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Asymmetric Michael Addition of γ,γ-Disubstituted α,β-Unsaturated Aldehydes to Nitroolefins via Dienamine Catalysis

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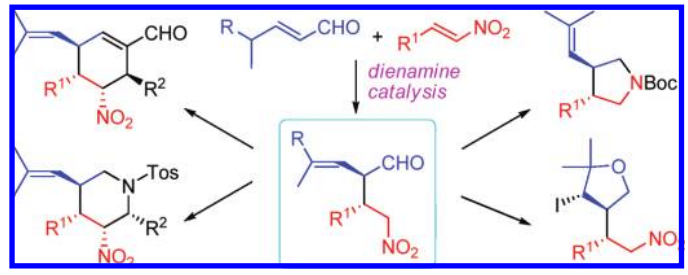
ABSTRACT



The first chemo- and α-regioselective asymmetric Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes to nitroolefins has been presented in excellent diastereo- and enantioselectivities (dr up to >99:1, 93−96% ee) via dienamine catalysis. The Michael adducts have been efficiently converted to a number of optically pure cyclic frameworks with versatile scaffold diversity.

The discovery of effective synthetic methodologies that can access chiral compounds with multifunctionalities is in increasing demand owing to the rapid development of chiral drugs.[1] It would be quite attractive if the obtained products could be further transformed to a broad spectrum of optically pure compounds with scaffold diversity in a highly economic way.[2] Over the past decade, asymmetric aminocatalysis has made great progress through a variety of activation modes for carbonyl compounds.[3] Among them, the direct Michael addition of saturated aldehydes or ketones to nitroolefins via enamine catalysis has triggered extensive interest because of the synthetic versatility of the bifunctional adducts.[4,5] In sharp contrast, the direct Michael addition of α,β-unsaturated aldehydes to nitroolefins, in which the inversion of the inherent electrophilicity of α,β-unsaturated aldehydes will be involved by dienamine activation,[6] has not been developed yet, probably because the rather challenging manipulations on chemo-, regio-, and stereoselectivities must be simultaneously fulfilled in a complex reaction system. Although a Baylis−Hillman-type reaction of α,β-unsaturated aldehydes and nitroolefins has been reported by a proline−Lewis base cocatalysis,[7] unfortunately, almost no enantioselectivity was

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(2) For a highlight on scaffold diversity synthesis, see: Galloway, W. R. J. D.; Diáz-Gavilán, M.; Isidro-Llobet, A.; Spring, D. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1194.

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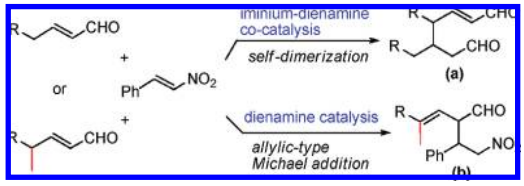
obtained.[8] Encouraged by our recent findings in an inverse-electron-demand aza-Diels−Alder reaction of *N*-Tos-1-aza-1,3-butadienes and α,β-unsaturated aldehydes,[9] we hope to develop the first direct chemo-, regio-, and stereoselective Michael addition of α,β-unsaturated aldehydes to nitroolefins via dienamine catalysis.

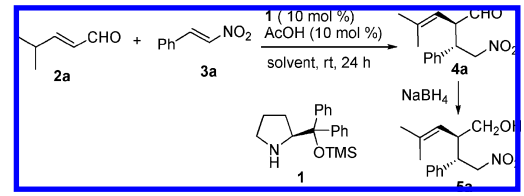
Nevertheless, the self-dimerization of α,β-unsaturated aldehyde was preferably observed in the reaction mixture of a linear enal and nitroolefin catalyzed by a secondary amine,[6a,c] which was ascribed to iminium−dienamine co-activation of α,β-unsaturated aldehyde [Scheme 1, (a)]. We

