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COMMUNICATION

Asymmetric organocatalytic Michael–α-amination sequence for the construction of a quaternary stereocenter†

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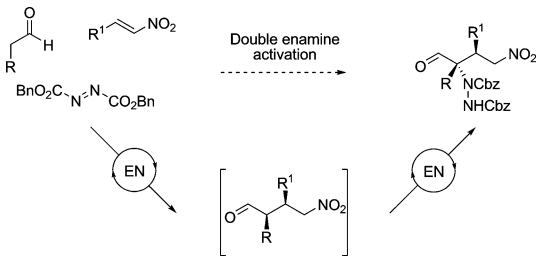
Combination of secondary and primary amine-catalyzed organocascade Michael–α-amination is described. This sequence afforded α-hydrazino aldehydes bearing a quaternary stereocenter with high yield and excellent stereoselectivity.

Introduction

Organocascade catalysis has emerged as a powerful strategy for the construction of highly functionalized molecules from simple achiral starting materials.[1] Taking advantage of the different modes of activation allowed in organocatalysis, a single catalyst or a combination of catalysts[2] is able to achieve two or more reactions with a high degree of stereocontrol. Until recently, this field was dominated by the use of aminocatalysis[3] and organocascade sequences involving iminium/enamine activation were the most reported.[4] By contrast, enamine/enamine activation, which would afford α,α disubstituted aldehydes or aldehydes containing a quaternary stereogenic center,[5] has received little attention. For example, List and co-workers[6] have reported a double Mannich reaction of acetaldehyde catalyzed by proline. Enders and co-workers[7] have described a sequence made up of a Michael addition of aldehydes to nitroalkenes followed by an intramolecular alkylation leading to substituted cyclopentanes. Herein, we would like to present a new example of double enamine activation of aldehydes outlined in Scheme 1. We envisioned a reaction sequence consisting of a Michael addition of aldehydes to nitroalkenes followed by subsequent electrophilic α-amination catalyzed by a combination of secondary and primary amines.

Results and discussion

Organocatalytic Michael addition of carbonyl compounds to nitroolefins[8] and α-amination of aldehydes and ketones[9] are well documented in the literature. The choice of the catalytic system was driven by the overall efficiency of both reactions in terms of low catalyst loading and availability, short reaction time and high level of stereocontrol. Primary[10] and secondary amines are able to catalyze the Michael addition of aldehydes to nitroalkenes whereas α-amination of hindered aldehydes proved to be difficult with a pyrrolidine core[11] (50 mol% catalyst loading is generally used for this transformation). Preliminary studies[12] revealed that a combination of diphenylprolinol silyl ether **1** used in the conditions described by Hayashi[13] (propionaldehyde (10 eq.), nitrostyrene (1 eq.), **1** (10 mol%) in hexane) and 9-amino(9-deoxy)*epi*-cinchonine **2** used in the conditions described by Melchiorre[14] (aldehyde (1 eq.), DBAD (1.5 eq.), **2** (20 mol%) in $CHCl_3$) was an efficient catalytic system for a sequential process (Scheme 2, eqn (1)). The challenge was then to optimize theses conditions toward a one pot procedure by lowering the amount of starting aldehyde and catalyst loading and homogenize the solvent conditions. In this way, Michael addition of propionaldehyde (1.2 eq.) to nitrostyrene (1 eq.) was achieved by using only 5 mol% catalyst **1** in $CHCl_3$ at 0 °C. After completion of the reaction, the electrophilic nitrogen reagent (DBAD, 1.5 eq.), TFA (15 mol%) and catalyst **2** (5 mol%) were added to the same vessel (Scheme 2, eqn (2)). The expected product was obtained as a single diastereoisomer[15] in 80% yield and 96% ee.



Scheme 1 Organocatalytic Michael–α-amination sequence.

