Asymmetric Aminocatalysis

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Organocatalytic Regio- and Stereoselective Inverse-Electron-Demand Aza-Diels–Alder Reaction of α,β-Unsaturated Aldehydes and *N*-Tosyl-1-aza-1,3-butadienes**

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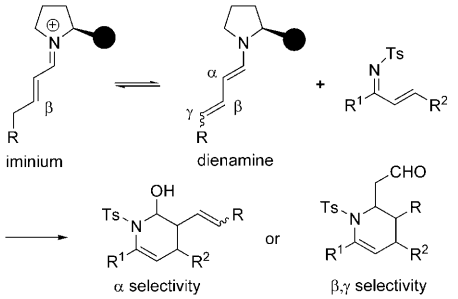
Aminocatalysis, the activation of carbonyl compounds by enamines, iminium ions, or the SOMO-activation strategy, has become a fundamental approach in asymmetric synthesis.[1] Moreover, the catalytic modes of amines are still under expansion.[2] Recently, Jørgensen and co-workers developed dienamine catalysis by inverting the inherent reactivity of α,β-unsaturated aldehydes, which acted as nucleophiles for direct enantioselective γ amination with diethyl azodicarboxylate.[3] However, the synthetic potential of dienamine catalysis seems to be underestimated, and very limited progress has been made to date[4] in spite of the extensive studies on asymmetric aminocatalysis over the past decade.

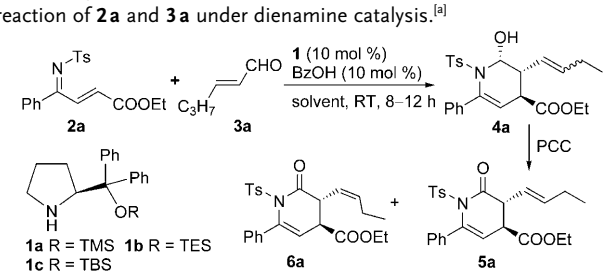
The development of efficient methodologies that enable simpler, cheaper, and more concise approaches to the generation of structural complexity with exquisite levels of stereocontrol remains a preeminent goal in modern organic chemistry. Recently, we presented a highly enantioselective inverse-electron-demand aza-Diels–Alder reaction of *N*-sulfonyl 1-aza-1,3-butadienes[5] and aliphatic aldehydes to form optically pure piperidines through enamine activation.[6–8] We were fascinated by the possible and conceptually unprecedented application of dienamine catalysis in an inverse-electron-demand aza-Diels–Alder reaction of α,β-unsaturated aldehydes with electron-deficient *N*-sulfonyl 1-aza-1,3-butadienes to construct chiral piperidine derivatives bearing several functional groups in a straightforward manner (Scheme 1).[9] We wondered whether the chemo-, regio-, and stereoselectivity of this complicated reaction could be controlled simultaneously in an elegant manner.

We initially investigated the reaction of *N*-tosyl-1-aza-1,3-butadiene (**2a**) and hexen-2-al (**3a**) in a mixture of THF and H_2O at room temperature under the catalysis of the chiral secondary amine **1a** (10 mol%) and benzoic acid (10 mol%).[10] The reaction proceeded smoothly with exclusive α regioselectivity. The chiral hemiaminal **4a** (an *E*/*Z* mixture) was isolated as the sole product. The oxidation of **4a** with pyridinium chlorochromate (PCC) gave a separable mixture of lactam **5a** and its *Z* isomer **6a**. Excellent enantioselectivity was observed for the formation of the *E* isomer **5a** (Table 1, entry 1). Similar results were obtained when the



Scheme 1. Proposed inverse-electron-demand aza-Diels–Alder reaction of a dienamine intermediate generated in situ as an electron-rich olefin. Ts = 4-toluenesulfonyl.

