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Asymmetric Dearomatic Diels–Alder Reactions of Diverse Heteroarenes via π-System Activation

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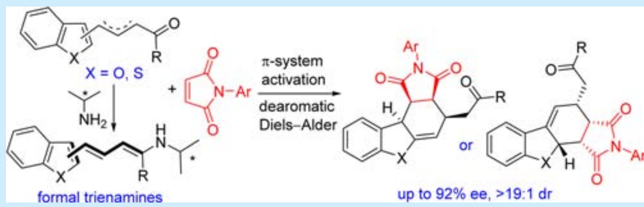
Supporting Information

ABSTRACT: An asymmetric dearomatic Diels–Alder protocol for various heteroarenes, such as benzofuran, benzothiophene, or even furan, has been developed via π-system activation. This method involves *in situ* generation of formal trienamine species embedding a heteroaromatic moiety, and an array of chiral fused frameworks with high molecular complexity and skeletal diversity were efficiently constructed in good to excellent stereoselectivity by the catalysis of a cinchona-based primary amine.



With their occurrence in many natural products and bioactive compounds as illustrated in Figure 1,[1]

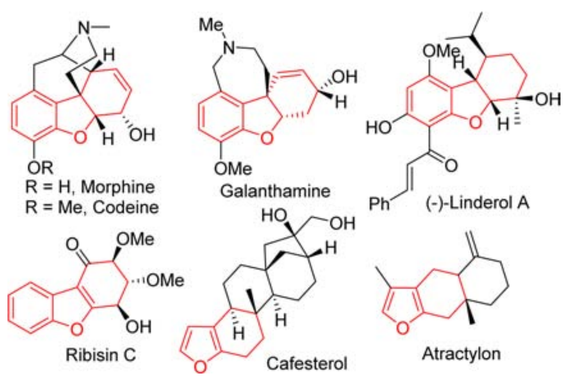
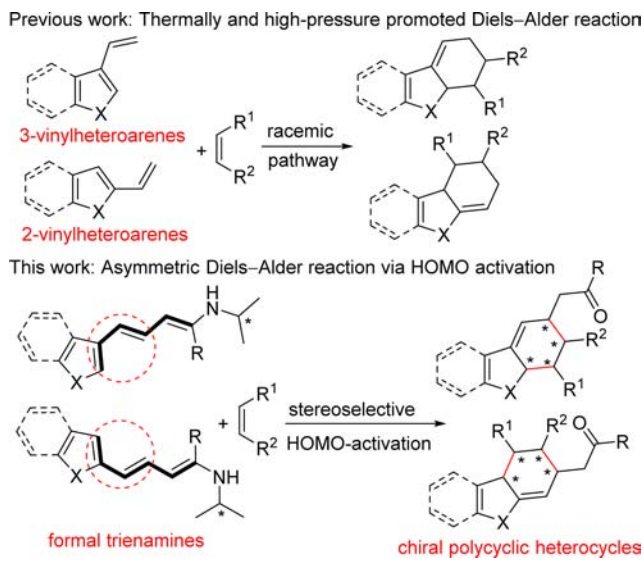


Figure 1. Representative benzofuran- or furan-based natural products.

polycyclic benzofuan- or furan-based architectures have attracted great attention in synthetic organic chemistry. Although there are many methods concerning the synthesis of such fused heterocycles, most of them are generally related to nonasymmetric examples.[2] One of the most common and straightforward ways to construct these frameworks is the dearomatic Diels–Alder reaction between vinylbenzofurans or vinylfurans and olefinic dienophiles, which was first reported by Kamthong and Robertson in 1939.[3] However, most of the previous presentations suffer from harsh conditions due to the relatively low reactivity of the diene moiety and high energy barrier encountered in the dearomatization process (Scheme 1).[4] In contrast to the extensive research in stereoselective cycloadditions of the analogous vinylindoles to access chiral hydrocarbazoles,[5] to the best of our knowledge, only a single example was reported with more reactive 3-siloxyvinylbenzofuran as the diene partner by the catalysis of a chiral Holmium complex to date.[6] Therefore, a general and efficient asymmetric protocol to construct these privileged structures is in high demand.

