

Aminocatalytic Asymmetric *exo*-Diels–Alder Reaction with Methiodide Salts of Mannich Bases and 2,4-Dienals to Construct Chiral Spirocycles

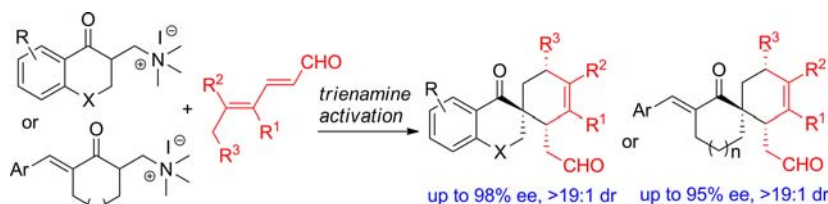
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ABSTRACT



An asymmetric *exo*-Diels–Alder reaction of α -methylene carbonyl compounds, generated in situ from stable methiodide salts of Mannich bases, with 2,4-dienals, has been developed through trienamine activation of a chiral secondary amine. A spectrum of spirocyclics with high molecular complexity was efficiently constructed in moderate to excellent diastereo- and enantioselectivity.

Spirocycles, having two rings connected by a single atom, were first created by von Baeyer in 1900.¹ The spirocyclic motifs are ubiquitous in a large number of natural products or synthetic materials, such as spirocyclics, spirobacillene A, β -vetivone, etc., exhibiting a broad spectrum of biological activities.² Moreover, spirocycles possess unique structural features with central chirality or even axial chirality (Figure 1), allowing for the development of an array of “privileged” chiral ligands and catalysts over the past decades.³ As a result, studies on spirocycles

provoke continuing interest in organic chemistry, and several synthetic strategies involving alkylation, rearrangement, radical cyclization, cleavage of bridged systems, etc., have been developed.⁴

Recently, enantioselective construction of spirocycles has made great progress. An abundance of highly asymmetric metal- or organocatalytic reactions have been developed to access chiral spirocyclic compounds⁵ but still suffer from limited structural diversity. Among them, we and other groups presented stereoselective Diels–Alder cycloadditions with 3-olefinic oxindoles and various trienamine intermediates in situ generated from 2,4-dienals or even 2,4-dienones and a chiral amine catalyst, providing efficient protocols to construct chiral spirocyclic oxindoles incorporating a six-membered ring system.⁶ Nevertheless, such a straightforward [4 + 2] cycloaddition strategy has been much less applied for the synthesis of chiral

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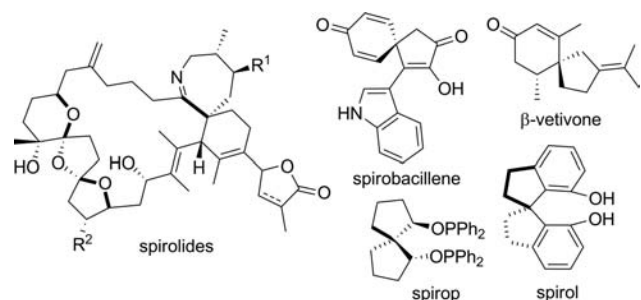
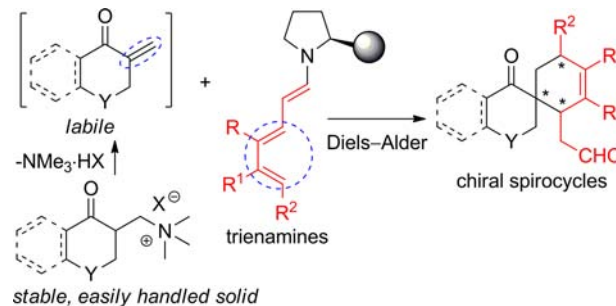


Figure 1. Natural products or chiral ligands containing spirocyclic motifs.

spirocycles with other ring architectures, probably because of the lower electrophilicity of the corresponding dienophiles and suitable catalytic systems.⁷

α-Methylene cyclic carbonyl compounds generally show good reactivity in Diels–Alder reactions⁷ or other cycloadditions⁸ to construct spirocyclic compounds; however, they are labile and may dimerize even stored in a refrigerator.⁹ It has been reported that such a type of compound could be in situ generated from Mannich bases but usually under harsh conditions.¹⁰ Fortunately, the formation of the methiodide salts of Mannich bases could significantly facilitate elimination to form the corresponding dienophiles in the presence of base.¹¹ We envisaged that an aminocatalytic asymmetric Diels–Alder cycloaddition with stable and easily handled methiodide salts of Mannich bases and 2,4-dienals could be developed via trienamine activation as outlined in Scheme 1, since the amine

Scheme 1. Asymmetric Diels–Alder Cycloaddition with Methiodide Salts of Mannich Bases and Trienamine Intermediates



catalysis should be well compatible with the presence of byproduct trimethylamine or its salt.

