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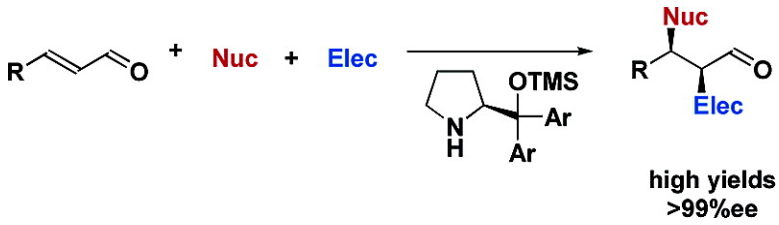

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Asymmetric Multicomponent Domino Reactions and Highly Enantioselective Conjugated Addition of Thiols to α,β-Unsaturated Aldehydes

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In the past few years, an increasing number of enantioselective reactions have been developed using chiral organic molecules as catalysts.[1] Among this class of catalysts, secondary amines and imidazole derivatives proved to be an important tool for the formation of C−H, C−C, and C−heteroatom stereocenters.[1]

These chiral amines have been found extremely useful as catalysts for the α-functionalization of aldehydes and ketones via formation of a nucleophilic enamine intermediate, or for the activation of α,β-unsaturated aldehydes and enones via formation of a reactive iminium ion intermediate. Using these strategies, many different classes of optically active products have been obtained with excellent enantiomeric excesses.

Recently, two contributions appeared presenting reactions that take advantage of both enamine and iminium ion activation. MacMillan et al.[2] presented a proline-catalyzed cyclopropanation reaction using α,β-unsaturated aldehydes with sulfur ylides, while we disclosed an asymmetric organocatalytic epoxidation of α,β-unsaturated aldehydes using hydrogen peroxide.[3] Nevertheless, to the best of our knowledge, no report has yet been published dealing with multicomponent reactions (MCR) involving these two different activation modes. The advantages of MCR over the two-component processes have been widely demonstrated and reviewed.[4] In particular, asymmetric organocatalytic MCR would lead us to simpler procedures for the formation of multiple stereocenters and closer to the goal of more environmentally friendly processes.

Here we wish to demonstrate the potential of the organocatalytic asymmetric MCR by presenting the domino-conjugated thiol addition−amination reaction. The soft sulfur nucleophile first reacts with the iminium ion intermediate, followed by addition of the electrophile to the enamine intermediate, giving nearly enantiopure products when 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine[5] (**3**) was used as the catalyst (Scheme 1).

For the first step of this MCR, we choose to study the reaction of α,β-unsaturated aldehydes with thiols. In fact, despite the fact that addition of thiols to electron-deficient olefins is an important strategy in the formation of C−S stereocenters,[6] the transformations reported in the literature involve almost exclusively aromatic thiols as nucleophiles.[7] Furthermore, according to our knowledge, only one example of enantioselective conjugated addition of thiols to α,β-unsaturated aldehydes has been reported (with up to 70% ee).[8]

We immediately realized that the temperature was the key factor for the optimization of the reaction between cinnamic aldehyde **1a** and *tert*-butyl mercaptan **2a** using the chiral pyrrolidine derivative **3** as organocatalyst. The thiol addition to α,β-unsaturated aldehydes is an equilibrium reaction, and the products quickly racemize at 20 °C.[9] However, when the transformation takes place at −24 °C, the background reaction is minimized and the enantiomeric excess of the product is stable for days in the reaction mixture. The lower temperature decreases also the reaction catalyzed by **3**, and an acid additive is necessary for the achievement of good chemical yields in a reasonable reaction time. On the contrary, the solvent has a minor impact on the enantioselectivity, and toluene was chosen because of the high reactivity of the catalytic system in this reaction media. Table 1 shows the results for the organocatalyzed conjugated addition of different thiols to various α,β-unsaturated aldehydes.

Scheme 1. Multicomponent Enantioselective Organocatalytic Addition to α,β-Unsaturated Aldehydes

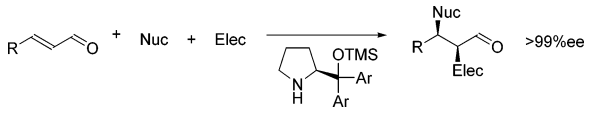
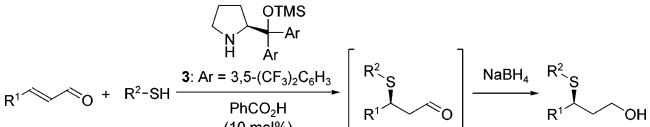


