DOI: 10.1002/chem.200801410

Reaction Control in the Organocatalytic Asymmetric One-Pot, Three-Component Reaction of Aldehydes, Diethyl α-Aminomalonate and Nitroalkenes: Toward Diversity-Oriented Synthesis

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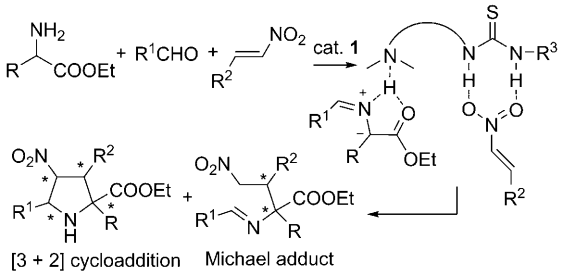
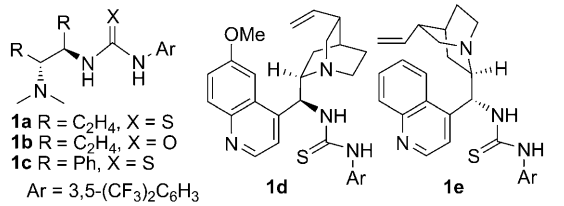
The demand for enantiomerically enriched compounds is continuously increasing as a result of the rapid development of the pharmaceutical industry. Therefore, asymmetric synthesis remains a major focus of organic chemistry over the past decades. For instance, enormous efforts have been devoted to the catalytic stereoselective transformations of imine derivatives of α-amino esters and α,β-unsaturated compounds, either by Michael addition[1] or [3+2] dipolar cycloaddition (via azomethine ylides)[2] reactions, leading to the efficient synthesis of biologically important unnatural amino acids, or pyrrolidines with multiple chiral centers. Most studies in the literature have utilized α-imino esters as the nucleophilic precursors,[3] and control of the reaction selectivity (Michael addition or cycloaddition) has generally been poor.[4] In the pursuit of more efficient methods for diversity-oriented synthesis,[5] it would be highly desirable that the Michael adducts or dipolar cycloaddition products could be selectively obtained from the same three-component reaction of aldehydes, α-amino esters and activated alkenes under easily controllable conditions, catalyzed by environmentally benign organic molecules.[6]

Our strategy is based on the following considerations: although α-amino esters might directly coordinate with a metal cation, which would affect the formation of α-imino esters with aldehydes and the subsequent reaction with the activated alkenes, such processes should happen in the presence of a bifunctional organic thiourea–tertiary amine catalyst.[7,8] As outlined in Scheme 1, the tertiary amine group would activate the in situ formed α-imino esters to produce azomethine ylides (or enolates). Nitroalkenes would be activated by the thiourea group, through a double hydrogen-bonding interaction. Thus the synergistic communication through bifunctional catalysis would ensure high stereoselectivity in the subsequent Michael addition or dipolar cycloaddition.[9,10]



Scheme 1. Proposed organocatalytic three-component reaction of α-amino esters, aldehydes and nitroalkenes. cat. **1** = thiourea–tertiary amine organocatalyst (see Scheme 2)

We first investigated the reaction of α-imino acetate **2a** and nitrostyrene **3a**, catalyzed by thiourea–tertiary amine **1a** (Scheme 2, 10 mol%) in toluene at ambient temperature. Unfortunately, no reaction occurred, probably because the tertiary amine group of **1a** could not remove the α-proton of **2a** to generate the azomethine ylide intermediate



Scheme 2. The structures of bifunctional organocatalysts **1a–e**.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801410.