Consequently, we initially investigated the reaction with readily available methiodide salt¹² **2a** from 1-tetralone and 2,4-dienal **3a** in the presence of amine catalyst **1a** and excess PhCO_2Na .¹³ Pleasingly, the desired cycloaddition occurred in chloroform at 60 °C, and product **4a** was isolated in a fair yield after 72 h but with high diastereo- (> 19:1) and enantioselectivity (94% ee) (Table 1, entry 1). Subsequently, a number of reaction parameters were explored. A few solvents were tested (entries 2–6), and better results were obtained in 1,2-dimethoxyethane (DME, entry 6). Using less amounts of PhCO_2Na significantly decreased the yield (entry 7). Other bases, such as *o*- FPhCO_2Na or AcONa , also gave lower yields but without effects on stereoselectivity (entries 8 and 9). While inferior data was obtained with chiral amine **1b** (entry 10), excellent enantioselectivity with higher yield was achieved by the catalysis of a bulky amine **1c** (entry 11).¹⁴ Nevertheless, both yield and enantiocontrol were decreased when the reaction was conducted at elevated temperature (entry 12). On the other hand, we also investigated the cycloadditions with other ammonium salts under the optimized conditions, but worse results (**2b**, entry 13) or even very poor conversion (**2c**, entry 14) were observed.

Consequently, an array of methiodide salts of various Mannich bases derived from cyclic ketones and 2,4-dienals were explored in DME in the presence of chiral amine **1c** (20 mol %) and PhCO_2Na (2 equiv) at 60 °C. The results are summarized in Scheme 2. In comparison with **2a**, a methiodide salt derived from 4-chromanone exhibited higher reactivity in the reaction with 2,4-dienal **3a**, giving spirocyclic product **4b** in a slightly better yield and with excellent stereoselectivity. In addition, cycloadducts **4c–4f** bearing either electron-withdrawing or -donating substitutions were produced with the similar good results. Nevertheless, much poor diastereoselectivity was observed for a

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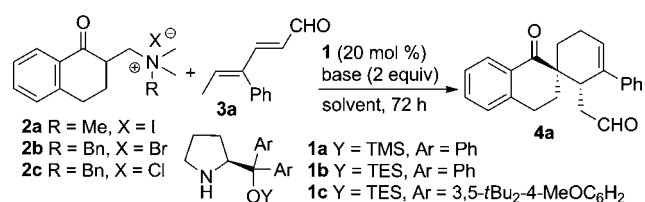
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Table 1. Screening of Conditions for Diels–Alder Reaction with Methiodide Salts **2** and 2,4-Dienal **3a**^a



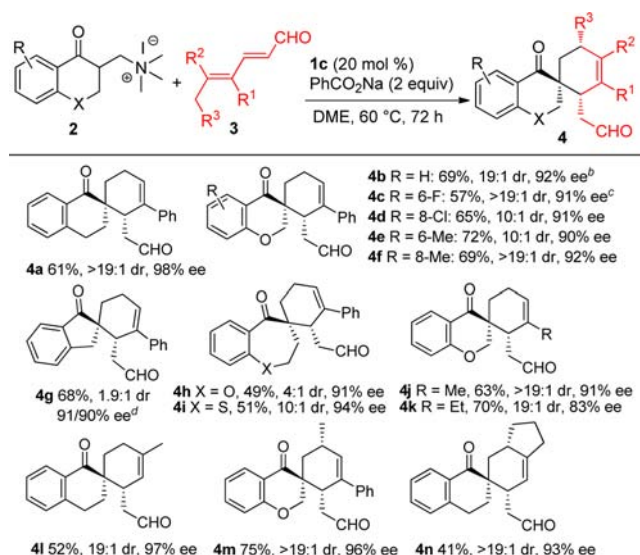
entry	1	solvent	base	yield ^b (%)	ee ^c (%)
1	1a	CHCl ₃	PhCO ₂ Na	42	94
2	1a	Toluene	PhCO ₂ Na		
3	1a	CH ₃ CN	PhCO ₂ Na		
4	1a	Dioxane	PhCO ₂ Na	52	90
5	1a	THF	PhCO ₂ Na	48	96
6	1a	DME	PhCO ₂ Na	55	96
7 ^d	1a	DME	PhCO ₂ Na	40	95
8	1a	DME	<i>o</i> -FPhCO ₂ Na	42	96
9	1a	DME	AcONa	36	96
10	1b	DME	PhCO ₂ Na	49	93
11	1c	DME	PhCO ₂ Na	61	98
12 ^e	1c	DME	PhCO ₂ Na	58	92
13 ^f	1c	DME	PhCO ₂ Na	59	90
14 ^g	1c	DME	PhCO ₂ Na	<10	/