Scheme 1. π-System Activation of Hetero Ring via Formal Trienamine Catalysis



Recently, a number of reactions have been developed through the HOMO-activation of the remote C═C bond of unsaturated carbonyl compounds via either dienamine[7] or trienamine catalysis.[8] Such a strategy has been utilized to activate aromatic compounds. Melchiorre reported an asym-

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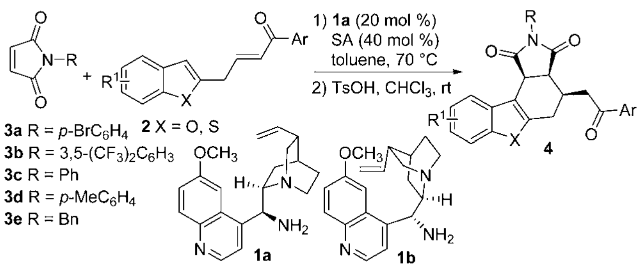
metric Diels–Alder reaction of *β*-indolyl enals through *in situ* dearomatic formation of indole-2,3-quinodimethanes.[9] Jørgensen et al. disclosed that the polycyclic core of anthracenes could be activated by a conjugated enamine intermediate, and highly stereoselective dearomatic Diels–Alder reactions have been developed with electron-deficient dienophiles.[10] Inspired by our recent studies on the asymmetric Friedel–Crafts reaction of furans[11] and diverse asymmetric cycloadditions via HOMO-activation of amine catalysts,[12] we envisaged that the relatively inert 2- or 3-vinyl heteroarenes could be HOMO-raised through generating formal trienamine species as outlined in Scheme 1; thus, the subsequent dearomatic Diels–Alder reaction for the synthesis of diverse chiral fused heterocycles, including benzofuran or furan-based frameworks, could be facilitated under mild and metal-free catalytic conditions (Scheme 1).

Initially, we designed substrate (*E*)-4-(benzofuran-2-yl)-1-phenylbut-2-en-1-one **2a** (Table 1, X = O, R^1 = H, Ar = Ph),

Table 1. Asymmetric Diels–Alder Reactions of Enones 2 and Maleimides 3[a]



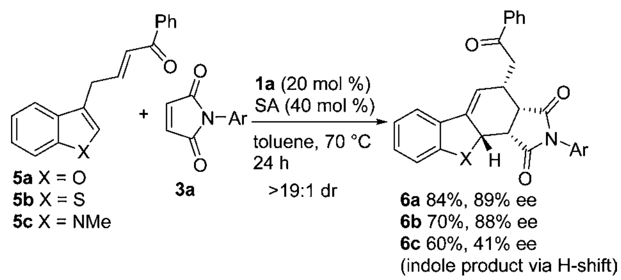
entry	Ar	R^1	3	yield[b] (%)	ee[c] (%)
1	Ph	H	**3a**	**4a**, 82 (60)	92 (−82)
2	Ph	H	**3b**	**4b**, 85	91
3	Ph	H	**3c**	**4c**, 76	90
4	Ph	H	**3d**	**4d**, 73 (70)	89 (−80)
5	Ph	H	**3e**	**4e**, 68	73
6	*p*-MeOC$_6$H$_4$	H	**3a**	**4f**, 81	86
7	*p*-ClOC$_6$H$_4$	H	**3a**	**4g**, 80	88
8	2-naphthyl	H	**3a**	**4h**, 76 (74)	83 (−97)
9	2-thienyl	H	**3a**	**4i**, 68	80
10	Ph	5-Me	**3a**	**4j**, 84	82
11	Ph	7-Me	**3a**	**4k**, 73	84
12	Ph	5-F	**3a**	**4l**, 81	85
13[d]	Ph	H	**3a**	**4m**, 72	92

[a]Unless noted otherwise, the reaction was conducted with enone **2** (X = O, 0.12 mmol), maleimide **3** (0.1 mmol), catalyst **1a** (20 mol %), and salicylic acid (40 mol %) in toluene (1.0 mL) at 70 °C for 36 h. Then the cycloadduct was treated with *p*-TsOH in CHCl$_3$ at rt for 2 h. [b]Isolated yield for two steps. [c]By chiral HPLC analysis; dr >19:1 by ^{1}H NMR analysis. [d]X = S.

