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Chiral Brønsted Acid-Catalyzed Inverse Electron-Demand Aza Diels−Alder Reaction

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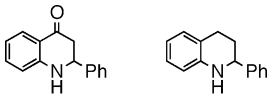
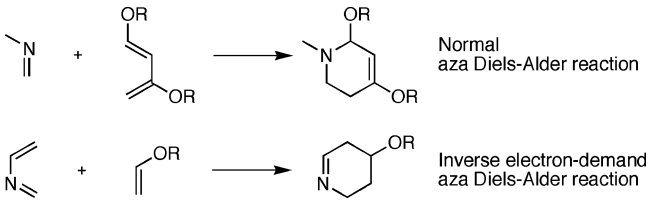
Tetrahydroquinoline derivatives exhibit interesting biological activity. For example, 2-aryl-2,3-dihydro-4-quinolone (**1**) exhibits antitumor activity,[1] and 2-aryl-1,2,3,4-tetrahydroquinoline (**2**) is a core structure of the compounds possessing 5-lipoxygenase inhibitory properties and potential therapeutic application in asthma.[2] Development of novel methods for the preparation of a tetrahydroquinoline framework in scalemic form continues to be an important goal of synthetic organic chemists.[3]



1 **2**

The inverse electron-demand aza Diels−Alder reaction of azabutadiene with an electron-rich alkene constitutes one of the efficient methods for the preparation of the tetrahydroquinoline derivatives.[4] Although several enantioselective Diels−Alder reactions of an electron-rich diene with an electron-deficient alkene have been developed,[5] a catalytic inverse electron-demand aza Diels−Alder reaction of azabutadiene with an electron-rich alkene has been scarcely studied. For example, Kobayashi et al. developed a BINOL-based chiral lanthanide catalyst,[6] while Sundararajan et al. reported an aminodiol-based Ti(IV) catalyst for the aza Diels−Alder reaction.[7] However, the enantioselectivities are not always high, and the development of more efficient chiral catalyst is desired.



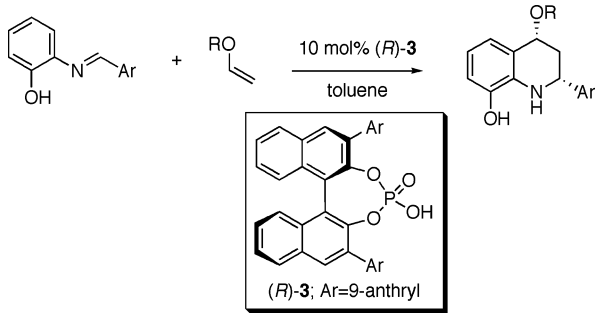
Recently, chiral Brønsted acid catalysts have continued to increase in popularity as green catalysts, which are free of metals.[8,9] We have designed and synthesized chiral phosphoric acid, derived from (*R*)-BINOL, and demonstrated its catalytic activity as chiral Brønsted acid catalysts.[10,11] As part of our continued effort on the development of chiral Brønsted acid-catalyzed reactions, we wish to report herein a chiral Brønsted acid-catalyzed enantioselective aza Diels−Alder reaction of azabutadiene with electron-rich alkenes, leading to tetrahydroquinolines with high enantioselectivity.

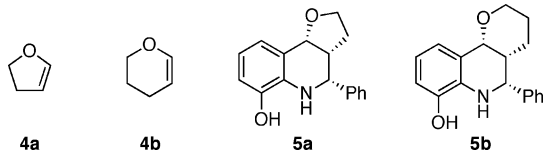
A phosphoric acid bearing 9-anthryl group on the 3,3′-position (*R*)-**3** turned out to be highly effective as a catalyst for the aza Diels−Alder reaction of aldimine, derived from aromatic aldehyde and *o*-hydroxyaniline, and ethyl vinyl ether in toluene at 0 °C. The results are shown in Table 1. A range of aldimines derived from aromatic aldehyde worked well to give tetrahydroquinoline derivatives in good to high yields with excellent diastereoselectivity in favor of the cis isomer, which exhibited high to excellent enantioselectivity (entries 1, 6, 8, 9, 10, 11). Not only ethyl ether, but also butyl and benzyl ethers proved to be good substrates, and the cycloadducts were obtained with excellent diastereo- and enantioselectivities (entries 2, 3, 7, 12). The absolute stereochemistry of the cycloadduct (entry 6), which was obtained by the reaction of an aldimine prepared from 4-bromobenzaldehyde and ethyl vinyl ether, was unambiguously determined by X-ray analysis, and those of other cycloadducts were surmised by analogy. The cycloaddition reaction with cyclic vinyl ethers such as dihydrofuran (**4a**) and dihydropyran (**4b**) also gave cycloadducts **5a** and **5b**, respectively, in excellent enantioselectivities (entries 4, 5).[12]