Table 1: Optimization of the inverse-electron-demand aza-Diels–Alder reaction of **2a** and **3a** under dienamine catalysis.[a]



Entry	1	Solvent	Yield [%][b] 5a/6a	*E*/*Z*[c]	*ee* [%][d]
1	**1a**	THF/H_2O	51/23	2.2:1	96
2	**1a**	CH_3CN/H_2O	56/24	2.3:1	97
3	**1a**	dioxane/H_2O	55/30	1.8:1	94
4	**1a**	CH_3CN	–	–	–
5	**1b**	CH_3CN/H_2O	49/20	2.4:1	97
6	**1c**	CH_3CN/H_2O	38/17	2.2:1	98
7[e]	**1a**	CH_3CN/H_2O	**68/8**	**8.1:1**	**99**
8[e,f]	**1a**	CH_3CN/H_2O	60/9	6.7:1	98

[a] Reaction conditions (unless otherwise noted): **2a** (0.1 mmol), **3a** (0.2 mmol), **1** (10 mol%), BzOH (10 mol%), room temperature, 8–12 h. [b] Yield of the isolated product. [c] The *E*/*Z* ratio was calculated from the yields of **5a** and **6a**. [d] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [e] The reaction was carried out at −10 °C for 12 h. [f] AcOH: 10 mol%. Bz = benzoyl, TMS = trimethylsilyl, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl.

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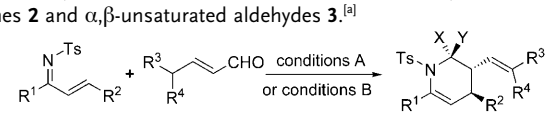
reaction was conducted in CH_3CN/H_2O or dioxane/H_2O (Table 1, entries 2 and 3). The presence of water was crucial for conversion: Almost no reaction occurred in neat CH_3CN (Table 1, entry 4).[6] Other chiral amine catalysts, **1b** and **1c**, afforded **5a** in lower yield (Table 1, entries 5 and 6). The *E*/*Z* ratio could be improved by carrying out the reaction at −10 °C, without much effect on the reactivity (Table 1, entry 7). Good results were also observed when AcOH was used as an additive (Table 1, entry 8).

We explored the new transformation for the synthesis of diverse chiral piperidine derivatives with a variety of *N*-tosyl-1-aza-1,3-butadienes **2** and α,β-unsaturated aldehydes **3**. As summarized in Table 2, the reaction showed substantial

Table 2: Asymmetric aza-Diels–Alder reaction of *N*-tosyl-1-aza-1,3-butadienes **2** and α,β-unsaturated aldehydes **3**.[a]



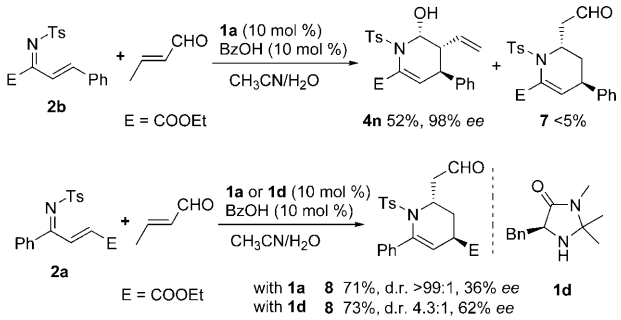
2 **3** **4** X = OH, Y = H; **5** X = Y = O

Entry	R^1	R^2	R^3	R^4	Yield[b] [%]	*E*/*Z*[c]	*ee*[d] [%]
1	Ph	COOEt	Et	H	68 (**5a**)	8.1:1	99
2	Ph	COOEt	Me	H	66 (**5b**)	5.8:1	98
3	Ph	COOEt	*n*Pr	H	70 (**5c**)	6.7:1	97
4	*p*-ClC_6H_4	COOEt	Et	H	71 (**5d**)	7.5:1	98
5	*p*-BrC_6H_4	COOEt	Et	H	68 (**5e**)	8.9:1	98
6	*p*-MeC_6H_4	COOEt	Et	H	72 (**5f**)	7.6:1	98
7	Ph	COOEt	Me	Me	95 (**4g**)	–	99
8	2-thienyl	COOEt	Me	Me	91 (**4h**)	–	99
9	COOEt	Ph	Me	Me	95 (**4i**)	–	>99
10[e]	COOEt	*o*-BrC_6H_4	Me	Me	91 (**4j**)	–	>99
11	COOEt	*p*-$MeOC_6H_4$	Me	Me	96 (**4k**)	–	>99
12[e]	Ph	Ph	Me	Me	89 (**4l**)	–	99
13[e]	Ph	Me	Me	Me	85 (**4m**)	–	98
14[f]	COOEt	Ph	Me	Me	92 (**4i**)	–	99