which could be considered as a 2,5-dienone-type substance,[13] and tested the potential Diels–Alder reaction with maleimide **3a** under the catalysis of 9-amino-9-deoxyepiquinine **1a** and salicylic acid (SA) in toluene.[14] Encouragingly, the desired regioselective dearomatic cycloaddition occurred smoothly at 70 °C, and a more stable aromatic product **4a** was obtained in good yield with high stereoselectivity after treatment with *p*-TsOH in chloroform (Table 1, entry 1, >19:1 dr, 92% ee).[15] Subsequently, we explored the scope of both types of substrates. The more stable fused heteroarenes were generated and analyzed after the asymmetric cycloaddition reactions. For other maleimides with an *N*-aryl group, good yields and high enantioselectivity were generally obtained (entries 2–4). Nevertheless, maleimide **3e** with an *N*-benzyl group gave a decreased yield and enantiocontrol (entry 5). On the other hand, *β*-(2-benzofuryl)methyl enones **2** bearing diverse *α*′-aryl groups could be well tolerated (entries 6–8), while a 2-thienyl-substituted substrate produced a slightly lower yield and ee value (entry 9). In addition, similar good results were obtained for enone partners with various substituents on the benzofuran ring (entries 10–12). Importantly, the enone substrate containing a 2-benzothiophenyl moiety was also compatible with this type of asymmetric Diels–Alder reaction, and a chiral tetrahydrodibenzo[*b*,*d*]thiophene framework was efficiently constructed with high enantioselectivity (entry 13). Moreover, the highly enantioenriched cycloadducts with an opposite configuration could be produced by the catalysis of 9-amino-9-deoxyepiquinidine **1b** under similar catalytic conditions (Table 1, data in parentheses).

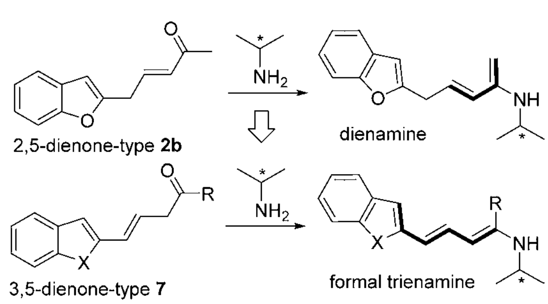
It was pleasing that both enones **5a** and **5b** substituted by the 3-benzofuryl and 3-benzothiophenyl group, respectively, exhibited comparable reactivity with maleimide **3a** under the same catalytic conditions, and dearomatic cycloadducts **6a** and **6b** were obtained as stable substances in good yields and with high enantioselectivity. A tetrahydrocarbazole **6c** was directly formed in a moderate yield through a 1,3-H shift of the cycloadduct, but only a moderate ee value was obtained (Scheme 2).[16]

Scheme 2. Asymmetric Diels–Alder Reactions of 3-Heteroaryl Enones



Unfortunately, 2,5-dienone-type substrate **2b** bearing an *α*′-enolizable methyl group exhibited no reactivity with dienophile **3a** catalyzed by amine **1a**, probably due to the preferable generation of an undesired dienamine intermediate as outlined in Scheme 3. As a result, we envisioned that deconjugated formal 3,5-dienone-type substrate **7** might be more likely to

Scheme 3. A Deconjugation Strategy To Realize the Formal Trienamine Catalysis for Enones with Enolizable *α*′-Alkyl Group



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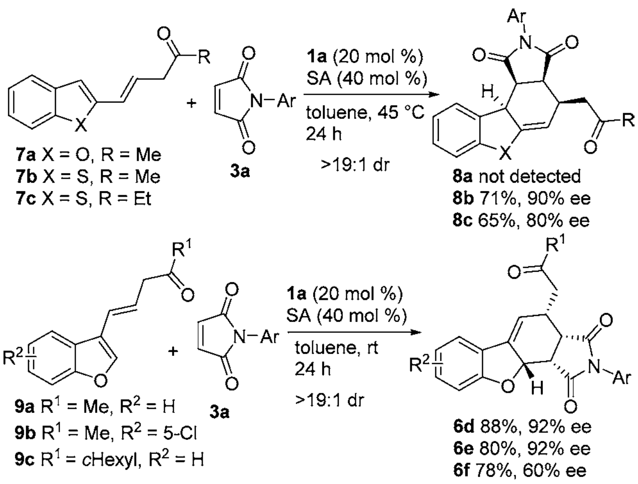
generate the required formal trienamine intermediate with the amine catalyst.[17]