Scheme 1. Switching Reactivity in Different α,β-Unsaturated Aldehyde and Nitroolefin Reaction Systems



envisaged that the self-dimerization process would be significantly prohibited if a more bulky γ,γ-disubstituted α,β-unsaturated aldehyde was applied. As a result, the intermolecular conjugate addition of an in situ formed dienamine intermediate to electrophilic nitroolefin might be enforced [Scheme 1, (b)]. In fact, we were pleased to find that the chemoselective Michael addition of 4-methyl-2-penten-1-al **2a** to β-nitrostyrene **3a** could be realized by the catalysis of α,α-diphenylprolinol *O*-TMS ether **1**[10] and AcOH in toluene at room temperature. Furthermore, an exclusive α-regioselectivity was noted, and the allylic alkylated product **4a** was obtained,[11] which was more easily isolated and analyzed as the corresponding alcohol **5a**. Gratifyingly, both diastereo- and enantioselectivities were remarkable (Table 1, entry 1).

Table 1. Screening Studies of Organocatalytic Direct Michael Addition of α,β-Unsaturated Aldehyde **2a** to Nitroolefin **3a**[a]



entry	solvent	yield[b] (%)	dr[c]	ee[c]
1	toluene	52	91:9	94
2	THF	<10	–	–
3	DCM	68	75:25	82
4	DMF	<10	–	–
5	DMSO	<10	–	–
6[d]	**MeCN**	**78**	**92:8**	**96**
7[e]	MeCN	41	89:11	95
8[f]	MeCN	67	94:6	96

[a] Unless otherwise noted, reactions were performed with 0.4 mmol of **2a**, 0.2 mmol of **3a**, 0.2 mmol of **1**, and AcOH in 0.5 mL of solvent, for 24 h. [b] Isolated yield of **5a** for two steps. [c] By HPLC analysis. [d] For 12 h. [e] Without AcOH. [f] With PhCOOH.

Subsequently, a variety of solvents were screened (entries 2−6), and higher efficacy was gained in CH_3CN (entry 6). Lower reaction rate was observed in the absence of AcOH (entry 7). In addition, similar good results were attained when PhCOOH was used (entry 8).

Consequently, a variety of nitroolefins were explored in the reaction with γ,γ-disubstituted α,β-unsaturated aldehydes catalyzed by **1** and AcOH in acetonitrile. As summarized in Table 2, for 4-methyl-2-penten-1-al **2a**, excellent enantioselectivities were obtained for an array of nitroolefins bearing β-aryl groups with diverse electron-withdrawing or -donating substitutions, while the diastereoselectivities were good to excellent (Table 2, entries 1−7). A modest dr ratio was obtained for a heteroaryl-substituted nitroolefin, but the ee value was still high (entry 8). In addition, β-alkyl-substituted nitroolefins could be successfully utilized, and the results were also outstanding (entries 9 and 10). Moreover, a racemic 4-phenyl-2-penten-1-al **2b** was synthesized and tested. To our gratification, the complete *E*-configuration was observed in the newly generated C=C bond of product **5k**, and excellent diastereo- and enantioselectivities were attained (entry 11).

(4) For selected examples of Michael addition of saturated carbonyl compounds to nitroolefins by enamine catalysis, see: (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (b) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (c) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (d) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (e) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (f) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (g) Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984. (h) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093. (i) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (j) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923. (k) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545. (l) Belot, S.; Sulzer-Mossé, S.; Kehrli, S.; Alexakis, A. *Chem. Commun.* **2008**, 4694. (m) Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem.−Eur. J.* **2008**, *14*, 9357. (n) Tan, B.; Zeng, X.; Lu, Y.; Chua, P. J.; Zhong, G. *Org. Lett.* **2009**, *11*, 1927.

