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A simple one-pot, three-component, catalytic, highly enantioselective isoxazolidine synthesis

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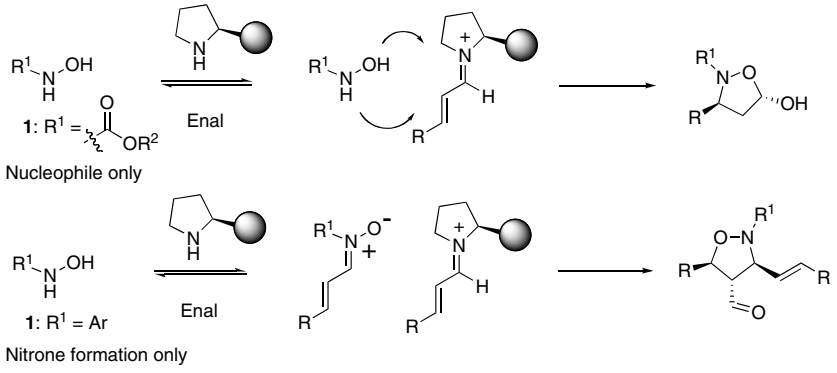
Abstract—The highly chemo- and enantioselective organocatalytic three-component reaction between *N*-arylhydroxylamines, aldehydes and α,β-unsaturated aldehydes is presented; the reaction gives access to isoxazolidines in high yields with >25:1 dr and 91–99% ee.

Isoxazolidines are valuable chiral building blocks,[1] which are readily converted to γ-amino alcohols, β-amino acids and β-lactams.[1,2] Thus, asymmetric methods that mainly rely on 1,3-dipolar cycloaddition reactions have been developed for their preparation.[1–3] In this area, Lewis-acid catalyzed enantioselective cycloaddition transformations between nitrones and electron-deficient alkenes (normal electron demand reaction) have been successfully employed for the synthesis of isoxazolidines.[3] More recently, MacMillan first reported an organocatalytic enantioselective synthesis of isoxazolidines based on the chiral imidazolidinone catalyzed reaction between preformed nitrones and enals.[4] Iminium activation which is central in this type of catalysis has been successfully used in several asymmetric reactions.[4–10] In this context, we recently reported that chiral pyrrolidines catalyze the formation of 5-hydroxyisoxazolidines via an asymmetric tandem aza-Michael/cyclization reaction pathway (Eq. 1).[9b]

There are several chemoselectivity issues that could arise in the amine conjugate addition step, such as non-productive imine formation and a racemic side reaction. However, the pK_a of the *N*-carbamate protected amine **1** together with the subsequent intramolecular cyclization controls the reaction pathway and pushes the equilibrium towards product formation. Intrigued by this, we became interested in whether simply changing the pK_a of amine **1** could modify its nucleophilicity towards the previously undesired 1,2-addition to the enal (Eq. 2).



(1)

(2)

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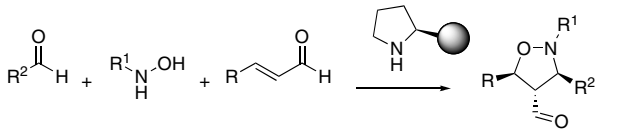
This would lead to in situ nitrone formation and the possibility for a completely different reaction to occur with the activated enal, which would give the corresponding isoxazolidine and not the 5-hydroxyisoxazolidine. Notably, if the inherent chemoselectivity issues could be controlled there would be a possibility for this catalytic enantioselective process to be the foundation for a novel one-pot, three-component reaction (Eq. 3). To the best of our knowledge, no report of a catalytic highly enantioselective isoxazolidine synthesis based on an asymmetric multi-component 1,3-dipolar cycloaddition has been disclosed to date.[11]



(3)

