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Organocatalytic Sequential Hetero-Diels–Alder and Friedel–Crafts Reaction: Constructions of Fused Heterocycles with Scaffold Diversity

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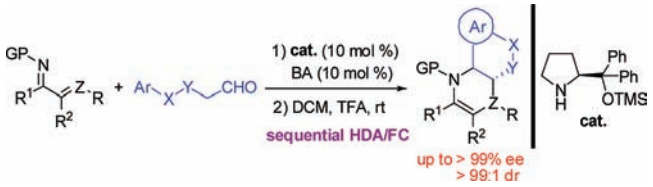
ABSTRACT



A highly enantioselective aza-Diels–Alder and Friedel–Crafts reaction sequence of *N*-sulfonyl-1-aza-1,3-butadienes and aliphatic aldehydes tethered to an arene motif has been developed, affording the fused chiral piperidine frameworks with a versatile scaffold diversity. A similar strategy has been applied for the construction of complex chiral tetrahydroquinoxaline structures.

The chiral fused piperidine structures have been widely embedded in natural alkaloids.[1] They are also the "privileged" skeletons in numerous pharmaceutically important compounds that exhibit broad biological activities as exemplified in Figure 1.[2] Not surprisingly, the development of efficient protocols to access enantioenriched fused piperidine frameworks has always attracted much attention in both synthetic and medicinal chemistry communities.[3] Notably, Franzén and co-workers presented a very effective one-pot organocatalytic reaction to complex quinolizidine derivatives, in which an intramolecular Friedel–Crafts reaction of an in situ formed acyliminium ion was utilized to complete the fused ring production.[4] Subsequently, Zhao et al. successfully expanded such a synthetic strategy.[5] Nevertheless, highly electron-rich 3-indolyl or 3,4-dimethoxyphenyl motifs usually have to be applied in the Friedel–Crafts sequence, which would significantly limit the structural diversity constructions.[6]

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(1) For a review, see: Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991.

(2) For selected examples, see: (a) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756. (b) Cannon, J. G.; Lee, T.; Goldman, H. D.; Long, J. P.; Flynn, J. R.; Verimer, T.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1980**, *23*, 1. (c) Augstein, J.; Ham, A. L.; Leeming, P. R. *J. Med. Chem.* **1972**, *15*, 466. (d) Kunstmann, R.; Fischer, G. *J. Med. Chem.* **1984**, *27*, 1312. (e) Cook, C. E.; Wani, M. C.; Jump, J. M.; Lee, Y.-W.; Fail, P. A.; Anderson, S. A.; Gu, Y.-Q.; Petrow, V. *J. Med. Chem.* **1995**, *38*, 753. (f) Rampin, O.; Jerome, N.; Susandeau, C. *Life Science* **2003**, *72*, 2329.

(3) For selected examples, see: (a) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (b) Dickmeiss, G.; Jensen, K. L.; Worgull, D.; Franke, P. T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1580. (c) Yamashita, M.; Yamada, K.-i.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1954. (d) Sarkar, N.; Banerjee, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 9222. (e) Xie, M.; Chen, X.; Zhu, Y.; Gao, B.; Lin, L.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799. (f) Pepe, A.; Pamment, M.; Georg, G. I.; Malhotra, S. V. *J. Org. Chem.* **2011**, *76*, 3527.

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(5) (a) Wu, X. Y.; Dai, X. Y.; Nie, L. L.; Fang, H. H.; Chen, J.; Ren, Z. J.; Cao, W. G.; Zhao, G. *Chem. Commun.* **2010**, *46*, 2733. (b) Fang, H.; Wu, X.; Nie, L.; Dai, X.; Chen, J.; Cao, W.; Zhao, G. *Org. Lett.* **2010**, *12*, 5366. (c) Wu, X.; Dai, X.; Fang, H.; Nie, L.; Chen, J.; Cao, W.; Zhao, G. *Chem.—Eur. J.* **2011**, *17*, 10510.

(6) For a recent study on *N*-acyliminium ion chemistry, see: Othman, R. B.; Affani, R.; Tranchant, M.-J.; Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 776.