[a] Conditions A (entries 1–6): The aza-DA reaction was conducted at −10 °C for 8–12 h, and the isolated hemiaminal was oxidized to the lactam with PCC. Conditions B (entries 7–14): The aza-DA was conducted at room temperature for 2–6 h, and the hemiaminal was isolated for analysis. [b] Yield of the isolated product. [c] The *E*/*Z* ratio was calculated from the yields of **5** and its *Z* isomer (after isolation). [d] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [e] The reaction was carried out at 35 °C for 6 h. [f] The reaction was carried out on a 1.0 mmol scale.

generality. A few linear enals were used successfully in the reactions with variously substituted *N*-tosyl-1-aza-1,3-butadienes. The resulting chiral hemiaminals **4a–f** were oxidized directly to the corresponding lactams, and the major *E* isomers **5a–f** were isolated in good yields with excellent *ee* values (Table 2, entries 1–6). Interestingly, a branched enal exhibited even better reactivity: Outstanding enantioselectivities and yields were observed for all examples tested (Table 2, entries 7–13; hemiaminals **4g–m** (d.r. > 99:1) were analyzed directly.) Simple 1-aza-1,3-butadienes also reacted efficiently with this branched enal (Table 2, entries 12 and 13). When one of the asymmetric reactions was conducted on a larger scale, similar excellent results were observed (Table 2, entry 14).

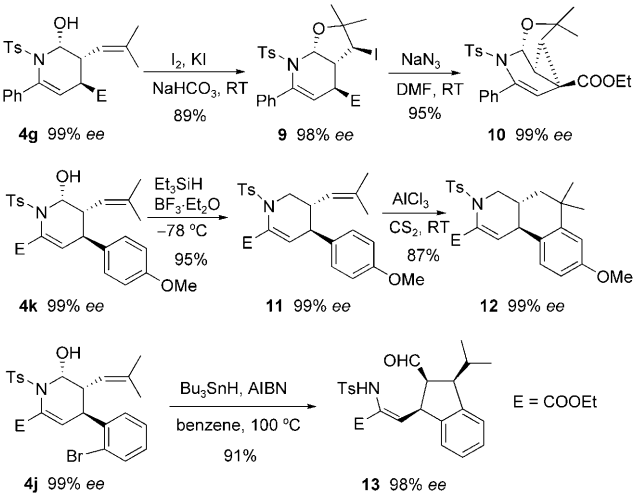
Unexpected regioselectivity was observed in an aza-Diels–Alder reaction of crotonaldehyde. The expected cycloadduct **4n** of an α-regioselective reaction was obtained from the reaction of the *N*-tosyl-1-aza-1,3-butadiene **2b** with crotonaldehyde, although a trace amount of **7**, formed through addition to the β,γ-bond of crotonaldehyde, was also detected (Scheme 2). However, aldehyde **8** was isolated



Scheme 2. Unexpected regioselectivity in the inverse-electron-demand aza-Diels–Alder reaction of crotonaldehyde. (The major enantiomer of **8** formed with catalyst **1d** was the opposite enantiomer to that formed in excess with **1a**.). Bn = benzyl.

exclusively when the *N*-tosyl-1-aza-1,3-butadiene **2a** was used. Low enantioselectivity was observed in this reaction as a result of the distance of the reaction sites from the chiral catalyst. A better *ee* value was observed when the MacMillan catalyst **1d** was used.[11] These findings may arouse more research interest in dienamine catalysis, as another cycloaddition pathway could be introduced.