With these conditions in hand, the scope of the sequence was surveyed using various nitroalkenes (Table 1). Reactions with aromatic nitroolefins afforded the corresponding α-hydrazino aldehydes bearing a quaternary stereocenter with high yields (73–90%) and excellent stereoselectivities. In each case, a single diastereoisomer is observed with high enantioselectivity

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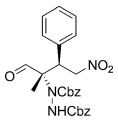
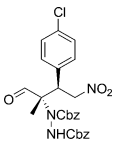
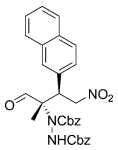
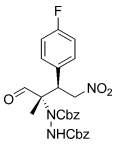
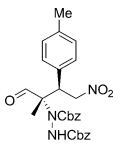
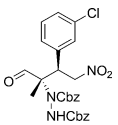
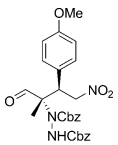
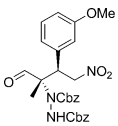
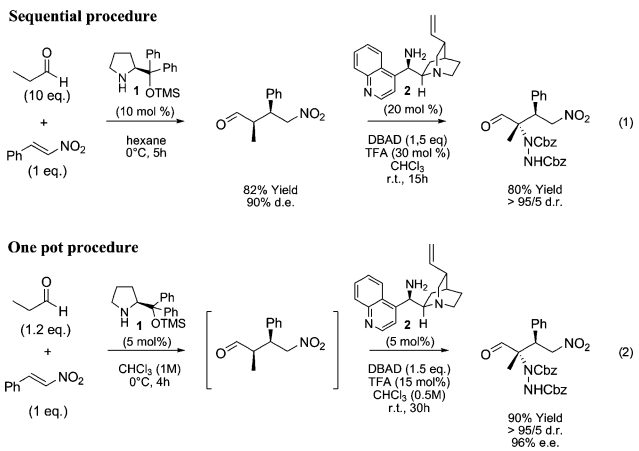
† Electronic supplementary information (ESI) available: Experimental details, NMR spectra and HPLC traces. CCDC reference number 784199. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00751j

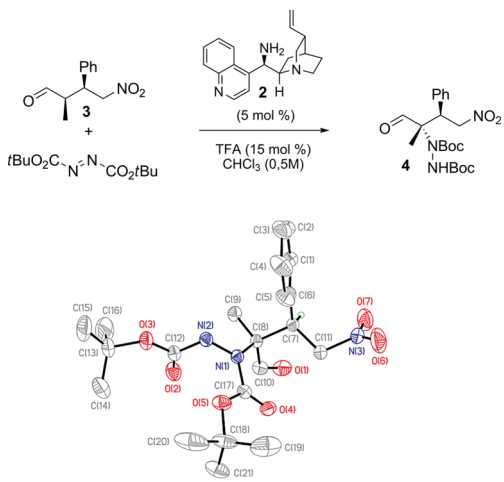
Table 1 Organocatalytic Michael addition–α-amination sequence of propionaldehyde with different nitroalkenes

Entry	Conditions	Product	Yield[a] (ee)[b]	Entry	Conditions	Product	Yield[a] (ee)[b]
1	Michael (0 °C, 4 h) Amination (r.t., 30 h)		90% (96%)	5	Michael (0 °C, 5 h) Amination (r.t., 70 h)		85% (98%)
2	Michael (0 °C, 4 h) Amination (r.t., 65 h)		73% (96%)	6	Michael (0 °C, 4 h) Amination (r.t., 140 h)		81% (97%)
3	Michael (0 °C, 6 h) Amination (r.t., 25 h)		85% (96%)	7	Michael (0 °C, 4 h) Amination (r.t., 90 h)		85% (98%)
4	Michael (0 °C, 8 h) Amination (r.t., 22 h)		85% (97%)	8	Michael (0 °C, 4 h)[c] Amination (r.t., 88 h)		76% (96%)

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] **1** (10 mol%) and **2** (5 mol%) were used for the reaction.



Scheme 2 Optimized conditions for the one pot sequence Michael–α-amination sequence.

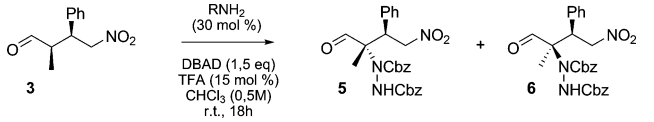


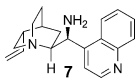
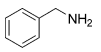
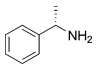
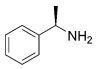
Scheme 3 ORTEP diagram of **4**.

