ORGANIC LETTERS

2006
Vol. 8, No. 26
6023−6026

Enantioselective Direct Aza Hetero-Diels–Alder Reaction Catalyzed by Chiral Brønsted Acids

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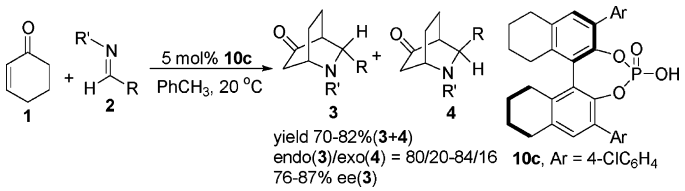
Received October 10, 2006

ABSTRACT



The first chiral Brønsted acid-catalyzed asymmetric direct aza hetero-Diels–Alder reaction has been described. The phosphoric acids, prepared from binol and H_8-binol derivatives, have shown catalytic ability for the reaction of cyclohexenone with *N*-PMP-benzaldimine. A chiral phosphoric acid, derived from 3,3-di(4-chlorophenyl)-H_8-binol, exhibited superior enantioselectivity, affording fairly good yields and enantioselectivities for the reaction of a range of aromatic aldimines with cyclohexenone.

The *N*-containing heterocylic compounds are of great importance in organic synthesis. The asymmetric aza Diels−Alder reaction is one of the most efficient transformations to approach chiral piperidine derivatives, the precursors of a large family of biologically important compounds such as alkaloids, peptides, and aza-sugars.[1] This importance has led to great efforts spent on the asymmetric aza Diels−Alder reactions.[2] Thus, a number of examples of highly enantioselective aza Diels−Alder reactions have been described in which active preformed dienes are used as a reaction component in conjuction with either chiral Lewis acids or chiral Brønsted acids as catalysts.[3−8] In contrast, the direct asymmetric aza Diels−Alder reaction, which avoids the use of preformed dienes, has been less extensively studied. To the best of our knowledge, only a single proline-catalyzed direct aza Diels−Alder reaction between cyclohexenone derivatives and imines generated from aldehydes and 4-methoxyphenylamine has been described.[9] Although almost

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(1) (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine*: *Structure, Preparation and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, The Netherlands, 1991. (b) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633. (c) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (d) Michael, J. P. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2001; Vol. 55. (e) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

(2) For reviews, see: (a) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(3) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264.

(4) (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979. (b) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220. (c) Kobayashi, S.; Kusakabe, K.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225. (d) Yamashita, Y.; Mizuki, Y.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 1803.

(5) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018.

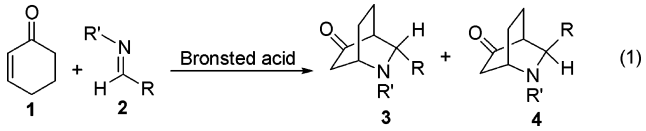
(6) Mancheno, O. G.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456.

(7) (a) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121. (b) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435.

(8) (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796. (b) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141.

10.1021/ol062499t CCC: $33.50
Published on Web 11/24/2006

perfect enantioselectivity was observed, the use of imines in such a direct aza Diels−Alder reaction was restricted to formaldimines and an ethyl *N*-PMP-α-imino glyoxylate. To date, there has been no report of a direct aza hetero-Diels−Alder reaction (eq 1) of cyclohexenone (**1**) with comparably sterically demanding aromatic aldimines (**2**).