We investigated the synthetic versatility of the multifunctional piperidine derivatives, especially for scaffold diversification.[12] The C=C bond in the alkenyl substituent on the piperidine ring served as a very valuable functionality in some intramolecular cyclization reactions, such as an iodine-mediated cyclization (to form **9**), a Friedel–Crafts reaction (to form **12**), and a radical cyclization (to form **13**; Scheme 3). All transformations proceeded in excellent yield with excellent



Scheme 3. Synthetic transformations of hemiaminals **4**. AIBN = azobisisobutyronitrile, DMF = *N*,*N*-dimethylformamide.

diastereoselectivity (when applicable). Notably, a fused tricyclic compound **10** containing a cyclopropane moiety[13] and four contiguous stereogenic centers was produced unexpectedly when we attempted to synthesize an N_3-substituted derivative from **9**.[14] The structure of **10** was confirmed unambiguously by X-ray crystallographic analysis (Figure 1).[15]

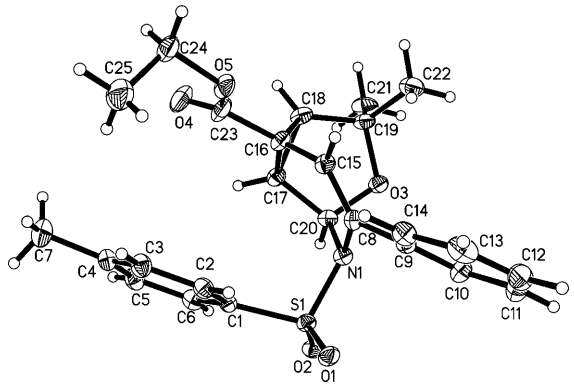


Figure 1. X-ray crystal structure of the enantiomerically pure cyclopropane derivative **10**.

In conclusion, we have developed an unprecedented and highly regio- and stereoselective dienamine-catalyzed inverse-electron-demand aza-Diels–Alder reaction of *N*-tosyl-1-aza-1,3-butadienes and α,β-unsaturated aldehydes.[16] The resulting densely functionalized enantiomerically pure piperidine derivatives and cyclic scaffolds derived from these compounds may be useful in the total synthesis of natural products and medicinal chemistry.[17] Moreover, this methodology may also prompt the development of further applications of α,β-unsaturated aldehydes in asymmetric synthesis.

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Keywords: asymmetric catalysis · aza-Diels–Alder reaction · dienamine catalysis · piperidines · α,β-unsaturated aldehydes

[1] For reviews on aminocatalysis, see: a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; c) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; d) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; e) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**.

[2] a) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2007**, *119*, 1910; *Angew. Chem. Int. Ed.* **2007**, *46*, 1878; b) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; for a Highlight, see: c) P. Melchiorre, *Angew. Chem.* **2009**, *121*, 1386; *Angew. Chem. Int. Ed.* **2009**, *48*, 1360.

[3] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973.

[4] For examples of dienamine catalysis for the γ activation of α,β-unsaturated aldehydes, see: a) B.-C. Hong, M.-F. Wu, H.-C. Tseng, J.-H. Liao, *Org. Lett.* **2006**, *8*, 2217; b) B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su, J.-H. Liao, *J. Org. Chem.* **2007**, *72*, 8459; c) B.-C. Hong, H.-C. Tseng, S.-H. Chen, *Tetrahedron* **2007**, *63*, 2840; d) R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem.* **2008**, *120*, 1472; *Angew. Chem. Int. Ed.* **2008**, *47*, 1450.

[5] For inverse-electron-demand aza-Diels–Alder reactions of *N*-sulfonyl 1-aza-1,3-butadienes, see: a) D. L. Boger, A. M. Kasper, *J. Am. Chem. Soc.* **1989**, *111*, 1517; b) D. L. Boger, W. L. Corbett, J. M. Wiggins, *J. Org. Chem.* **1990**, *55*, 2999; c) D. L. Boger, W. L. Corbett, T. T. Curran, A. M. Kasper, *J. Am. Chem. Soc.* **1991**, *113*, 1713; d) D. L. Boger, K. C. Cassidy, S. Nakahara, *J. Am. Chem. Soc.* **1993**, *115*, 10733; e) D. L. Boger, J. Hong, *J. Am. Chem. Soc.* **1998**, *120*, 1218; f) M. J. Schnermann, D. L. Boger, *J. Am. Chem. Soc.* **2005**, *127*, 15704; g) R. C. Clark, S. S. Pfeiffer, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 2587; h) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418; i) J. Esquivias, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480; j) J. Esquivias, I. Alonso, R. G. Arrayás, J. C. Carretero, *Synthesis* **2009**, 113; k) for a recent review, see: B. Groenendaal, E. Ruijter, R. V. A. Orru, *Chem. Commun.* **2008**, 5474.

