Organocatalysis

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# Asymmetric Organocatalytic Cascade Reactions with α-Substituted α,β-Unsaturated Aldehydes**

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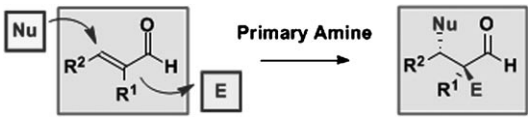
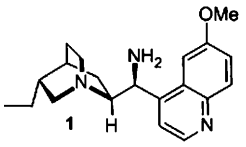
In the past decade, asymmetric aminocatalysis has become a fundamental synthetic strategy for the stereoselective construction of chiral molecules.[1] The extraordinary pace of innovation and progress in aminocatalysis has been dictated mainly by the discovery of distinct catalytic activation modes which have enabled previously inaccessible transformations.[2] To the same extent, the design of novel structural classes of organic catalysts has also ignited the field, enabling the activation of challenging types of carbonyl substrates. Whereas chiral secondary amines have proven invaluable for the asymmetric functionalization of aldehydes, primary amine catalysis has offered the unique possibility of participating in processes between sterically demanding partners.[3] Therefore it overcomes the inherent difficulties of chiral secondary amines in generating congested covalent intermediates. Chiral primary amine based catalysts have been successfully used for the enamine activation of challenging substrates, such as α,α-disubstituted aldehydes[4] and ketones.[5] In 2005, Ishihara and Nakano[6a] additionally extended the potential of chiral primary amines to include the iminium ion activation of α-acyloxy-acroleins toward a stereoselective Diels–Alder process.[6] However, the use of α,β-disubstituted unsaturated aldehydes still represents an elusive and fundamental target for asymmetric aminocatalysis.[7] This is particularly true when considering that an alternative asymmetric metal-catalyzed strategy for the functionalization of this compound class is also lacking.[8]

Herein we show that the chiral primary amine catalyst **1** provides an efficient solution to this longstanding and sought after issue, activating α,β-disubstituted enals toward a well-defined iminium/enamine tandem sequence (Scheme 1). Specifically, we developed organocascade reactions[9] which combine two intermolecular and stereoselective steps involving a Michael addition/amination pathway. The described



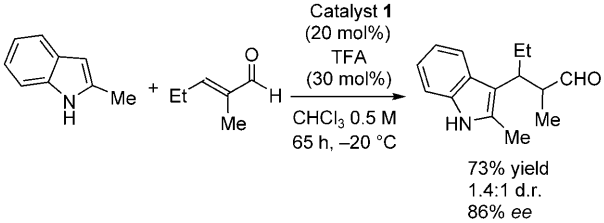

***Scheme 1.*** Targeting α,β-disubstituted unsaturated aldehydes.




olefin aryl-amination and thio-amination processes afford straightforward access to valuable precursors of α-amino acids which have two adjacent stereogenic centers, one of which is quaternary, with very high optical purity.

Recently we and others, independently,[4b,5] established chiral primary amine **1**—directly derived from natural cinchona alkaloids—as an effective catalyst for ketone activation. We additionally demonstrated the versatility of **1**, which can combine orthogonal catalysis modes (iminium and enamine activations) into one mechanism, thus promoting an intramolecular tandem reaction with α,β-unsaturated ketones.[10] On this basis, we hypothesized whether the unique ability of catalyst **1** to engage in iminium ion formation with encumbered enones while enforcing high geometric control and facial discrimination, might be extended to the challenging class of α,β-disubstituted enals. Preliminary investigations revealed that the TFA salt of **1** was able to promote the Friedel–Crafts alkylation of 2-methyl-1*H*-indole with (*E*)-2-methylpent-2-enal with high enantioselectivity, indicating that a selective π-facial shielding of the iminium intermediate is effective [Eq. (1)]. The poor diastereocontrol, however, clearly demonstrates that the enamine-based protonation step escapes catalyst control.