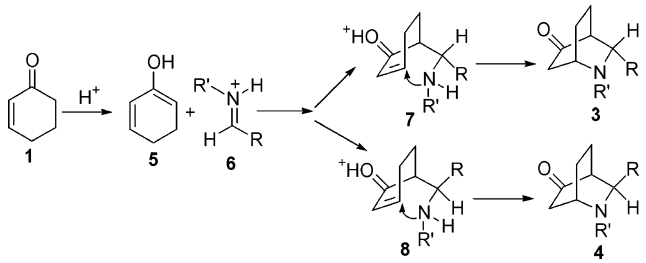


(1)

It is well-known that a carbonyl compound possessing α-hydrogens will enolize in acid and the formed enolate will attack carbonyl compounds and activated imines to undergo the classical aldol and Mannich reactions. Similarly, we reasoned that under the acidic conditions cyclohexenone (**1)** would be enolized into **5**, which would first attack the protonated aldimine **6** to undergo a Mannich reaction, generating intermediates **7** and **8**, after a tandem intramolecular 1,4-addition reaction to afford the predicted products **3** and **4**.

Recently, chiral Brønsted acids have been frequently used for asymmetric catalysis.[10,11] In particular, chiral phosphoric acids have emerged as a class of powerful organocatalysts for the activation of imine functional groups, resulting in a number of asymmetric additions of various nucleophiles to imines.[12] In light of these facts and following our consideration of the proposed mechanism of Brønsted acid-catalyzed direct aza Diels−Alder reaction (Scheme 1), we

Scheme 1. Proposed Direct Aza Diels−Alder Reaction of Cyclohexenone with Aldimines



further hypothesized that chiral Brønsted acids would be able to catalyze the asymmetric direct aza Diels−Alder reaction of cyclohexenone with aldimine without the assistance of enamine catalysis. Herein, we report the first Brønsted acid-catalyzed asymmetric direct aza hetero-Diels−Alder reaction of a variety of aromatic aldimines with cyclohexenone, yielding the adducts **3** with good enantioselectivity.[13]

(9) Sundén, H.; Ibrahem, H.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877.

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

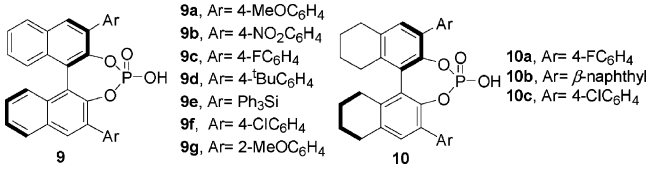
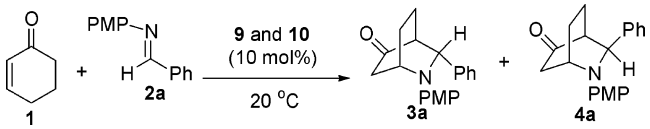


Figure 1. Phosphoric acids evaluated in this study

An initial validation of the hypothesis commenced with experiments of reacting cyclohexenone with benzaldimines, derived from *various amines*, in the presence of binol- and H_8-binol-derived phosphoric acids,[12o] leading to a finding that aromatic aldimines with an *N*-PMP group are reactive toward the cyclohexenone to afford the desired product in a modest yield and enantioselectivity.[14] The NOE spectrum of the major product showed that endo-isomer **3a** was favorably formed (see the Supporting Information). In light of these primary results, a survey of the ability of phosphoric acids **9** and **10** to catalyze the direct aza Diels−Alder reaction was performed with the reaction of cyclohexenone (**1**) and **2a** in CH_2Cl_2 at 20 °C. As the data in Table 1 indicated, all

Table 1. Catalyst Screening[a]



entry	catalyst	yield (%)[b]	**3a/4a** (endo/ exo)[c]	ee (%)[d]
1	**9a**	65	83/17	65
2	**9b**	35	79/ 21	70
3	**9c**	67	76/ 24	66
4	**9d**	32	67/33	34
5	**9e**	45	85/15	37
6	**9f**	47	80/20	70
7	**9g**	72	84/16	64
8	**10a**	67	81/19	72
9	**10b**	77	79/21	79
10	**10c**	58	85/15	85
11	**10c**	32	81/19	89[e]