^a Unless noted otherwise, reactions were performed with 0.2 mmol of **2a**, 0.1 mmol of **3a**, 20 mol % of **1** and 0.2 mmol of base in 0.5 mL solvent at 60 °C for 72 h. ^b Isolated yield. ^c By chiral HPLC analysis; dr > 19:1 by ¹H NMR analysis. ^d Base (0.02 mmol) was used. ^e At 70 °C. ^f With salt **2b**. ^g With salt **2c**.

methiodide salt from 1-indanone, while the enantioselectivity was high for both diastereomers (**4g**). In addition, methiodide salts with a seven-membered ring showed lower reactivity, but the corresponding cycloadducts **4h** and **4i** were produced in good diastereoselectivity and with noteworthy ee values. On the other hand, several 2,4-dienals with diverse substitution patterns were tested, and spirocyclic products **4j–4n** were generally obtained in high stereoselectivity, while the isolated yields were fair to moderate. However, simple 2,4-hexadienal showed much lower reactivity, and very poor conversion was observed.

In order to introduce more structural diversity into spirocyclic architectures, methiodide salts of other cyclic ketones were further explored. While methiodide salts from simple cyclohexanone or cyclopentanone failed to afford the desired [4 + 2] cycloadducts,¹¹ it was pleasing that the reactivity could be enhanced by introducing an α -alkylidene moiety into cyclic aliphatic ketones, and complete regioselective cycloaddition occurred at less hindered α -methylene motif. Moreover, much better conversion could be attained by adding a catalytic amount of (*S,S*)-TADDOL, which is thought to activate the dienophiles via hydrogen bonding interaction.¹⁵ As summarized in Scheme 3, a number of spirocyclic products **6a–6g** were

Scheme 2. Substrate Scope of Diels–Alder Reactions with Methiodide Salts from Cyclic Aryl Ketones^a



^a Conditions: Unless noted otherwise, reactions were performed with 0.2 mmol of salt **2**, 0.1 mmol of dienal **3**, 20 mol % of **1c** and 0.2 mmol of PhCO₂Na in 0.5 mL of DME at 60 °C for 72 h; isolated yields of pure *exo*-isomers; ee was determined by chiral HPLC analysis after conversion, see the SI; dr was determined by ¹H NMR analysis of crude products. ^b At 40 °C. ^c 0.4 mmol of salt was used. ^d Combined yield of diastereomers.

efficiently constructed with modest yields and high stereoselectivity from methiodide salts **5** bearing various β -aryl groups, even with less reactive 2,4-hexadienal (**6f**). It should be noted that salts **5** with β -alkyl groups could not participate in such cycloadditions under the current catalytic conditions due to reduced reactivity. Moreover, we gratifyingly found that methiodide salts **7** derived from 3-aryl or 3-phenylethynyl cyclic enones could be successfully applied, delivering multifunctional spirocyclic products **8a–8c** in good stereocontrol, though the isolated yields were not satisfactory.

