Lewis acid catalysis • 1-azaallyl cations • multicomponent reactions • aza-Friedel-Crafts reaction

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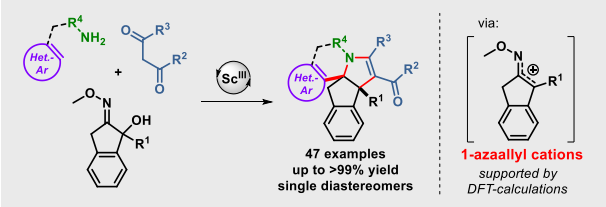

Creating complexity: A highly chemo- and diastereoselective synthesis of densely functionalized, multicyclic 2-pyrrolines by $Sc(OTf)_3$-catalyzed multicomponent reactions of *in situ*-generated 1-azaallyl cations was established. A sequential dehydration/C–C-coupling/enaminone-aminal formation/aza-Friedel-Crafts reaction was initiated to furnish complex *N*-heterocycles with excellent yields in a one-pot operation.

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A Novel $Sc(OTf)_3$-Catalyzed (2+2+1)-Cycloannulation/Aza-Friedel-Crafts Alkylation Sequence toward Multicyclic 2-Pyrrolines