Thus, ketone **7a** was prepared and tested, but it was unstable under the catalytic conditions, and the desired cycloadduct **8a** was not detected. Gratifyingly, the analogous **7b** with a benzothiophene skeleton successfully participated in the Diels–Alder cycloaddition with dienophile **3a**, and product **8b** was isolated in a moderate yield and with excellent stereoselectivity. Ketone **7c** with an α'-ethyl group smoothly afforded the cycloadduct **8c**, albeit in a lower yield and enantioselectivity. It is interesting that 3-benzofuryl enones **9** with α'-enolizable alkyl groups showed better stability and reactivity and efficiently produced the expected cycloadducts **6d**–**6f** even at rt, though only a modest ee value could be attained for **9c** with a branched cyclohexyl group (Scheme 4).

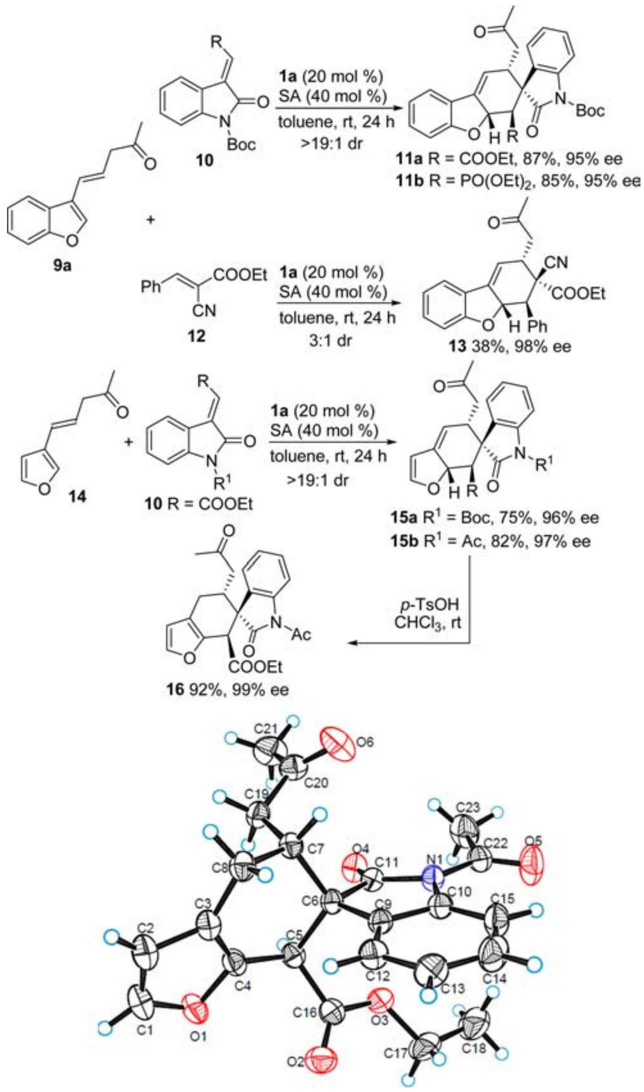
Scheme 4. Asymmetric Diels–Alder Cycloadditions of Deconjugated Enones



To further explore the generality of this method, more dienophiles were investigated with substrate **9a**. As illustrated in Scheme 5, 3-olefinic oxindoles[18] **10** could smoothly react with **9a** to deliver the spirocyclic[19] cycloaddition products **11a** and **11b** with high molecular complexity in excellent yields and ee's. Besides, benzylidenecyanoacetate **12** also showed good reactivity with enone **9a**. The diastereoselectivity was poor, while the major cycloadduct **13** could be isolated in a low yield but with excellent enantioselectivity. Nevertheless, β-nitrostyrene did not react in a cycloaddition manner but gave an α-regioselective Michael addition product (see the Supporting Information (SI)).[20] Importantly, even enone **14** derived from 3-furaldehyde could be utilized in the asymmetric dearomatic Diels–Alder reactions with dienophiles **10** at rt, and chiral tetrahydrobenzofurans **15a** and **15b** incorporating a spirooxindole skeleton were constructed in high yields and with excellent stereoselectivity. The absolute configuration of cycloadduct **15b** was determined by X-ray analysis after conversion to furan derivative **16**, as outlined in Scheme 5.[21] It should be noted that the analogous enones derived from 2-furaldehyde, thiophene-2- or 3-aldehydes have not been successfully used through the same dearomatic cycloaddition strategy (see the SI).