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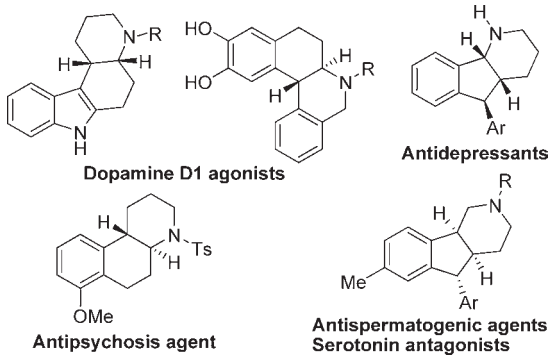
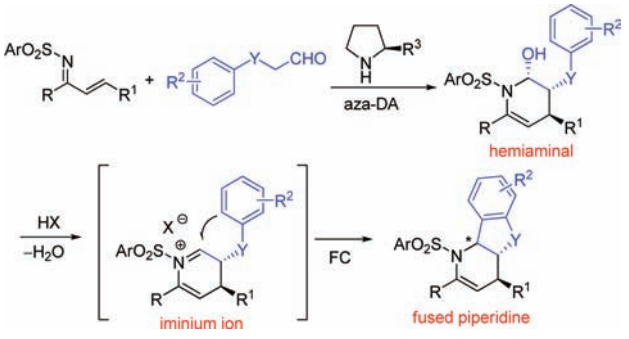


Figure 1. Selected fused piperidine systems showing broad biological activity.

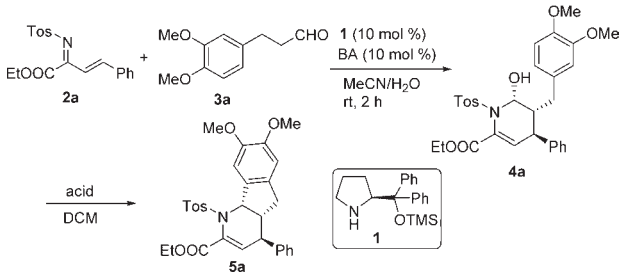
Recently, we developed an asymmetric inverse-electron-demand aza-Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes and aliphatic aldehydes catalyzed by a chiral secondary amine, which delivered almost enantiopure piperidine derivatives containing a hemiaminal functionality.[7] As illustrated in Scheme 1, we envisaged that an electrophilic iminium ion would be generated from the hemiaminal intermediate under proper acidic conditions; consequently, an intramolecular Friedel–Crafts reaction with a tethered arene system would proceed to give the fused piperidine derivatives with high molecular complexity.[8] The iminium ion bears a strongly electron-withdrawing *N*-sulfonyl group, which would be expected to enhance the electrophilicity and might enable the utilization of simple aromatic systems in Friedel–Crafts cyclization step.

Scheme 1. Proposed Sequential Aza-Diels–Alder/Friedel–Crafts Reaction to the Fused Piperidines



Based on the above considerations, the initial investigation was conducted with readily available *N*-Tos

Table 1. Screening Studies of Sequential Aza-Diels–Alder and Friedel–Crafts Reaction[a]



entry	acid	equiv	temp (°C)	*t* (h)	yield[b] (%)	ee[c] (%)
1[d]	TFA	1	rt	24	<10	–
2	HCl	1	−25	24	<10	–
3	HCl	1	rt	24	decomp.	–
4	H_2SO_4	0.2	rt	24	decomp.	–
5	TFA	5	rt	24	<10	–
6	**TFA**	**10**	**rt**	**16**	**75**	**>99**
7	TFA	20	rt	1	67	>99
8	TFA	10	−78–rt	48	70	>99

[a] Unless noted otherwise, reactions were performed with 1-azadiene **2a** (0.1 mmol), aldehyde **3a** (0.2 mmol), cat. **1** (0.01 mmol), and benzoic acid (0.01 mmol) in MeCN/H_2O (10:1, 0.5 mL) at rt for 2 h. Then solvent was removed, and DCM (1.0 mL) and acid were added. The conditions in the table (temp and *t*) refer to the FC step. [b] Isolated yield of two steps. [c] Determined by chiral HPLC analysis. [d] FC reaction was conducted in MeCN/H_2O solution.