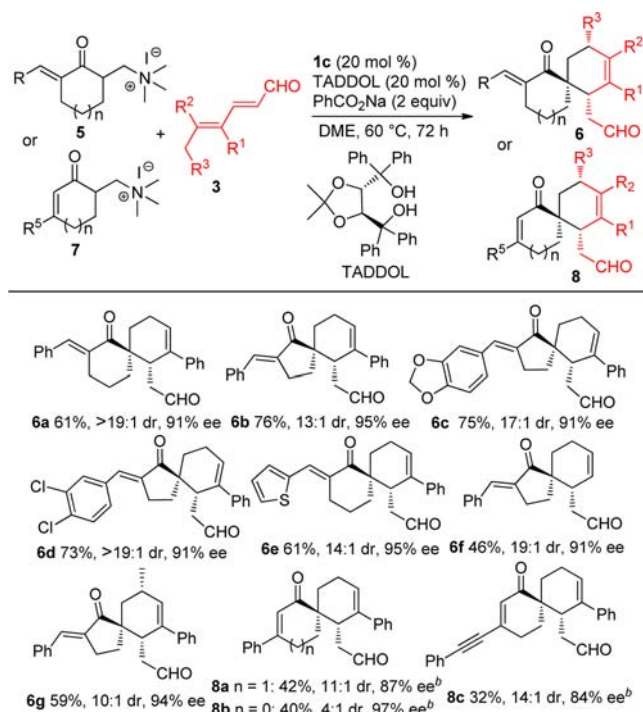
In addition, it was possible to introduce more substitutions into the spirocycles with β -substituted enone substrates. As illustrated in Scheme 4, although α -benzylideneindanone **9a** was inert in the reaction with 2,4-dienals, using enone **9b** bearing a β -ethoxycarbonyl group smoothly produced the densely substituted spirocyclic products **10a** and **10b** in excellent enantioselectivity and modest diastereoselectivity. The absolute configuration of **10a** was ambiguously determined by X-ray crystallographic analysis, which shows anomalous *exo*-selectivity.^{7,16}

The spirocycles with multifunctional groups enable further synthetic transformations to produce more complex molecules. As outlined in Scheme 5, double reductive

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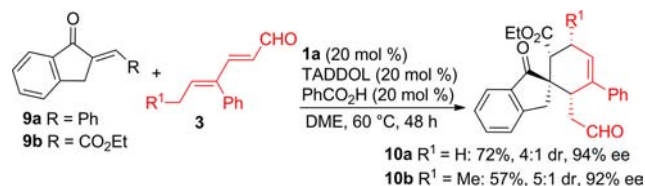
(16) CCDC-920336 (**10a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Substrate Scope of Diels–Alder Reactions with Methiodide Salts from Functional Cyclic Enones^a



^a Unless noted otherwise, reactions were performed with 0.2 mmol of salt **5** or **7**, 0.1 mmol of 2,4-dienal **3**, 20 mol % of **1c** and TADDOL, 0.2 mmol of PhCO₂Na in 0.5 mL of DME at 60 °C for 72 h; isolated yields of pure *exo*-isomers; ee was determined by chiral HPLC analysis; dr was determined by ¹H NMR analysis of crude products. ^b With catalyst **1a**.

Scheme 4. Synthesis of Highly Substituted Spirocycles

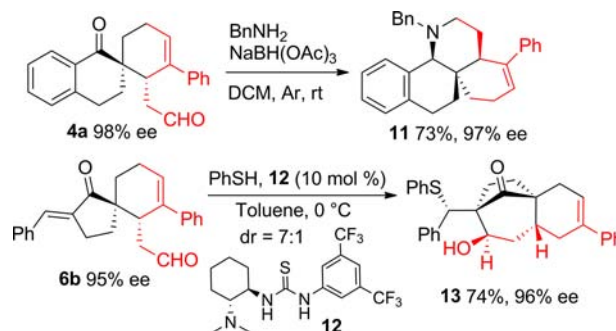


amination reactions with spirocycle **4a** and BnNH₂ proceeded efficiently in the presence of NaBH(OAc)₃, producing a highly fused piperidine derivative **11** with exclusive diastereo-control. Moreover, spirocycle **6b** was used in a domino diastereoselective sulfur-Michael addition–intramolecular

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aldol reaction sequence catalyzed by a chiral thiourea-tertiary amine **12**,¹⁷ delivering a framework **13** containing a polyhydromethanobenzo[7]annulen-10-one motif, a ubiquitous bridged substructure in many tetracyclic diterpenes and other natural products.¹⁸

Scheme 5. Transformations of Spirocyclic Products



In conclusion, we have presented an asymmetric *exo*-Diels–Alder reaction with bench-stable methiodide salts of Mannich bases and 2,4-dienals, which relies on the in situ generation of labile α -methylene carbonyl dienophiles and subsequent cycloaddition with HOMO-activated trienamine intermediates. A spectrum of multifunctional spirocyclic frameworks has been efficiently constructed with moderate to excellent diastereo- and enantioselectivity. Moreover, the products could be smoothly transformed into polycyclic compounds with high molecular complexity. We believe that such easily handled methiodide salts of Mannich bases would find more applications in asymmetric catalysis, and the results will be reported 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 **10a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.