Nevertheless, the ability of **1** to impart high stereocontrol in the iminium activation of α-branched enals prompted us toward a more intriguing target: the creation of multifunctional compounds, having two contiguous stereocenters, in a one-step process. In addition to the benefit of generating

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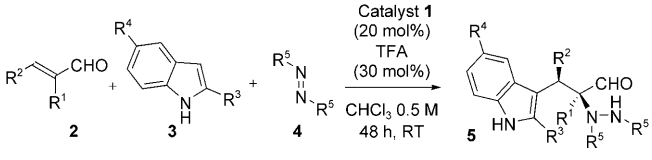
complex scaffolds in a rapid and atom-economical way, the combination of multiple asymmetric transformations in a cascade sequence[9] also imparts increased enantiomeric excess to the final product when compared to the corresponding discrete transformations.[11]

Our organocascade strategy was first examined by mixing three commercially available reagents, (*E*)-2-methylpent-2-enal, 2-methyl-1*H*-indole and diethyl azodicarboxylate (Table 1, entry 1). Such a combination is rather challenging,[12]

***Table 1:*** Organocascade catalysis with α,β-disubstituted enals: indole and azodicarboxylate combinations.




| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield [%][a] | d.r.[b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | Et | Me | H | $CO_2Et$ | 57 (**5a**) | 8:1 | 99 |
| 2 | Me | Et | Me | H | $CO_2Bn$ | 49 (**5b**) | 6:1 | 99 |
| 3 | Me | Et | Me | H | $CO_2tBu$ | 80 (**5c**) | 11:1 | 98 |
| 4[d] | Me | Et | H | H | $CO_2tBu$ | 51 (**5d**) | 3:1 | 94 |
| 5[e] | Me | Et | H | Cl | $CO_2tBu$ | 43 (**5e**) | 4:1 | 91 |
| 6[d] | Me | Et | H | OMe | $CO_2tBu$ | 54 (**5f**) | 3:1 | 96 |
| 7[d] | Me | Et | H | Me | $CO_2tBu$ | 47 (**5g**) | 3:1 | 91 |
| 8 | Et | $CH_3(CH_2)_2$ | H | H | $CO_2tBu$ | 31 (**5h**) | 3:1 | 83 |

[a] Yield of isolated **5**. [b] Determined by $^1$H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis using chiral stationary phases. [d] Reaction conducted at −10 °C over 96 h. [e] Reaction conducted at 0 °C over 65 h.

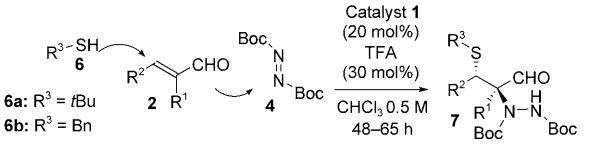
because of the competitive coupling between the π-rich nucleophile and the electrophilic component **4**. A survey of the reaction conditions revealed that using enal **2**/nucleophile **3**/electrophile **4**, in a 1:1.2:1.5 ratio, in the presence of the catalytic salt—made by combining **1** (20 mol %) and TFA (30 mol %) in $CHCl_3$ (0.5 M)—provides product **5a** with excellent levels of stereoinduction and in good yield, thus minimizing deleterious side reactions. We next examined the scope of the presented aryl-amination of disubstituted olefins. As shown in Table 1, excellent stereoselectivity is achieved with azodicarboxylates having orthogonal protecting groups (Table 1, entries 1–3). Given the superior diastereomeric ratio and chemical yield, *tert*-butyl azodicarboxylate was selected for additional exploration.

Different substituents on the indole core are well-tolerated, since electronic and architectural modification of the aromatic ring can be accomplished without affecting the efficiency of the system, leading to valuable tryptophan derivatives **5** in moderate to good yield and diastereomeric ratio and with high optical purity (Table 1, entries 4–7).[13] As expected, the presence of a more encumbered ethyl group ($R^1$) at the α position of the enal decreases the overall reaction rate (Table 1, entry 8). The requirement to perform the cascade at room temperature leads to a slightly lower level of stereocontrol in the formation of product **5h** (83 % *ee*).