1-azadiene **2a**[9] and 3-(3,4-dimethoxyphenyl)propanal **3a** by the catalysis of α,α-diphenylprolinol *O*-TMS ether **1**[10] under the established conditions.[7a] The aza-Diels–Alder reaction proceeded smoothly at room temperature, cleanly affording the expected hemiaminal intermediate **4a**. Thus we set out to explore the intramolecular Friedel–Crafts reaction to generate an indeno[1,2-*b*]piperidine system without the isolation of **4a**. A very sluggish reaction was observed by directly adding trifluoroacetic acid (TFA) to the mixture (Table 1, entry 1). The desired Friedel–Crafts reaction also did not occur in DCM at −25 °C by using a solution of HCl in ethyl acetate as the promoter (entry 2),[4] and the decomposition of **4a** happened at room temperature (entry 3). Concentrated H_2SO_4 was not successful too (entry 4). Nevertheless, it seems that TFA might be an optimal selection because it does not destruct hemiaminal **4a** even in the presence of excess TFA (entry 5). To our gratification, the reaction was greatly accelerated when 10 equiv of TFA were used, and indeno[1,2-*b*]piperidine derivative **5a** was isolated in good yield in an enantio- and diastereomerically pure manner (entry 6).[4a] The reaction time could be dramatically shortened by employing a larger amount of TFA, but a slightly diminished yield

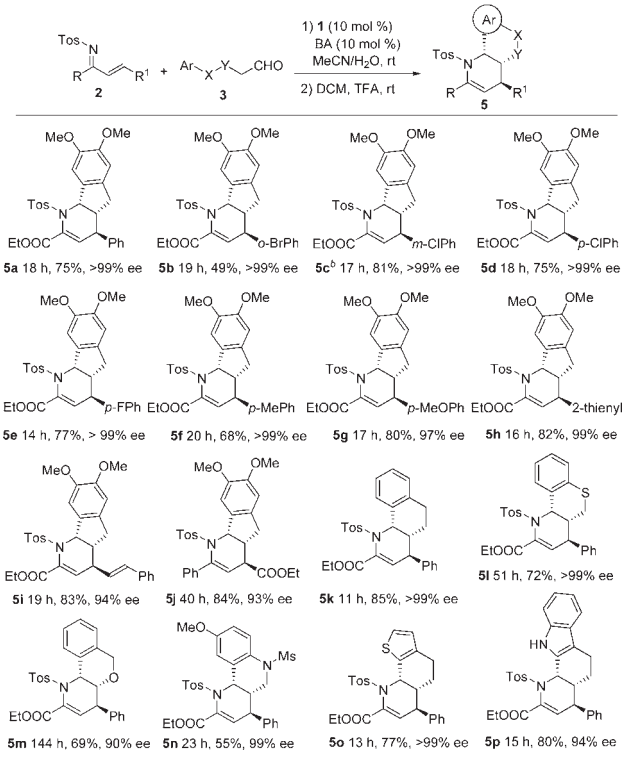
(7) (a) Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2008**, *47*, 9971. (b) He, Z.-Q.; Han, B.; Li, R.; Wu, L.; Chen, Y.-C. *Org. Biomol. Chem.* **2010**, *8*, 755. (c) Li, J.-L.; Zhou, S.-L.; Han, B.; Wu, L.; Chen, Y.-C. *Chem. Commun.* **2010**, *46*, 2665.

(8) For an excellent review, see: Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492.

(9) (a) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517. (b) Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2587. (c) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

(10) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Rec.* **2011**, *44*, DOI: 10.1021/ar200149w.

Scheme 2. Substrate Scope Studies[a]

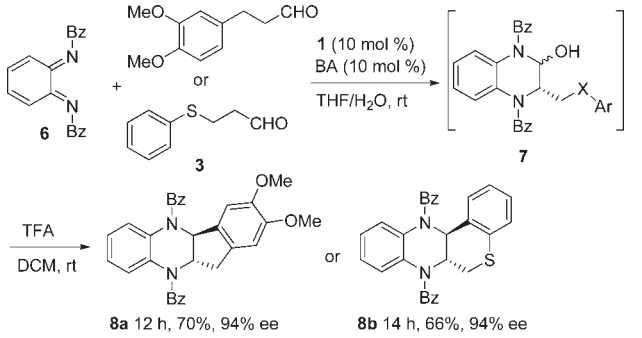


[a] Reactions were performed with 1-azadiene **2** (0.1 mmol), aldehyde **3** (0.2 mmol), cat. **1** (0.01 mmol), and benzoic acid (0.01 mmol) in MeCN/H_2O (10:1, 0.5 mL) at rt. After completion, the solution was concentrated, and DCM (1.0 mL) and TFA (10 equiv) were added at rt. Reaction time and yield refer to two steps; dr >99:1 by ^{1}H NMR analysis. [b]The absolute configuration of **5c** was determined by X-ray analysis, see the Supporting Information. The others were assigned by analogy.

was obtained (entry 7). The reaction has been tested at lower temperature, but the results could not be further improved (entry 8).