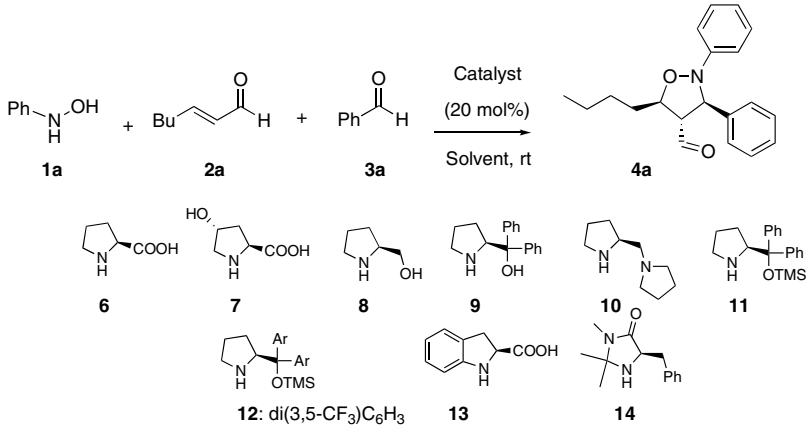
Herein, we present a highly chemo-, distereo- and enantioselective one-pot, three-component catalytic route to the synthesis of valuable isoxazolidines (58–74% yield, >25:1 dr, 91–99% ee).

In an initial catalyst screen for the reaction between *N*-phenylhydroxylamine **1a** (0.5 mmol), enal **2a** (0.25 mmol) and benzaldehyde **3a** (0.5 mmol), we found that proline **6**, proline derivative **7** and simple chiral pyrrolidines such as **9**, **11** and **12** catalyzed the chemoselective formation of isoxazolidine **4a** (Table 1). Aldehyde **4a** slightly epimerized upon silica-gel column chromatography. We therefore reduced it in situ with $NaBH_4$, to the more stable alcohol **5a**. For example, (*S*)-proline catalyzed the formation of *ent*-**4a** in high yield as a single diastereomer (>25:1 dr, *endo*:*exo*) with 77% ee (entry 1). To our delight, the protected diarylprolinol **11**[12] catalyzed the formation of **4a** with high efficiency and excellent diastereo- and enantioselectivity (entry 6). The highest enantioselectivity was achieved when $CHCl_3$ or toluene was used as the solvent.

Thus, we decided to investigate the scope of the catalytic asymmetric one-pot, three-component reaction using $CHCl_3$ as the solvent and chiral amine **11** as the catalyst (Table 2).

The organocatalytic enantioselective three-component reactions were highly chemo-, diastereo- and enantioselective. The corresponding isoxazolidines **5** were obtained in 58–74% yield with >25:1 dr and 91–99% ee. For example, the reaction between *N*-4-chlorophenyl hydroxylamine **1b**, enal **2a** and aldehyde **3a** gave the corresponding product **5b** after in situ reduction in 65% yield with >25:1 dr and 97% ee (entry 2). The one-pot reaction with aliphatic acceptor aldehydes such as *iso*-valeraldehyde **3d** exhibited excellent chemo- and stereoselectivity (entry 7). Several useful functionalities such

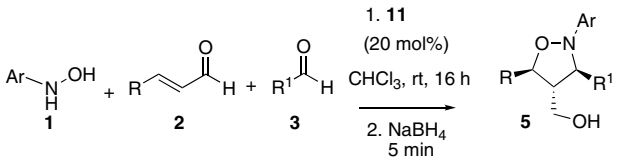
Table 1. Catalyst screen for the one-pot reaction between **1a**, **2a** and **3a**

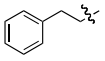


Entry	Catalyst	Solvent	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	**6**	$CHCl_3$	72	84	>25:1	77[d]
2	**7**	$CHCl_3$	182	22	>25:1	32[d]
3	**8**	Toluene	24	0	—	—
4	**9**	Toluene	16	24	>25:1	39
5	**10**	Toluene	24	0	—	—
6	**11**	$CHCl_3$	16	74	>25:1	98
7	**12**	$CHCl_3$	16	54	>25:1	93
8	**13**	$CHCl_3$	24	0	—	—
9	**14**	Toluene	24	0	—	—

[a] Isolated yield of the pure product **4a**.
[b] *endo*/*exo*-ratio determined by NMR analyses of the crude reaction mixture.
[c] Determined by chiral-phase HPLC analyses of alcohol **5a**.
[d] *ent*-**4a** was formed.