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(6) For limited examples on dienamine catalysis, see: (a) Ramachary, D. B.; Ramakumar, K. K. *Tetrahedron Lett.* **2005**, *46*, 7037. (b) M. Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett.* **2006**, *8*, 2217. (c) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (d) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Huang, G.-F.; Su, C.-F.; Liao, J.-H. *J. Org. Chem.* **2007**, *72*, 8459. (e) Hong, B.-C.; Tseng, H.-C.; Chen, S.-H. *Tetrahedron* **2007**, *63*, 2840. (f) de Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1450. (g) Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figueiredo, R. M.; Christmann, M. *Org. Lett.* **2009**, *11*, 4116.

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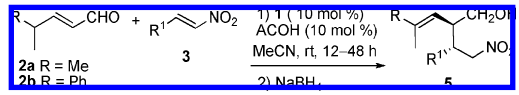
(10) For reviews on α,α-diarylprolinol ethers catalysis, see: (a) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.

(11) The absolute configuration of **4a** was assigned based on an X-ray structure of the derivative **6e** (see Figure 1). Thus, the origin of the stereoselectivity in this dienamine catalysis by catalyst **1** is similar to that observed in its enamine catalysis (see ref 3f).

Table 2. Asymmetric Direct Michael Addition of α,β-Unsaturated Aldehydes **2** to Nitroolefins **3**[a]

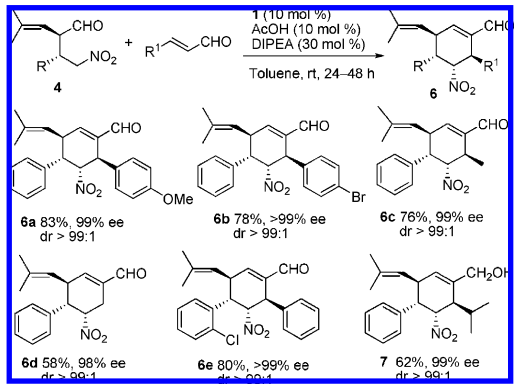


entry	**2**	R^1	**5**	yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**	Ph	**5a**	78	92:8	96
2	**2a**	*o*-ClC_6H_4	**5b**	76	96:4	95
3	**2a**	*m*-ClC_6H_4	**5c**	80	93:7	95
4	**2a**	*p*-ClC_6H_4	**5d**	72	95:5	93
5	**2a**	*o*-BrC_6H_4	**5e**	75	96:4	96
6	**2a**	*m*-$MeOC_6H_4$	**5f**	69	85:15	94
7	**2a**	3,4-$(MeO)_2C_6H_3$	**5g**	62	84:16	94
8	**2a**	thienyl	**5h**	71	75:25	94
9	**2a**	*c*-Hexyl	**5i**	58	98:2	95
10	**2a**	*n*-Propyl	**5j**	52	92:8	95
11	**2b**	*o*-BrC_6H_4	**5k**	68	>99:1	94

[a] Unless otherwise noted, reactions were performed with 0.4 mmol of **2**, 0.2 mmol of **3**, 0.2 mmol of **1**, and AcOH in 0.5 mL of CH_3CN at rt. [b] Isolated yield of **5** for two steps. [c] By ^1H NMR and HPLC analysis. [d] By HPLC analysis.

With the multifunctional Michael adducts **4** in hand, we then conducted a cascade reaction with another α,β-unsaturated aldehyde by the tandem iminium−enamine catalysis of **1**, similar to that reported by Enders and co-workers.[12] The presence of additional base catalyst diisopropylethylamine (DIPEA) was crucial for the reaction conversion. As illustrated in Scheme 2, the densely functionalized 1-cyclohexene-1-carboxaldehydes **6a**−**6e** with multiple chiral centers could be directly isolated with almost complete enantiopurity in moderate to good yields. The absolute configuration of **6e** was confirmed by an X-ray crystallographic analysis (Figure 1). The alcohol **7** was obtained by $NaBH_4$ reduction of the corresponding 1-cyclohexene-1-carboxaldehyde from the cascade reaction of two molecules of **2a** with **3a**.