To probe the scope of the nucleophilic component and expand the synthetic utility of this organocascade methodology, we focused on a sulfa-Michael/amination sequence, using mercaptanes **6** which have easily removable and orthogonal sulfur protecting groups (Table 2).[14]

The tandem sequence[10d] provides a fast way to stereoselectively forge a quaternary stereocenter contiguous to a C–S tertiary one. As summarized in Table 2, the reaction shows a

***Table 2:*** Organocascade catalysis with α-branched α,β-unsaturated aldehydes: sulfa-Michael/amination strategy.[a]




| Entry | $R^1$ | $R^2$ | Thiol | *t* [°C] | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|
| 1 | Me | Et | **6a** | 0 | 54 (**7a**) | 6.5:1 | >99 |
| 2[e] | Me | Et | **6b** | 0 | 57 (**7b**) | 5:1 | 72 |
| 3[e] | Me | Et | **6b** | −20 | 27 (**7b**) | 6:1 | 89 |
| 4[f] | Et | $CH_3(CH_2)_2$ | **6b** | 40 | 45 (**7c**)[g] | 4:1 | 92 |
| 5[h] | Ph | Et | **6b** | 40 | 47 (**7d**) | 4:1 | 92 |
| 6 | Me | Ph | **6a** | 40 | 40 (**7e**) | 20:1 | 99 |

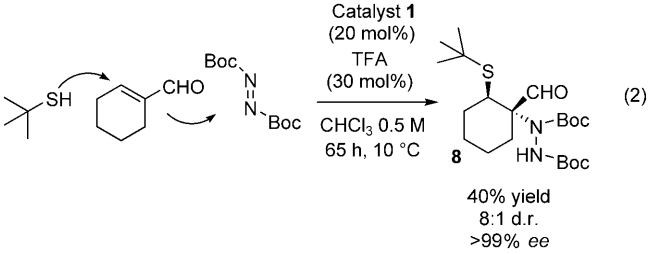
[a] Reactions conditions: **2** (1 equiv), **6** (1.2 equiv), and **4** (1.5 equiv). [b] Yield of the isolated, single, major diastereoisomer. [c] Determined by $^1$H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using chiral stationary phases. [e] Reaction carried out in toluene. [f] The *ee* value was determined after reduction and cyclization to form oxazolidinone. [g] Sum of diastereoisomers (4.5:1 ratio). [h] Yield and *ee* value were determined after in situ reduction and cyclization. Boc = *tert*-butyloxycarbonyl.

good substrate generality: both *tert*-butyl (**6a**) and benzyl (**6b**) mercaptanes are suitable nucleophiles, although the latter induces a less selective organocascade path (Table 2, entries 1–3). There appears to be a remarkable latitude in the electronic and steric demands of the aldehydic component. Different aliphatic substituents and even a phenyl group in both the α and β position of the enals are well-tolerated (Table 2, entries 4–6), enabling access to a broad variety of multifunctional complex molecules that have adjacent stereocenters with high stereoselectivity. For example, when α-substituted cinnamic aldehyde is involved in the organocascade, the corresponding product **7e** is produced as a single stereoisomer (Table 2, entry 6). Notably, compounds **7** can be isolated as a single diastereoisomer by using standard flash column chromatography.

Finally, we explored the possibility of extending the organocascade to 1-cycloalkene-1-carboxaldehydes[7] to access complex products having a quaternary stereogenic center embedded in a cycle. Catalyst **1** also proved efficient with this substrate class, leading to compound **8** with complete enantiocontrol [Eq. (2)].

The configuration of a derivative of compound **7a** was unambiguously determined by anomalous dispersion X-ray crystallography,[15] whereas the relative and absolute configurations of a derivative of compound **8** were assigned by NMR NOE analyses and by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra, as described in the Supplementary Information.