[6] B. Han, J.-L. Li, C. Ma, S.-J. Zhang, Y.-C. Chen, *Angew. Chem.* **2008**, *120*, 10119; *Angew. Chem. Int. Ed.* **2008**, *47*, 9971.

[7] For selected examples of the construction of piperidine derivatives through iminium catalysis, see: a) L. Zu, H. Xie, H. Li, J. Wang, X. Yu, W. Wang, *Chem. Eur. J.* **2008**, *14*, 6333; b) Y. Hayashi, H. Gotoh, R. Masui, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4076; *Angew. Chem. Int. Ed.* **2008**, *47*, 4012; c) J. Franzén, A. Fisher, *Angew. Chem.* **2009**, *121*, 801; *Angew. Chem. Int. Ed.* **2009**, *48*, 787.

[8] For selected examples of enamine-catalyzed inverse-electron-demand hetero-Diels–Alder reactions, see: a) K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1536; *Angew. Chem. Int. Ed.* **2003**, *42*, 1498; b) S. Samanta, J. Krause, T. Mandal, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 2745; c) J. Wang, F. Yu, X. Zhang, D. Ma, *Org. Lett.* **2008**, *10*, 2561; d) H. Xie, L. Zu, H. R. Oueis, H. Li, J. Wang, W. Wang, *Org. Lett.* **2008**, *10*, 1923; e) F. A. Hernandez-Juan, D. M. Cockfield, D. J. Dixon, *Tetrahedron Lett.* **2007**, *48*, 1605.

[9] For a review, see: M. Rubiralta, E. Giralt, A. Diez, *Piperidine: Structure, Preparation, and Synthetic Applications of Piperidine and Its Derivatives*, Elsevier, Amsterdam, **1991**.

[10] For a review on catalysis by α,α-diaryl prolinol ethers, see: a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; for selected leading references, see: b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; c) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; d) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; e) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354; f) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608; g) P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem.* **2008**, *120*, 4797; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719; h) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722; i) L. Zu, S. Zhang, H. Xie, W. Wang, *Org. Lett.* **2009**, *11*, 1627.

[11] For more preliminary experiments to improve the enantioselectivity of the β,γ-selective reaction to form cycloadduct **8**, see the Supporting Information.

[12] For an excellent example of scaffold diversification, see: a) D. Morton, S. Leach, C. Cordier, S. Warriner, A. Nelson, *Angew. Chem.* **2009**, *121*, 110; *Angew. Chem. Int. Ed.* **2009**, *48*, 104; for a Highlight, see: b) W. R. J. D. Galloway, M. Diáz-Gavilán, A. Isidro-Llobet, D. R. Spring, *Angew. Chem.* **2009**, *121*, 1216; *Angew. Chem. Int. Ed.* **2009**, *48*, 1194.

[13] For reviews on cyclopropane derivatives, see: a) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; b) F. Gnad, O. Reiser, *Chem. Rev.* **2003**, *103*, 1603.
[14] The formation of compound **10** might be the result of an azide-catalyzed enolization followed by an intramolecular substitution.
[15] CCDC 730750 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.
[16] The reaction mechanism may involve an *endo*-selective aza-Diels–Alder transformation similar to that of saturated aldehydes (see references [6] and [8a]). However, a formal α-regioselective 1,4-addition followed by ring closure can not be ruled out at this stage.
[17] For selected examples of analogous cyclic scaffolds that exhibit significant biological activity, see: a) R. L. Clarke, A. J. Gambino, S. J. Daum, *J. Med. Chem.* **1974**, *17*, 1040; b) M. G. N. Russell, R. Baker, D. C. Billington, A. K. Knight, D. N. Middlemiss, A. J. Noble, *J. Med. Chem.* **1992**, *35*, 2025; c) M. D. Meyer, J. F. DeBernardis, A. A. Hancock, *J. Med. Chem.* **1994**, *37*, 105.