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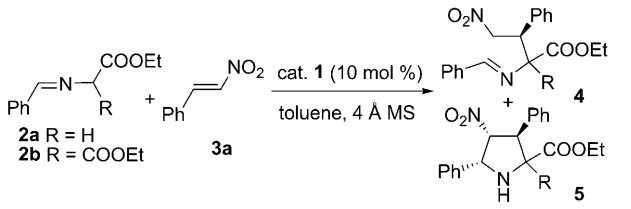
(Table 1, entry 1). 5 mol% of LiBr (or AgF with urea catalyst **1b**) was added in order to increase the acidity of the proton by metal-coordination.[11] The dipolar cycloaddition indeed occurred but only the racemic product **5a** (R=H)

Table 1. Screening studies of organocatalytic reaction of α-imino esters and nitrostyrene.[a]



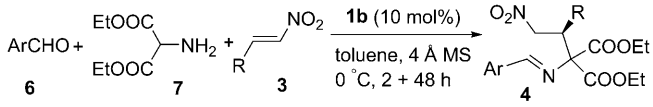
Entry	Cat.	Conditions.	Yield [%][b]	*ee* [%][c]
1[d]	1a	A	–	–
2[e]	1a	A	**5a** 80	**5a** 0
3[f]	1b	A	**5a** 85	**5a** 0
4[g]	1a	A	**4a** 50 **5b** 20	**4a** 91 **5b** 20
5	1a	B	**4a** 70 **5b** 18	**4a** 93 **5b** 20
6	1c	B	**4a** 30 **5b** 65	**4a** 57 **5b** 5
7	1d	B	**4a** 81 **5b** 18	**4a** 82 **5b** 14
8	1e	B	**4a** 66 **5b** 20	**4a** 90 **5b** 6
9	1b	B	**4a** 93 **5b** 6	**4a** 96 **5b** 40

[a] Conditions A: reaction performed with **2** (0.1 mmol), **3a** (0.12 mmol), **1** (10 mol%), and 4 Å molecular sieves (MS, 50 mg) in toluene (0.8 mL) at room temperature for 24 h. B: benzaldehyde **6a** (0.1 mmol), diethyl α-aminomalonate **7** (0.1 mmol) and 4 Å MS (80 mg) were stirred at 0°C for 2 h before adding nitrostyrene **3a** (0.12 mmol) and catalyst **1** (10 mol%). The mixture was then stirred for a further 48 h at 0°C. **5a**: R=H; **4a**/**5b**: R=COOEt. [b] Yield of isolated product. [c] Determined by HPLC analysis on chiral column, d.r. >99:1 for cyclic product **5**. [d] **2a** was used. [e] **2a** was used in addition to 5 mol% of LiBr. [f] **2a** was used in addition to 5 mol% of AgF. [g] **2b** was used.

was isolated (Table 1, entries 2 and 3). We envisaged that the introduction of another ethoxycarbonyl group at the α-position of **2a** would facilitate the generation of the azomethine ylide intermediate through tertiary amine activation.[2k] In this case, employing **2b** as the starting material, the Michael adduct **4a** (R=COOEt) was the major product, isolated as a stable compound after 24 h with promising enantioselectivity (91% *ee*, Table 1, entry 4). A low yield of cycloaddition product **5b** (20%) was delivered but with very poor enantioselectivity (20% *ee*). Subsequently, the potential three-component reaction of benzaldehyde **6a**, diethyl α-aminomalonate **7** and nitrostyrene **3a** was explored, catalyzed by **1a** in the presence of 4 Å molecular sieves to remove water (a by-product of the reaction). Although a very low yield was attained when the three reagents were added together in one vessel, the reaction proceeded much better when **6a** and **7** were previously stirred at 0°C for 2 h, before adding **3a**.[8] A good yield with excellent enantioselectivity for the Michael adduct **4a** was obtained, whereas the results for cyclic product **5b** were still poor (Table 1, entry 5). Other bifunctional thiourea–tertiary amine catalysts **1c**–**1e** with various chiral scaffolds were also screened, affording the Michael adduct **4a** with inferior enantioselectivities (Table 1, entries 6–8). Pleasingly, the urea catalyst **1b**[12] displayed better efficacy and excellent enantioslectivity (96% *ee*) with high chemoselectivity for the Michael reaction was obtained (Table 1, entry 9). It should be noted that poor enantioselectivities for cycloaddition product **5b** were detected in all the screened reactions.