Table 2. Scope of the organocatalytic three-component reaction



Entry	Ar	R	R^1	Product	Yield[a] (%)	dr[b]	ee[c] (%)
1	Ph	*n*-Bu	Ph	**5a**	74	>25:1	98
2	4-ClC_6H_4	*n*-Bu	Ph	**5b**	65	>25:1	97
3	Ph		Ph	**5c**	68	>25:1	97
4	Ph	*n*-Bu	4-ClC_6H_4	**5d**	65	>25:1	99
5	Ph	CO_2Et	Ph	**5e**	63	>25:1	91
6	Ph	*n*-Bu	4-BrC_6H_4	**5f**	71	>25:1	99
7	Ph	*n*-Bu	*i*-Pr	**5g**	74	>25:1	97
8	Ph	*n*-Bu		**5h**	58	>25:1	99
9	Ph	*n*-Bu		**5i**	73	>25:1	97
10	Ph	Me	Ph	**5j**	71	>25:1	94
11	4-ClC_6H_4	*n*-Pr	4-$MeOC_6H_4$	**5k**	66	>25:1	99

[a] Isolated yield of the pure product **5** after silica-gel chromatography.
[b] *endo*/*exo*-ratio determined by NMR analyses of the crude reaction mixture.
[c] Determined by chiral-phase HPLC or GC analyses.

as aromatic, ester and olefins were tolerated on enal **2** and aldehyde **3** components. The reaction between hydroxylamine **1a**, heptenal and cinnamic aldehyde was highly chemoselective and the corresponding isoxazolidine **5i** was the only product formed in 73% yield with >25:1 dr and 97% ee (entry 9). Thus, the organocatalytic one-pot, three-component reactions showed that the substitution on amine **1** and enal **2** was very important in directing the outcome of the different possible catalytic reaction pathways (Eqs. 1–3). In fact, chiral amine **11**- or **12**-catalyzed asymmetric three-component reaction between hydroxylamine **1c**, heptenal **2a** and aldehyde **3a** gave the corresponding oxa-Michael product **15**, which is in accordance with Jørgensen,[10a] and not isoxazolidine **5l** (Eq. 4). Thus, by tuning the reactivity of hydroxylamines **1**, several completely different catalytic transformations can be achieved which lead to the formation of valuable compounds.

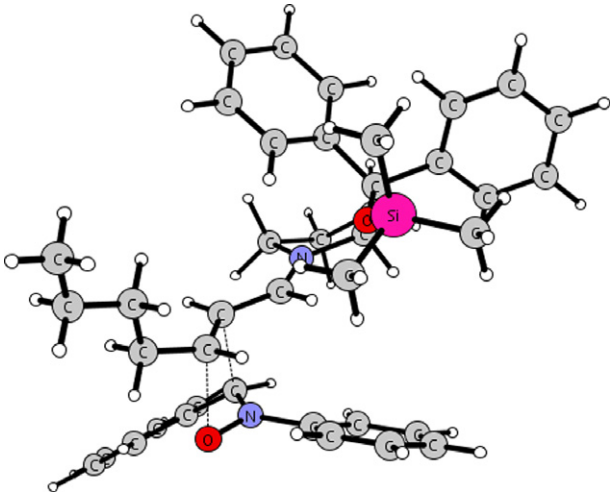
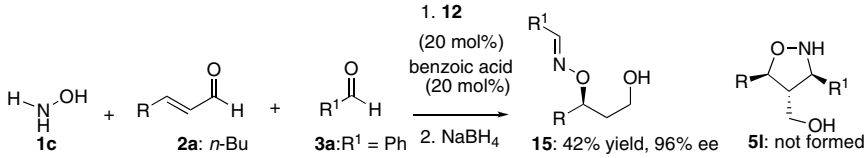


Figure 1. Proposed transition state.[14]



(4)

Comparison with the literature revealed that the absolute configuration of **5j** at C3, C4 and C5 was *R*, *R*, *R*, respectively.[13] Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups of **11** leads to stereoselective *Re*-facial *endo*-addition to the activated olefin via the plausible transition state depicted in Figure 1.