Scheme 2. Cascade Reaction to Densely Substituted 1-Cyclohexene-1-carboxaldehydes



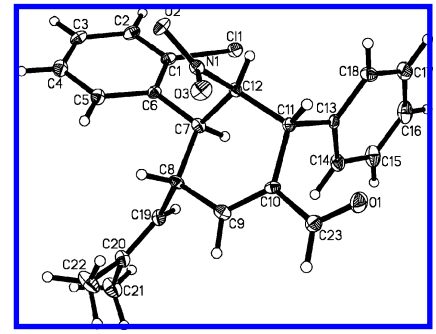


Figure 1. X-ray structure of enantiopure **6e**.

On the other hand, the highly diastereoselective nitro-Mannich reaction could be performed with aldehyde **4a** and *N*-Tos aryl or alkyl imines by the catalysis of an achiral base tetramethylguanidine (TMG). The hemiaminals **8** were generated by a domino intramolecular cyclization process, which were further transformed to diverse chiral piperidine derivatives **9**−**11** (Scheme 3).[13] It should be noted that such nitro group-containing piperidine compounds are very valuable intermediates for the synthesis of novel Farnesyltransferase inhibitors[14] or selective dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes.[15]

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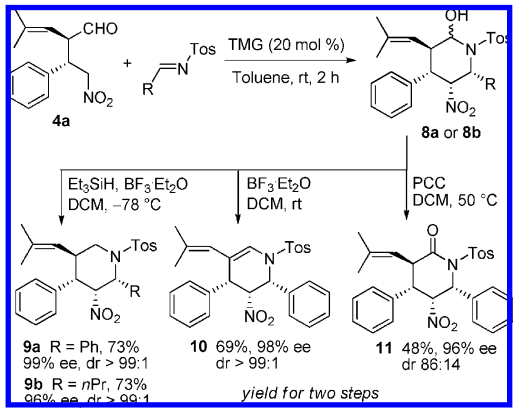
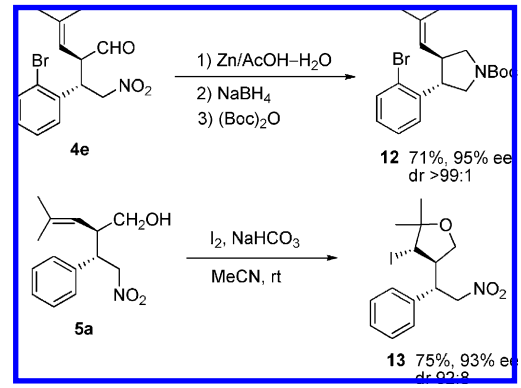
Scheme 3. Synthesis of Chiral Piperidine Derivatives



Scheme 4. Synthesis of Five-Membered Heterocycles



We have further explored the synthetic utilities of the Michael adducts to afford some five-membered heterocycles. As outlined in Scheme 4, the chiral pyrrolidine compound **12** with a side olefin functionality could be efficiently prepared from **4e**,[4m] which might allow more transformations for molecular complexity.[9] Furthermore, a chiral tetrahydrofuran framework **13** was smoothly obtained from **5a** by an iodine-mediated cyclization reaction.

In conclusion, we have developed the first direct chemo- and regioselective Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes to nitroolefins via dienamine catalysis. In general, excellent enantioselectivities and diastereoselectivities have been obtained for a spectrum of substrates (dr up to >99:1, 93−96% ee). Moreover, we have demonstrated that the obtained multifunctional Michael adducts are very versatile synthons for further organic transformations. Some valuable cyclic frameworks with scaffold diversity, which might have synthetic significance in medicinal chemistry, have been efficiently prepared. Currently, more studies on asymmetric reactions via dienamine catalysis are being investigated in our laboratory.

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Supporting Information Available: Experimental procedures, structural proofs including NMR spectra and HPLC chromatograms, and CIF file of **6e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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