(2)

In summary, we have described an efficient solution to the longstanding issue associated with the aminocatalytic activation of α,β-disubstituted enals. The use of the primary amine catalyst **1** allows inclusion of this challenging substrates class into iminium/enamine cascade sequences which lead to valuable precursors of α-amino acids having two adjacent stereogenic centers, one of which is quaternary, with very high enantiomeric purity. In addition to the synthetic merit of this method, we anticipate that the versatility of catalyst **1** will be useful for designing more complex asymmetric, catalytic transformations of α-branched unsaturated compounds, thus expanding the field of application of aminocatalysis.

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[1] For reviews, see: a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; b) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; d) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79.

[2] For recent overviews: a) P. Melchiorre, *Angew. Chem.* **2009**, *121*, 1386; *Angew. Chem. Int. Ed.* **2009**, *48*, 1360; b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

[3] L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807.

[4] Selected examples: a) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366; b) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599.

[5] For reviews on primary amine **1**-catalyzed reactions of ketones, see: a) G. Bartoli, P. Melchiorre, *Synlett* **2008**, 1759; b) Y.-C. Chen, *Synlett* **2008**, 1919, and references therein.

[6] a) K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2005**, *127*, 10504. For a more recent example, see: b) T. Kano, Y. Tanaka, K. Osawa, T. Yurino, K. Maruoka, *Chem. Commun.* **2009**, 1956. In this report, a single, low enantioselective example of Diels–Alder reaction using 2-methyl but-2-enal has been described.

[7] Chiral secondary amines enforce moderate stereoselectivity in the activation of 1-cycloalkene-1-carboxaldehydes, see: a) S. Karlsson, H.-E. Högberg, *Eur. J. Org. Chem.* **2003**, 2782; b) D. H. King, Z. Meng, D. Denhart, R. Mattson, R. Kimura, D. Wu, Q. Gao, J. E. Macor, *Org. Lett.* **2005**, *7*, 3437.

[8] Chiral Lewis acid mediated activation of α-branched unsaturated compounds is generally based on the use of bidentate chelating carbonyl groups. See for example: a) M. P. Sibi, J. Coulomb, L. M. Stanley, *Angew. Chem.* **2008**, *120*, 10061; *Angew. Chem. Int. Ed.* **2008**, *47*, 9913, and references therein. For a metal-catalyzed activation of α-substituted enones, see: b) W.-J. Lu, Y.-W. Chen, X.-L. Hou, *Angew. Chem.* **2008**, *120*, 10287; *Angew. Chem. Int. Ed.* **2008**, *47*, 10133.

[9] For reviews, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134. For meaningful examples using secondary amine catalysis, see: c) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; d) M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710; e) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861.

[10] a) F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831; *Angew. Chem. Int. Ed.* **2008**, *47*, 8703; b) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336–7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200–7203; c) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7329–7331; *Angew. Chem. Int. Ed.* **2009**, *48*, 7196–7199; See also: d) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070.

[11] Horeau's principle of chiral amplification: J. P. Vigneron, M. Dhaenens, A. Horeau, *Tetrahedron* **1973**, *29*, 1055.

[12] During the preparation of the manuscript, the first example of organocatalytic aryl-amination of β-substituted enals was described: B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem.* **2009**, *121*, 4413; *Angew. Chem. Int. Ed.* **2009**, *48*, 4349.

[13] The aryl-amination cascade with α,β-disubstituted enals bearing an aryl group at either the α or β position gave a sluggish reaction rate. Carrying out the reaction at higher temperature (40 °C) does not afford the desired improvement, while facilitating the competitive coupling between the π-rich nucleophile and the azodicarboxylate.

[14] For a comprehensive review on asymmetric sulfa-Michael additions, see: D. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, 959.

[15] CCDC 741211 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

  