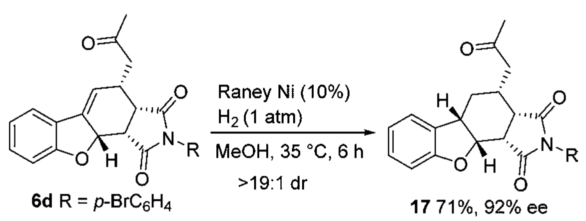
Finally, the Diels–Alder cycloadduct **6d** was submitted to further transformation. The multifunctional hexahydrodibenzofuran **17** with five continuous stereogenic centers was smoothly

Scheme 5. More Exploration of Dearomatic Diels–Alder Reactions



and chemoselectively obtained under the mild catalytic hydrogenation with Raney Ni (Scheme 6).

Scheme 6. Hydrogenation of Diels–Alder Product 6d



In summary, a simple and highly stereoselective dearomatic Diels–Alder cycloaddition reaction with diverse five-membered heteroarenes has been developed. This method relies on *in situ* generation of formal trienamine species from a variety of enone substrates properly tethered to a benzofuran, benzothiophene, or even furan ring, which raises the HOMO-energy of the relatively inert heteroaromatic diene moiety and promotes the subsequent pericyclic reactions with electron-deficient dienophiles. A spectrum of fused or spiro hydrodibenzofuran, hydrodibenzothiophene, and tetrahydrobenzofurans with highly structural complexity were efficiently constructed in good yields and with moderate to excellent enantioselectivity, which might find further application in medicinal chemistry and biological studies. We also hope that the HOMO-activation strategy presented in this work would provide more opportunities to develop new asymmetric reactions with diverse heteroarenes.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization of new products, CIF file of enantiopure product **16**, NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109. (b) Marco Contelles, J.; Carreiras, M. D. C.; Rodriguez, C.; Villarroya, M.; Garcia, A. G. *Chem. Rev.* **2006**, *106*, 116. (c) Mimaki, Y.; Kameyama, A.; Sashida, Y.; Miyata, Y.; Fujii, A. *Chem. Pharm. Bull.* **1995**, *43*, 893. (d) Liu, Y.; Kubo, M.; Fukuyama, Y. *J. Nat. Prod.* **2012**, *75*, 2152. (e) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717. (f) Schultz, A. G.; Godfrey, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 2414.

(2) For selected examples of nonasymmetric synthesis of hydrodibenzofurans, see: (a) Hosokawa, T.; Ohkata, H.; Moritani, I. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1533. (b) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036. (c) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237. (d) Nguyen, R.-V.; Yao, X. Q.; Li, C.-J. *Org. Lett.* **2006**, *8*, 2397. (e) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415. (f) Liu, Q.; Han, B.; Zhang, W.; Yang, L.; Liu, Z. L.; Yu, W. *Synlett* **2005**, *14*, 2248. For an asymmetric version, see: (g) Wang, Z.-Yu; Wong, W.-T.; Yang, D. *Org. Lett.* **2013**, *15*, 4980.