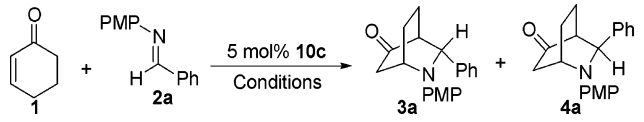
[a] Unless specified otherwise, the reaction of benzaldimine (0.2 mmol) and cyclohexanone (0.4 mmol) was performed in CH_2Cl_2 (1.5 mL) for 4 days. [b] Isolated yield of **3** and **4**. [c] Determined by ^{1}H NMR. [d] The enantiomeric excess of the major product was determined by HPLC. [e] In the presence of 5 mol % **10c**.

the phosphoric acids are catalytically active and afforded the endo-isomer **3a** as a major product in varying yields and diastereo- and enantioselectivities, depending on the structure, particularly of the 3,3′-Ar substituents, of the catalysts. Generally, the more highly sterically congested Ar substituents had more deleterious effects on the enantioselectivity. For example, much lower enantioselectivities were observed with **9d** and **9e**, which possess bulkier *p-tert*-butylphenyl and

triphenylsilyl substituents, respectively, compared with their structural analogues **9a**,**b** and **9f** (entries 1−7). In terms of enantioselectivity, **9f** turned out to be the best catalyst among the binol-derived phosphoric acids (entry 6). The selectivity could be further improved by using H_8-binol-derived phosphoric acids **10** (entries 8−12). Comparably higher enantioselectivity was observed with **10c** (entry 10) and was maintained even after reducing the catalyst loading from 10 mol % to 5 mol % (entry 11).

With an optimal catalyst in hand, we further optimized the reaction conditions, such as solvents and the reaction temperature. As revealed in Table 2, nonpolar solvents, such

Table 2. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	yield (%)[b]	3a/4a (endo/ exo)[c]	ee (%)[d]
1	CH_2Cl_2	25	64	82/18	79
2	toluene	25	71	85/15	85
3	*m*-xylene	25	66	83/17	85
4	$ClCH_2CH_2Cl$	25	60	82/18	79
5	THF	25	39	83/17	85
6	$CHCl_3$	25	57	83/17	76
7	toluene	20	70	83/17	85
8	toluene	10	57	83/17	88
9	toluene	0	45	84/16	89
10	toluene	20	76	84/16	87[e]

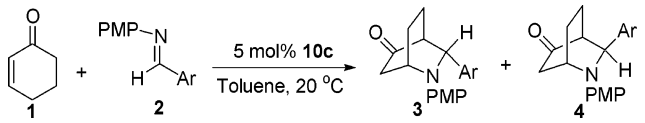
[a] Unless specified otherwise, the reaction of benzaldimine (0.2 mmol) and cyclohexanone (10.0 equiv) was performed in toluene (1.5 mL) for 4 days. [b] Isolated yield of **3** and **4**. [c] Determined by ^{1}H NMR. [d] The enantiomeric excess of the major product was determined by HPLC. [e] The reaction continued for 6 days.

as toluene and *m*-xylene, led to higher yields than their polar counterparts. In addition, the use of halogenated solvents resulted in lower enantioselectivity (entries 1, 4, and 6). Thus, toluene is the solvent of choice in this case. Lowering reaction temperature slightly improved the selectivity, but sacrificed the reaction rate (entries 8 and 9). Interestingly, the diastereoselectivity was not so sensitive to the reaction conditions. The performance of the reaction at 20 °C could give the desired product in 76% yield with 84/16 dr and 87% ee (entry 10).

The phosphoric acid **10c**-catalyzed direct aza Diels−Alder reaction was extended to a series of benzaldimines, including

(11) For selected leading literature references see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (c) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094. (d) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1267. (e) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (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) Fuerst, E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.