Table 1. Chiral Brønsted Acid-Catalyzed Aza Diels−Alder Reaction of Aldimines with Vinyl Ethers[a]

entry	Ar	R	yield (%)	cis/trans	ee(%)[b]
1[c]	Ph	Et	89	99:1	94
2[c]	Ph	*n*-Bu	82	99:1	96
3[d]	Ph	Bn	76	99:1	91
4[c]	Ph	**4a**	86	99:1	90
5[d]	Ph	**4b**	95	99:1	97
6[c]	4-BrC_6H_4	Et	77	99:1	90
7[c]	4-BrC_6H_4	*n*-Bu	86	99:1	89
8[c]	4-ClC_6H_4	Et	79	99:1	88
9[d]	4-MeC_6H_4	Et	59	99:1	91
10[d]	2-ClC_6H_4	Et	72	96:4	87
11[d]	2-naphthyl	Et	74	99:1	95
12[d]	2-naphthyl	*n*-Bu	80	99:1	88

[a] The reaction time is 10−55 h by use of 10 mol % of (*R*)-**3**. [b] ee of the cis isomer. [c] The reaction was carried out at −10 °C. [d] The reaction was carried out at 0 °C.





4a **4b** **5a** **5b**

Next, the cycloadducts were transformed into the compounds bearing a 2-aryl-2,3-dihydro-4-quinolone and 2-aryl-1,2,3,4-tetra-

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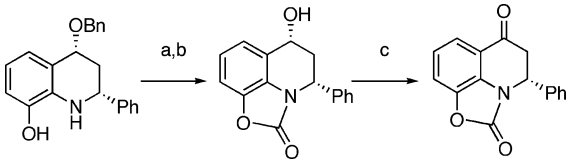
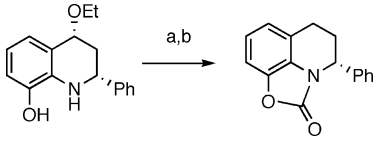
Scheme 1. Preparation of Dihydro-4-quinolone Derivatives[a]



[a] Conditions: (a) triphosgene, Et_3N, CH_2Cl_2, 8 h, 88%; (b) H_2, Pd/C, AcOH, 98%; (c) MnO_2, CH_2Cl_2, 40 min, 56%.

hydroquinoline core structure. The 2-aryl-2,3-dihydro-4-quinolone framework was synthesized starting from benzyl ether by use of carbamate (Scheme 1). The 2-aryl-1,2,3,4-tetrahydroquinoline derivative was obtained starting from ethyl ether (Scheme 2).

Scheme 2. Preparation of Tetrahydroquinoline Derivatives[a]



[a] Conditions: (a) triphosgene, Et_3N, CH_2Cl_2, 4 h, 95%; (b) H_2, $Pd(OH)_2$, AcOH, 39 h, 83%.

Because the presence of the OH moiety on the *N*-aryl group is essential for attaining high enantioselectivity,[13] we surmised that the present aza Diels−Alder reaction proceeds via a nine-membered cyclic transition state, wherein phosphoryl oxygen forms a hydrogen bond with the hydrogen of the imine OH moiety with the nucleophile attacking the *re*-face of the imine preferentially (Figure 1).

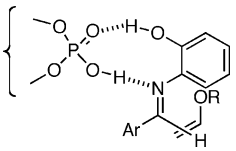


Figure 1. Plausible transition state.

In summary, we have developed a chiral Brønsted acid-catalyzed inverse electron-demand aza Diels−Alder reaction of aldimines with electron-rich alkenes. Tetrahydroquinoline derivatives were obtained with high to excellent enantioselectivity.

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Supporting Information Available: Experimental procedure, spectra data, and data of single-crystal X-ray analysis (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155.

(2) Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669.

(3) For recent examples of the asymmetric synthesis, see (a) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (b) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5317.

(4) For reviews, see (a) Waldmann, H. *Synthesis* **1994**, 535. (b) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetradedron* **1996**, *52*, 15031. (c) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (e) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (f) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002.

(5) (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979. (b) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5476. (c) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121. (d) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (e) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456.

(6) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357.

(7) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973.

(8) For reviews on Brønsted acid catalysis, see (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (c) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758. (d) Pihko, P. M. *Lett. Org. Chem.* **2005**, *2*, 398. (e) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (f) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (g) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (h) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909.

(9) For recent representative papers, see (a) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094. (c) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (d) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (e) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231. (f) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (g) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846. (h) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (i) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080. (j) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336. (k) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680. (l) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790. (m) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (n) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680. (o) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.

(10) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (c) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523. (d) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141. (e) Itoh, J.; Fuchibe, K. Akiyama, T.; *Angew. Chem., Int. Ed.* **2006**, *45*, 4796.

(11) (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (d) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (e) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (f) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (g) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (h) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (i) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (j) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617. (k) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (l) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

(12) The absolute stereochemistries of **5a** and **5b** were also determined by the analogy after X-ray analysis of a bromo analogue of **5a**. For details, please see Supporting Information.

(13) An aldimine, derived from *p*-methoxyaniline, did not give the corresponding cycloadduct.

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