Subsequently, we explored an array of *N*-sulfonyl-1-aza-1,3-butadienes and aliphatic aldehydes tethered to an aryl or heteroaryl group. As shown in Scheme 2, for the reactions of 3-(3,4-dimethoxyphenyl)propanal, in general, *N*-Tos 1-azadienes carrying a diversely substituted aryl or heteroaryl group could be well tolerated, giving the tricyclic piperidine derivatives **5a**–**5h** in good isolated yield and excellent diastereo- (>99:1) and enantioselectivity, except that a modest yield was obtained for an *ortho*-bromophenyl substrate (**5b**). Good results were also attained for 1-azadienes with a differently substituted pattern (**5i** and **5j**). On the other hand, we paid much attention on the scope and limitations of the aldehyde counterpart, which would allow the formation of the fused piperidines with more scaffold diversity. Pleasingly, 4-phenylbutanal could be efficiently applied, and a polyhydrobenzo[*h*]quinoline **5k** was obtained in remarkable enantioselectivity and yield. It was noteworthy that the simple phenyl group also exhibited high reactivity in the Friedel–Crafts step owing to the strong activation effects of the *N*-Tos group.[4,5] More importantly, we found that the heteroatoms, such as S, O, and N, could be successfully incorporated into the aldehyde

Scheme 3. A Hetero-Diels–Alder and Friedel–Crafts Sequence to the Fused Tetrahydroquinoxalines[a]



[a] Reactions were performed with diimide **6** (0.1 mmol), aldehyde **3** (0.2 mmol), cat. **1** (0.01 mmol), and benzoic acid (0.01 mmol) in THF/H_2O (10:1, 0.5 mL) at rt. After completion, the solution was concentrated, and DCM (1.0 mL) and TFA (10 equiv) were added at rt. Reaction time and yield refer to two steps; dr >99:1 by ^{1}H NMR analysis.

skeleton; thus the more complex heterocyclic architectures **5l**–**5n** were smoothly constructed, though longer reaction times were required. Moreover, the heteroaryl motifs, the 3-thienyl or 3-indolyl group, were also smoothly employed in the Friedel–Crafts reaction, and the cyclic products **5o** and **5p** were produced, respectively, with outstanding results.

In addition, this sequential reaction strategy has been expanded to construct other fused heterocyclic systems. As outlined in Scheme 3, a diimide substrate[11] **6** could effectively react with 3-(3,4-dimethoxyphenyl)propanal or 3-(phenylthio)propanal to generate the chiral hemiaminal intermediates **7** by the catalysis of chiral amine **1**.[12] Then the similar TFA-mediated intramolecular Friedel–Crafts reaction was conducted to deliver the fused tetrahydroquinoxaline[13] derivatives **8a** or **8b**, respectively, also in excellent diastereo- (>99:1) and enantioselectivity and good yields.[14]

In conclusion, we have developed an organocatalytic and asymmetric sequential reaction to construct chiral heterocyclic scaffolds with high molecular complexity, which may have potential in medicinal chemistry. This method relies on the chiral secondary amine-catalyzed aza-Diels–Alder of *N*-sulfonyl-1-aza-1,3-butadienes and aliphatic aldehydes via enamine catalysis, followed by the intramolecular Friedel–Crafts reaction of the hemiaminal functional group with a tethered arene motif in the presence of TFA. A spectrum of enantioenriched piperidines with

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(12) Li, J.-L.; Han, B.; Jiang, K.; Du, W.; Chen, Y.-C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3952.

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(14) The stereochemistry of products **5** and **8** has been assigned by X-ray and NOE studies. For more discussion on the formation of *cis*-fused **5** and *trans*-fused **8**, see the Supporting Information.

fused frameworks were produced in a highly efficient and economical manner. In addition, the fused chiral tetrahydroquinoxaline skeletons have been similarly constructed. Currently, more explorations on these chiral heterocyclic systems were underway, and the results will be presented in due course.

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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products, cif file of enantiopure **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.