(96–98% ee).[15] Electron-rich and electron-deficient aryl groups and the position of the substituent (*i.e. para* or *meta*) on the aromatic ring provided the same results. The limitation of the present methodology was found when butyraldehyde was used instead of propionaldehyde. In this case, the amination step was very slow and only 50% conversion was observed after a week. The determination of the absolute and relative configuration was achieved by means of an X-ray crystallographic analysis of compound **4**[16] (Scheme 3). Suitable crystals were obtained by using D*t*BAD instead of DBAD as the electrophilic nitrogen source for the amination step of the known compound **3**.[13]

A *syn* relationship between Me and Ph groups was observed and it was concluded that **4** was di-*tert*-butyl-1-((2*S*,3*S*)-2-methyl-4-nitro-1-oxo-3-phenylbutan-2-yl)hydrazine-1,2 dicarboxylate.[17]

Table 2 α-Amination of α-disubstituted aldehyde **3** with different primary amines



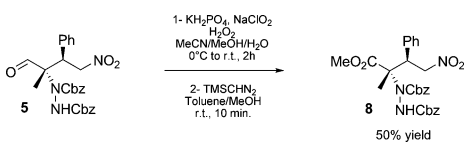
Entry	Primary amine catalyst	Ratio **5**/**6**[a]	Yield
1[b]		>19/1	88%
2		1/1	86%
3		3.4/1	89%
4		1/1.9	87%

[a] Determined by ^{1}H NMR on the crude product. [b] 5 mol% of catalyst **7** was used for the reaction.

Then, we envisioned synthesizing the diastereomer of compound **5** by simply changing catalyst **2** for its pseudo enantiomer catalyst **7** (Table 2, entry 1). Surprisingly, these conditions afforded the same product **5** with similar results as described above (Table 1, entry 1).

Finally, we screened different alkyl benzylamines as catalysts for the C–N bond forming step. As expected, benzylamine led to a 1/1 mixture of stereoisomer **5** and **6** (entry 2). When (*R*)-α-methylbenzylamine was used to promote the reaction, the diastereomeric ratio increased to 3.4/1 in favour of aldehyde **5** (entry 3). If the enantiomer (*S*)-α-methylbenzylamine was used as the catalyst, we observed the formation of aldehyde **6** as the major diastereomer (**5**/**6**: 1/1.9; entry 4). The diastereomeric mixture was separated by flash chromatography on silica gel and compound **6** was isolated in 52% yield and 96% ee.

To improve the synthetic scope of this methodology, we transformed the resulting aldehyde compound. As illustrated in Scheme 4, the aldehyde moiety was oxidized under smooth conditions (KH_2PO_4, $NaClO_2$ and H_2O_2) and esterified to afford the α-hydrazino ester in 50% yield.



Scheme 4

Conclusion

In summary, a new organocatalytic Michael–α-amination sequence has been developed based on a double enamine activation of aldehydes. This reaction generates α-hydrazino aldehydes bearing a quaternary stereogenic center with high yields and excellent stereoselectivities.

Further investigations into this reaction sequence, including its synthetic applications, are presently underway.

Acknowledgements

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14 P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7892.
15 Diastereomeric excesses were determined by ^{1}H NMR on the crude product and enantiomeric excesses were determined by chiral HPLC using AS-H or OD-H columns.
16 Crystal data: $C_{21}H_{31}N_3O_7$, $_M$w = 437.49, monoclinic, space group $P21/c$; dimensions: a = 10.158(3) Å, b = 14.069(4) Å, c = 17.637(4) Å, β = 99.962(11), V = 2482.5(11) Å^3; Z = 4; μ = 0.088 mm^{-1}; 136 829 reflections measured at RT; independent reflections: 4347 [4107 $F_o > 4\sigma(F_o)$]; data were collected up to a $2\Theta_{max}$ value of 50° (99.6% coverage). Number of variables: 287; R_1 = 0.0659, wR_2 = 0.1933, S = 1.216; highest residual electron density 0.532 e Å^{-3} (all data R_1 = 0.0861, wR_2 = 0.2158). CCDC 784199.
17 This compound was also synthesized according the one-pot procedure in 85% yield.