In the case of (*S*)-proline and its derivatives, the opposite facial attack occurs leading to formation of *ent*-**4**.

In summary, we have described a simple highly chemo-, diastereo- and enantioselective organocatalytic one-pot, three-component reaction between *N*-aryl hydroxylamines, aldehydes and α,β-unsaturated aldehydes.[15] The reaction represents a versatile asymmetric entry to a variety of valuable isoxazolidines in high yields with >25:1 dr and 91–99% ee. Mechanistic studies, synthetic applications of this transformation as well as development of other enantioselective multi-component reactions are ongoing in our laboratory.

Acknowledgements

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13. Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313, Compound **5j**: Colourless oil. $[\alpha]_D$ +135.2 (*c* 1.3, $CHCl_3$). IR (KBr): 3422, 1597 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$–6.71 (m, 10H), 4.53 (d, $J = 7.6$ Hz, 1H), 4.17 (dq, $J = 8.6$ Hz, 6.2 Hz, 1H) 3.78–3.65 (m, 2H), 2.47–2.38 (m, 1H), 1.47 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.2, 142.5, 128.8, 127.5, 127.4, 126.5, 121.1, 113.9, 77.2, 73.4, 63.1, 61.1, 17.6. HRMS (ESI): calcd for $[M+Na]^+$ ($C_{17}H_{19}NO_2$) requires *m*/*z* 292.1313, found 292.1318. The enantiomeric excess was determined by HPLC with an OD column (*n*-hexane/*i*-PrOH = 90:10, $\lambda = 250$ nm), 1.0 mL/min; t_R = minor enantiomer 13.4 min, major enantiomer 21.3 min. The NMR data matched those of **5j** given in Ref. 13. The absolute configuration was assigned by comparison with the HPLC data given in Ref. 13: HPLC OD column (*n*-hexane/*i*-PrOH = 90:10, $\lambda = 250$ nm), 1.0 mL/min; t_R (3*S*,4*S*,5*S*) = 12.3 min, t_R (3*R*,4*R*,5*R*) = 18.1 min.
14. The figure was prepared with molecular mechanics using frozen C–C and C–O distances.
15. Typical experimental procedure for the organocatalytic one-pot, three-component reaction: To a stirred solution of aldehyde (0.5 mmol, 2.0 equiv) in $CHCl_3$, 0.5 mmol (2.0 equiv) of *N*-arylhydroxylamine was added. The reaction was stirred at room temperature for 1 h and then the

catalyst (0.05 mmol, 20 mol %) and 0.25 mmol (1.0 equiv) of α,β-unsaturated aldehyde were added. The reaction was stirred at room temperature for the time shown in Tables 1 and 2. Next, the crude was reduced 'in situ' at 0 °C with $NaBH_4$ in MeOH. After 5 min the reaction was quenched with AcOEt/HCl 1 M, dried over Na_2SO_4, filtered and concentrated. Purification of the resultant residue by silica gel chromatography provided the corresponding isoxazolidine **5**. Compound **5a**: Colorless solid. IR (KBr): 3397, 2928, 2392, 1722, 1597, 1519, 1346, 1261, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$–6.88 (m, 10H), 4.54 (d, $J = 6.5$ Hz, 1H), 4.05–3.99 (m, 1H), 3.76–3.69 (m, 2H), 2.42–2.34 (m, 1H), 1.79–1.73 (m, 2H), 1.63–1.57 (m, 2H), 1.45–1.38 (m, 2H), 0.95 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.3, 142.9, 129.1, 129.0, 127.6, 126.8, 121.4, 114.3, 81.3, 73.4, 61.1, 62.0, 33.0, 29.0, 23.0, 14.3. $[\alpha]_D$ +48.9 (*c* 1.0, $CHCl_3$). HRMS (ESI): calcd for $[M+Na]^+$ ($C_{20}H_{25}NO_2$) requires *m*/*z* 334.1778, found 334.1763. The enantiomeric excess was determined by HPLC with an AD column. (*n*-hexane/*i*-PrOH = 93:7, $\lambda = 250$ nm), 0.5 mL/min; t_R = major enantiomer 22.1 min, minor enantiomer 16.2 min.