Having found the favourable reaction conditions, we then examined a variety of nitroalkene and aldehyde substrates to establish the general utility of the catalytic transformation.[14] The one-pot, three-component Michael addition of aldehydes **6**, diethyl α-aminomalonate **7** and nitroalkene **3** was commonly performed with 10 mol% of **1b** at 0°C for 48 h (after prior stirring of **6** and **7** at 0°C for 2 h). Only trace amounts of dipolar cycloaddition products were formed with all the tested substrates. As illustrated in Table 2, for benzaldehyde **6a**, excellent enantioselectivities and high yields were obtained for nitrostyrenes **3a**–**h**, bearing diverse electron-withdrawing or -donating substituents (Table 2, entries 1–8). High *ee* values were also attained for

Table 2. Asymmetric one pot, three-component Michael addition of aldehydes **6**, diethyl α-aminomalonate **7** and nitroalkenes **3**.[a]



Entry	Ar	R	Yield [%][b]	*ee* [%][c,13]
1	Ph	Ph	**4a** 93	96
2	Ph	*p*-ClPh	**4b** 87	98
3	Ph	*m*-ClPh	**4c** 93	98
4	Ph	*o*-ClPh	**4d** 80	94
5	Ph	*p*-BrPh	**4e** 84	96
6	Ph	*p*-FPh	**4f** 83	98
7	Ph	*p*-MePh	**4g** 95	96
8	Ph	*p*-MeOPh	**4h** 83	95
9	Ph	2-thienyl	**4i** 90	96
10	Ph	2-furyl	**4j** 89	98
11[d]	Ph	*n*-propyl	**4k** 56	97
12[d]	Ph	isopropyl	**4l** 60	98
13[d]	Ph	cyclohexyl	**4m** 48	98
14	*p*-FPh	Ph	**4n** 93	96
15	*p*-MePh	Ph	**4o** 86	97
16[e]	Ph	Ph	**4a** 90	94

[a] Unless otherwise noted, reactions were performed with **6** (0.1 mmol), **7** (0.1 mmol), **3** (0.12 mmol), **1b** (10 mol%), 4 Å MS (80 mg), in toluene (0.8 mL) at 0°C for 48 h. [b] Yield of isolated product. [c] Based on HPLC analysis on chiral column. [d] At room temperature for 72 h. [e] At 5.0 mmol scale with respect to aldehyde **6**, for 60 h.

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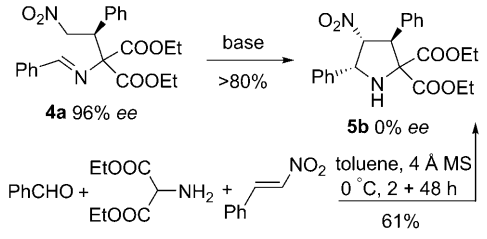
nitroalkenes **3i** and **3j**, with heteroaryl groups (Table 2, entries 9 and 10). Alkyl-substituted nitroalkenes exhibited lower reactivity, although high enantioselectivities were still obtained with moderate yields for reactions at ambient temperature for 72 h (Table 2, entries 11–13). Furthermore, other aryl aldehydes could be successfully applied in the Michael addition reaction (Table 2, entries 14 and 15). This catalytic reaction could be smoothly scaled up, affording similar results (Table 2, entry 16). Conversely, aliphatic aldehydes failed to afford the desired Michael adducts under the current catalytic conditions.

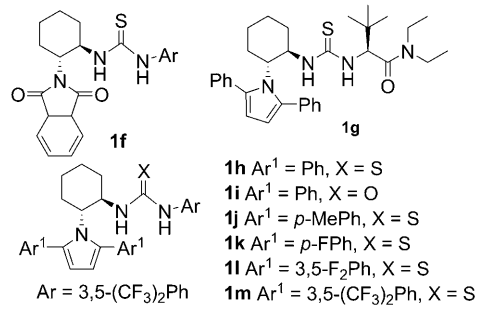
As the 1,3-dipolar cycloaddition products were generated in low yields and enantioselectivities, we investigated whether these pyrrolidine derivatives could be synthesized in a more enantioenriched manner. When chiral Michael adduct **4a** (96% *ee*) was treated with various bases (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), potassium *tert*-butoxide at room temperature, or lithium diisopropylamide (LDA) at −40°C), surprisingly, cyclic product **5b** was isolated in its racemic form (Scheme 3). Drawing on the results of



Scheme 3. Synthesis of [3+2] cycloaddition product **5b**.