Table 3. Direct Organocatalytic Asymmetric Diels−Alder Reaction of Cyclohexenone with Aldimines[a]

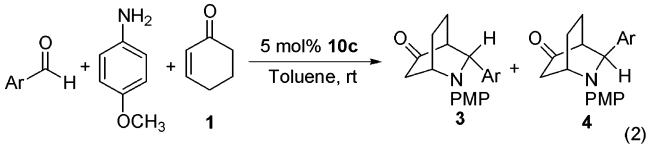


entry	Ar	yield (%)[b]	3/4 (endo/ exo)[c]	ee (%)[d]
1	C_6H_5 (**2a**)	76	84/16	87
2	3-ClC_6H_4 (**2b**)	74	81/19	83
3	4-ClC_6H_4 (**2c**)	82	82/18	85
4	2-ClC_6H_4 (**2d**)	73	81/19	77
5	4-FC_6H_4 (**2e**)	72	80/20	85
6	3-FC_6H_4 (**2f**)	76	82/18	84
7	4-BrC_6H_4 (**2g**)	81	82/18	85
8	3-BrC_6H_4 (**2h**)	79	81/19	87
9	4-MeC_6H_4 (**2i**)	81	83/17	83
10	4-CNC_6H_4 (**2j**)	70	83/17	76

[a] Unless specified otherwise, the reaction of aldimine **2** (0.2 mmol) and cyclohexanone (10.0 equiv) was performed in toluene (1.5 mL) for 6 days. [b] Isolated yield of **3** and **4**. [c] Determined by ^{1}H NMR. [d] The enantiomeric excess of the major product was determined by HPLC.

those bearing either an electron-donating or electron- withdrawing substituent (Table 3). The reactions all proceeded smoothly to favor the formation of endo-isomer **3** in good yields (70−82%) and with fairly good enantioselectivities (76−87% ee) and diastereoselectivities (80/20−84/16 dr).

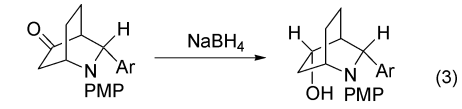
The one-pot, three-component asymmetric aza Diels−Alder reaction of cyclohexenone with *p*-methoxyphenylamine and a number of aromatic aldehydes catalyzed by **10c** (5 mol %) were also successful, furnishing the products in good yields with enantioselectivities similar to those observed for the corresponding reactions with preformed aldimines (eq 2).



(2)

Ar = 4-ClC_6H_4(**3c**), 70% yield, endo/exo = 78/22, 83%ee
Ar = 4-BrC_6H_4(**3g**), 68% yield, endo/exo = 76/24, 84%ee
Ar = 3-$CH_3C_6H_4$(**3k**), 71% yield, endo/exo = 87/13, 85%ee

The resulting products are of synthetic usefulness and can be converted into some chiral building blocks. For example, diastereoselective reduction of **3a** with sodium boronhydride gave a γ-amino alcohol **11** in >99% yield with >99/1 dr (eq 3).



(3)

3c (Ar = 4-ClC_6H_4)
85%ee

11 (Ar = 4-ClC_6H_4)
>99% yield
>99/1 dr, 85%ee

In summary, we have developed *the first direct hetero-Diels−Alder reaction catalyzed by phosphoric acids*. The presence of 5 mol % phosphoric acid **10c**, derived from H_8-binol, could promote the reaction for a range of aromatic aldimines in high yields with good enantioselectivities and diastereomeric ratioes, and with no assistance of enamine catalysis. The reaction actually avoids the substrate limitation associated with proline-catalyzed direct aza Diels−Alder reaction[9] and provides a new method for the preparation of chiral multiply substituted piperidines.

Acknowledgment. We are grateful for financial support from NSFC (203900505 and 20325 211).

Supporting Information Available: Experimental procedures, spectra data, characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (d) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (e) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (f) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (g) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (h) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (i) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (j) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (k) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (l) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617. (m) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (n) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193. (o) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802.

(13) After submission of this paper, Rueping and Azap reported a similar reaction: Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, DOI: 10.1002/anie.200603199.

(14) The use of $BocNH_2$, $TsNH_2$, diphenylphosphinamide, and 2-aminophenol led to no reaction.