(3) For selected examples of Diels–Alder reactions with vinyl heteroarenes, see: (a) Kamthong, B.; Robertson, A. *J. Chem. Soc.* **1939**, *925*, 933. (b) Davidson, W. J.; Elix, J. A. *Aust. J. Chem.* **1970**, *23*, 2119. (c) Pearson, J. R.; Porter, Q. N. *Aust. J. Chem.* **1991**, *44*, 1085. (d) Strat, F. L.; Vallette, H.; Toupet, L.; Maddaluno, J. *Eur. J. Org. Chem.* **2005**, 5296. (e) Marrocchi, A.; Minuti, L.; Taticchi, A.; Scheeren, H. W. *Tetrahedron* **2001**, *57*, 4959. (f) Kotsuki, H.; Kondo, A.; Nishizawa, H.; Ochi, M.; Matsuoka, K. *J. Org. Chem.* **1981**, *46*, 5454. (g) Benítez, A.; Herrera, F. R.; Romero, M.; Talamás, F. X. *J. Org. Chem.* **1996**, *61*, 1487. (h) Drew, M. G. B.; Jahans, A.; Harwood, L. M.; Apoux, S. A. B. H. *Eur. J. Org. Chem.* **2002**, 3589. (i) Cherry, W. H.; Craig, J. T.; Porter, Q. N. *Aust. J. Chem.* **1979**, *32*, 133. (j) Kim, P.; Tsuruda, J. M.; Olmstead, M. M.; Eisenberg, S.; Kurth, M. J. *Tetrahedron Lett.* **2002**, *43*, 3963.

(4) For a review on catalytic asymmetric dearomatization reactions, see: Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662.

(5) For selected examples of asymmetric Diels–Alder reactions of vinyl indoles, see: (a) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236. (b) Wang, X.-F.; Chen, J.-R.; Cao, Y.-J.; Cheng, H.-G.; Xiao, W.-J. *Org. Lett.* **2010**, *12*, 1140. (c) Zheng, C.; Li, Y.; Zhang, J.; Chen, X.; Chai, Z.; Ma, W.; Zhao, G. *Chem.—Eur. J.* **2010**, *16*, 5853. (d) Tan, B.; Hernández-Torres, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354.

(6) Harada, S.; Morikawa, T.; Nishida, A. *Org. Lett.* **2013**, *15*, 5314.

(7) For a review on dienamine catalysis, see: Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865.

(8) For reviews on trienamine catalysis, see: (a) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. (b) Arceo, E.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 5290. (c) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709. (d) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287. (e) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869.

(9) (a) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212. (b) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310.

(10) (a) Jiang, H.; Rodríguez-Escrich, C.; Johansen, T. K.; Davis, R. L.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10271. (b) Rodríguez-Escrich, C.; Davis, R. L.; Jiang, H.; Stiller, J.; Johansen, T. K.; Jørgensen, K. A. *Chem.—Eur. J.* **2013**, *19*, 2932.

(11) Li, J.-L.; Yue, C.-Z.; Chen, P.-Q.; Xiao, Y.-C.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5449.

(12) For a review, see: Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. *Acc. Chem. Res.* **2012**, *45*, 1491.

(13) (a) For trienamine catalysis with 2,4-dienones, see: Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2012**, *51*, 4401. (b) With cyclic 2,5-dienones, see: Feng, X.; Zhou, Z.; Ma, C.; Yin, X.; Li, R.; Dong, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2013**, *52*, 14173. (c) With 2,5-dienals, see: Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem.—Eur. J.* **2014**, *20*, 2145.

(14) For reviews of cinchona-based primary aminocatalysis, see: (a) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748. (b) Jiang, L.; Chen, Y.-C. *Catal. Sci. Technol.* **2011**, *1*, 354.

(15) For more screening conditions, see the Supporting Information.

(16) The cycloaddition of **5c** and **3a** also occurred by using DABCO as the catalyst, probably via a trienol intermediate after deprotonation. Changing the N-protecting group to Bn or Boc has no benefit for the Diels–Alder reaction.

(17) Chen, P.-Q.; Xiao, Y.-C.; Yue, C.-Z.; Chen, Y.-C. *Org. Chem. Front.* **2014**, *1*, 490.

(18) (a) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. (b) Zhou, Q.-Q.; Yuan, X.; Xiao, Y.-C.; Dong, L.; Chen, Y.-C. *Tetrahedron* **2013**, *69*, 10369.

(19) For a review on the catalytic synthesis of chiral spirocyclic compounds, see: Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060.

(20) (a) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638. (b) See ref 13c.

(21) The absolute configuration of other cycloadducts was assigned on the basis of a presumed common catalytic mechanism similar to that of cycloadduct **15b**. See the Supporting Information.