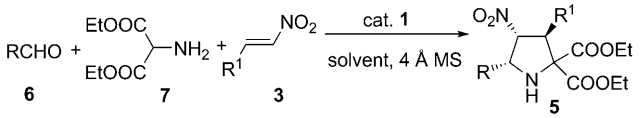
the chiral urea (thiourea)–tertiary amine-catalyzed reaction (see Table 1), we realized that the cyclic product was not produced from the Michael-addition intermediate by intramolecular cyclization.[15] Instead, a retro-Michael reaction of chiral **4a** would occur in the presence of a strong base, and the racemic **5b** would form in a concerted [3+2] cycloaddition mechanism. In fact, we found that **5b** could be directly isolated in 61% yield from the three-component reaction of benzaldehyde, diethyl α-aminomalonate and nitrostyrene without any catalyst at 0°C for 48 h. The Michael addition product **4a** was not detected (Scheme 3).[10] The presence of a tertiary amine functionality seems to be essential for the catalytic Michael addition, but not to be cooperative in the dipolar cycloaddition. Moreover, it has been documented that α-imino ester **2b** can undergo thermal 1,2-prototropy to produce the active azomethine ylide.[2k] The use of chiral monofunctional thioureas with bulkier substituents might aid stereocontrol in the asymmetric 1,3-dipolar cycloaddition.

To investigate these predictions, a range of catalysts **1f–m**,[16] bearing only an active thiourea (or urea) moiety (Scheme 4, 10 mol%), were screened in the one-pot, three-component reaction of benzaldehyde, diethyl α-aminomalonate and nitrostyrene in toluene at 0°C (Table 3, entries 1–8). Pleasingly, pyrrolidine **5b** was isolated as the sole product with complete *endo*-selectivity.[10] Thiourea–pyrrole compound **1l** was identified as the optimal catalyst (Table 3, entry 7). The *ee* value was improved to 81% at −20°C with 20 mol% of **1l** (Table 3, entry 9), and even higher *ee* could be attained in methyl *tert*-butyl ether (MTBE, Table 3, entry 10). The reaction of imine **2b** and nitrostyrene **3a** was also tested under the same catalytic conditions, affording the cycloaddition product **5c** in a better yield and with a



Scheme 4. The structures of chiral monofunctional thiourea (urea) catalysts **1f–m**.

Table 3. Asymmetric one-pot, three-component [3+2] cycloaddition of aldehydes **6**, diethyl α-aminomanolonate **7** and nitroalkenes **3**.[a]



Entry	Cat.	Conditions	R	R^1	Yield [%][b]	*ee* [%][c]
1	**1f**	A	Ph	Ph	**5b** 86	4
2	**1g**	A	Ph	Ph	**5b** 88	0
3	**1h**	A	Ph	Ph	**5b** 92	57
4	**1i**	A	Ph	Ph	**5b** 95	4
5	**1j**	A	Ph	Ph	**5b** 85	36
6	**1k**	A	Ph	Ph	**5b** 88	65
7	**1l**	A	Ph	Ph	**5b** 93	76
8	**1m**	A	Ph	Ph	**5b** 91	70
9[d]	**1l**	A	Ph	Ph	**5b** 70	81
10	**1l**	B	Ph	Ph	**5b** 73	90[e]
11[f]	**1l**	B	Ph	Ph	**5b** 92	89
12	**1l**	B	Ph	*p*-ClPh	**5c** 79	89
13	**1l**	B	Ph	*m*-ClPh	**5d** 83	90
14	**1l**	B	Ph	*o*-ClPh	**5e** 69	84
15	**1l**	B	Ph	*p*-FPh	**5f** 73	86
16	**1l**	B	Ph	*p*-MeOPh	**5g** 75	91
17	**1l**	B	Ph	2-furyl	**5h** 77	91
18	**1l**	B	Ph	*n*-propyl	**5i** 62	60
19	**1l**	B	*p*-ClPh	Ph	**5j** 90	86
20	**1l**	B	β-styryl	Ph	**5k** 56	83
21[g]	**1l**	B	Ph	Ph	**5b** 80	85