Table 1. Scope of the Organocatalyzed Conjugated Addition of Thiols to α,β-Unsaturated Aldehydes[a]



1a-g 2a-c 4a-h 5a-h

entry	R^1	R^2	time (h)	yield[b] (%)	ee[c] (%)
1	Ph − **1a**	*t*-Bu − **2a**	30	**5a** − 80	95
2	*p*-F−Ph − **1b**	*t*-Bu − **2a**	30	**5b** − 87	97
3	*p*-MeO−Ph − **1c**	*t*-Bu − **2a**	30	**5c** − 73	90
4	*o*-Me-Ph − **1d**	*t*-Bu − **2a**	30	**5d** − 76	97
5	Me − **1e**	Bn − **2b**	40	**5e** − 80	89
6	ethyl − **1f**	Bn − **2b**	40	**5f** − 85	93
7[d]	*i*-Pr − **1g**	Bn − **2b**	16[c]	**5g** − 82	95
8	Me − **1e**	EtO_2CCH_2 − **2c**	16	**5h** − 85	94

[a] Reaction conditions: The thiol (1 equiv) was added to the α,β-unsaturated aldehyde (1.5 equiv), catalyst (10 mol %), and $PhCO_2H$ in toluene at −24 °C for the stated period of time. The reaction product was isolated after reduction to the corresponding alcohol. [b] Isolated by FC. [c] Enantiomeric excess determined by chiral HPLC. [d] Reaction performed without acid additive at −5 °C.

The reaction showed good substrate generality. Aromatic (Table 1, entries 1−4) and aliphatic α-substituted enals (entries 5−8) were all converted with very high level of stereocontrol to **4a**−**h**, and after reduction, the alcohols **5a**−**h** were isolated in high yields. Cinnamic aldehyde **1a** and *p*-fluorocinnamic aldehyde **1b** reacted efficiently with *tert*-butyl mercaptan **2a**, and the products were obtained with 95 and 97% ee, respectively (entries 1 and 2). It is important to notice how also the presence of electron-donating substituents in the *para*- or *ortho*-position of the aromatic ring is well tolerated (entries 3 and 4). When R^1 is an alkyl group, the products formed in combination with benzyl mercaptan **2b** were isolated in high yields over the two steps maintaining the high enantiomeric excess (entries 5−7). The screening has been mainly focused on the use of benzyl and *tert*-butyl mercaptans because these protecting groups can be removed releasing the free thiol

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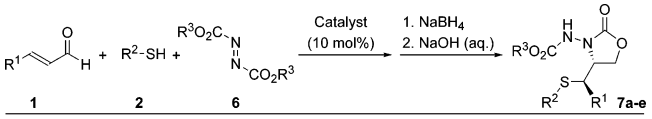
Table 2. Multicomponent Domino Organocatalyzed Conjugated Addition−Amination Reaction of α,β-Unsaturated Aldehydes[a]



entry	R^1	R^2	R^3	catalyst	time (h)	yield[b] (%)	dr[c]	ee[e] (%)
1[d]	Me	Bn	Et	**3**	3	**7a** − 72	93:7	>99
2	Me	Bn	Et	**3**	3.5	**7a** − 57	95:5	>99
3[d]	Et	Bn	Et	**3**	24	**7b** − 63	95:5	>99
4	Et	Bn	Et	**3**	16	**7b** − 42	96:4	>99
5	Me	Bn	Bn	**3**	16	**7c** − 44	89:11	>99
6	Me	Et	Bn	**3**	16	**7d** − 51	88:12	>99
7	Et	Et	Bn	**3**	16	**7e** − 38	95:5	97
8[e]	Me	Bn	Et	L-proline	1	**7a** − n.d.	47:53	78/61

[a] Reaction conditions: The thiol (1 equiv) was added to the α,β-unsaturated aldehyde (1.5 equiv), catalyst, and benzoic acid in toluene at −15 °C. Compound **6** (1.3 equiv) was added after 30 min. [b] Isolated by FC after reduction and cyclization (see Supporting Information). [c] Diastereomeric excesses and enantiomeric excesses were determined by chiral HPLC. [d] Compound **6** (1.3 equiv) was added after 16 h. [e] No benzoic acid additive was used.

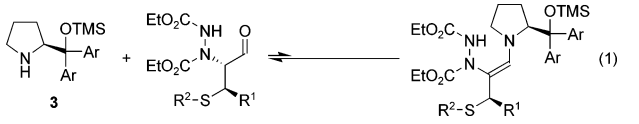
functionality. Nevertheless, more complex optically active products such as **5h** can be obtained under the same reaction conditions (entry 8).