[a] Unless otherwise noted, reactions were performed with **6** (0.1 mmol), **7** (0.1 mmol), **3** (0.12 mmol), 4 Å MS (80 mg). Conditions A: with **1** (10 mol%) in toluene (0.8 mL) at 0°C for 48 h; Conditions B: with **1l** (20 mol%) in MTBE (0.8 mL) at −20°C for 72 h. [b] Yield of isolated product. [c] Based on chiral HPLC analysis. *endo*-selectivity > 99:1. [d] With **1l** (20 mol%) at −20°C for 72 h. [e] The absolute configuration of **5b** was determined by X-ray crystallographic analysis after some derivation (see Supporting Information). The others were assigned by analogy. [f] With imine **2b**. [g] At 3.0 mmol scale with respect to aldehyde **6**, for 120 h.

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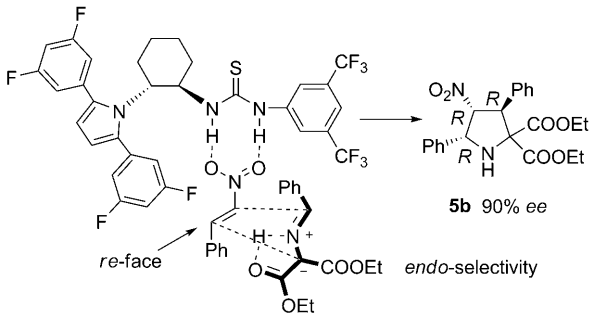
similar *ee* value (Table 3, entry 11). Subsequently, the substrate scope for the one-pot, three-component 1,3-dipolar cycloaddition was explored. Highly stereoselective reactions were proceeded using an array of nitrostyrenes with electron-withdrawing or donating substituents (Table 3, entries 12–16). Excellent enantioselectivity was also gained for 2-furyl-substituted nitroalkene (Table 3, entry 17). The use of an alkyl-substituted nitroalkene, however, led to more modest *ee* values (Table 3, entry 18). The reaction of *p*-chlorobenzaldehyde with nitrostyrene **3a** afforded good results in the cycloaddition reaction (Table 3, entry 19). Notably high enantioselectivity was detected when cinnamaldehyde was applied (Table 3, entry 20). We also tested the dipolar cycloaddition reaction at a larger scale, and a good *ee* value was attained (Table 3, entry 21). However, aliphatic aldehydes again could not be successfully used in the 1,3-dipolar cycloaddition.

Based on the absolute configuration of **5b**, a plausible catalytic mechanism for the concerted 1,3-dipolar cycloaddition was proposed. The steric hindrance of the bulky 2,5-diarylpyrrole substituent on the catalyst would lead to the formation of the aforementioned double hydrogen-bonding interaction between the thiourea moiety and nitrostyrene with the β-phenyl group directed away from the catalyst. Subsequently, *endo*-attack on the in situ-formed azomethine ylide from the *re*-face of nitrostyrene would generate the chiral pyrrolidine product **5b** (Scheme 5).



Scheme 5. Proposed catalytic mechanism for the 1,3-dipolar cycloaddition.

In conclusion, we have investigated the organocatalytic one-pot, three-component reaction of aldehydes, diethyl α-aminomalonate and nitroalkenes. Either the Michael addition or [3+2] dipolar cycloaddition products could be selectively obtained in high enantioselectivities from the same reactants catalyzed by either a bifunctional urea–tertiary amine or monothiourea compound, respectively, providing facile methods to access diverse chiral nitrogen-containing molecules. Furthermore, direct experimental evidence suggests that the 1,3-dipolar cycloaddition of in situ-formed azomethine ylides and nitroalkenes proceeds by a concerted [3+2] mechanism, rather than a formal stepwise Michael addition–cyclization.[9] Investigation into further application of thiourea (urea)-based asymmetric catalysis is currently in progress in our laboratory.

Acknowledgements

We are grateful for the financial support from NSFC (20502018), Ministry of Education (NCET-05-0781) and Chinesisch-Deutsches Zentrum für Wissenschaftsförderung [GZ422 (362/6)].

Keywords: azomethine ylides · cycloaddition · Michael addition · nitroalkenes · organocatalysis

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Received: July 11, 2008
Published online: October 2, 2008

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