During our studies, we observed that the high initial reaction rate decreased with the conversion. ^{1}H NMR spectroscopic studies revealed that this phenomenon was the consequence of the series of equilibriums that constitute the catalytic cycle. Catalyst **3** was mainly bound to the thio-addition product in a stable enamine species, and only a minor amount of catalyst was available for the iminium ion activation of the substrate. With a well-optimized conjugated addition step and this experimental evidence in hand, we moved our attention to the second step of the MCR. We decided to take advantage of the enamine intermediate by adding a new electrophile to the reaction mixture, aiming at an efficient and stereoselective formation of a second chiral center.

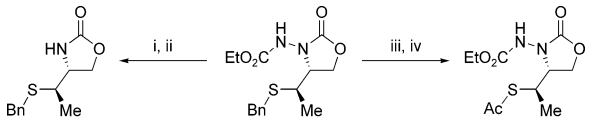
We were pleased to find that the addition of azodicarboxylates **6** followed by in situ reduction and cyclization resulted in the formation of the highly functionalized oxazolidinones **7a**−**e** in nearly enantiopure form. The products were isolated in moderate to good yields as a result of the four steps and one-pot procedure (Table 2).

It is important to highlight the role of catalyst **3** in controlling the formation of both stereocenters. L-Proline, a very selective catalyst for the amination of simple aldehydes, catalyzed the formation of the desired product in moderate enantiomeric excess and with a poor diastereomeric ratio (Table 2, entry 8).[10]

Comparing the multicomponent domino reaction[11] (Table 2, entries 2 and 4) with the analogous one-pot procedures (entries 1 and 3), we can observe that the overall reaction time is decreased, while the enantioselectivity is not influenced by the different procedures. This acceleration is due to the fact that the aminated product is too sterically demanding to form a new enamine species, and in the reaction mixture, we have a constant amount of free amine **3** that catalyzes the conjugated addition step (eq 1).



Scheme 2. Selective Deprotection of **7**[a]



[a] Conditions: (i) Ac_2O, pyridine, DMAP, 50 °C, 64 h, 87%. (ii) SmI_2, HMPA, THF, rt, 30 min, 81%. (iii) Li, NH_3(l), 30 min. (iv) AcCl, Et_3N, CH_2Cl_2, 73% yield (over two steps).

Chiral amino thiols show interesting inhibition properties, for example, in the case of leukotriene A_4-hydrolase[12a] and other aminopeptides,[12b] and to prove the synthetic utility of this new MCR, we have demonstrated selective N−N bond cleavage and thiol deprotection, respectively (Scheme 2).

In summary, we have developed a novel simple approach to the synthesis of highly functionalized molecules having two adjacent stereocenters. In particular, we presented the first multicomponent domino conjugated nucleophilic addition−electrophilic amination reaction that gives access to 1,2-aminothiol derivatives with >99% ee in a one-pot process using 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]pyrrolidine as organocatalyst. Furthermore, we presented the first organocatalytic conjugated addition of thiols to α,β-unsaturated aldehydes with excellent yields and enantiomeric excesses.

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Supporting Information Available: Complete experimental procedures and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews on organocatalysis, see: (a) Dalko, P. L.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; WCH: Weinheim, Germany, 2004.
(2) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.
(3) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.
(4) See, for example: (a) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
(5) For application of **3** in enamine catalysis, see: (a) Marigo, M.; Wabntiz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. See also: (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (d) Chi, Y.; Gellmann, S. H. *Org. Lett.* **2005**, *7*, 4253.
(6) For some recent examples, see: (a) Li, B.; Jiang, L.; Chen, Y.; Ding, L.; Wu, Y. *Synlett* **2005**, 603. (b) Palomo, C.; Oiarbide, M.; Dias, F.; López, R.; Linden, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3307. (c) Nishimura, K.; Tomioka, K. *J. Org. Chem.* **2002**, *67*, 431. (d) McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338 and references therein.
(7) For an exception, see: Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043.
(8) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589.
(9) When the crude reaction mixture containing the product **4a** with 97% ee is allowed to reach room temperature overnight, we observed the partial reformation of thiol and complete racemization.
(10) For a recent review on enantioselective amination reactions, see: Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292.
(11) We observed that only 10−20% of **2a** and **1e** was converted after 30 min, while we observed almost full conversion after 16 h.
(12) (a) Yuan, W.; Munoz, B.; Wong, C. *J. Med. Chem.* **1993**, *36*, 211. (b) Gordon, E. M.; Godfrey, J. D.; Delaney, N. G.; Asad, M. M.; Von Lagen, D.; Cushman, D. W. *J. Med. Chem.* **1988**, *31*, 2199.

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