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exo-Selective Asymmetric Diels–Alder Reaction Catalyzed by Diamine Salts as Organocatalysts

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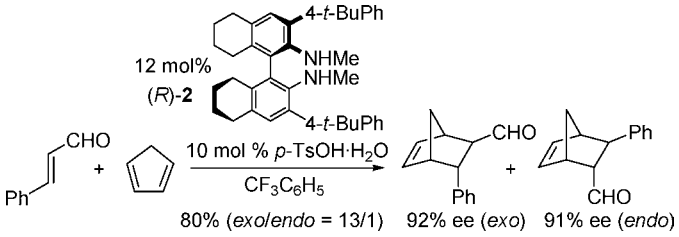
ABSTRACT



A novel binaphthyl-based diamine (*R*)-2 was designed and synthesized. A protonic acid–(*R*)-2 salt catalyst has the advantage of exhibiting unprecedented high *exo* selectivity in the asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes. For instance, the reaction between cinnamaldehyde and cyclopentadiene in the presence of 12 mol % of binaphthyl-based diamine (*R*)-2 and 10 mol % of *p*-TsOH·H_2O in α,α,α-trifluorotoluene at −20 °C gave the corresponding *exo* cycloadduct with 92% ee as a major diastereomer (*exo*/*endo* = 13/1).

The Diels−Alder reaction remains one of the most powerful tools in synthetic organic chemistry as exemplified by its broad application to the regio- and stereochemically defined synthesis of a wide variety of natural products, and hence, a number of enantioselective as well as diastereoselective Diels−Alder reactions have been developed to date.[1] Among such stereoselective processes, the enantioselection is controlled by chiral reagents or catalysts, while the degree of diastereoselectivity depends mainly on the structure of substrates. For instance, the Diels−Alder reaction of cyclopentadiene with α,β-unsaturated carbonyl compounds such as acrolein, methyl vinyl ketone, and methyl acrylate is known to give the *endo* cycloadducts predominantly. This *endo* selectivity is considered to be a general attribute of the Diels−Alder family of reactions. In contrast, the opposite *exo* selectivity, particularly the catalyst-controlled *exo*-selective Diels−Alder reaction, is not readily attainable by deliberate modification of existing methodologies especially with simple α,β-unsaturated aldehydes and ketones.[2,3] In consideration of the current importance and the rapid development of organocatalytic reactions in practical organic synthesis,[4] we have been interested in the possibility of

(1) For recent reviews of enantioselective Diels−Alder reactions: (a) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, p 1177. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5. (c) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (d) Diaz, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289. (e) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (f) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

(2) (a) Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (c) Kündig, E. P.; Saudan, C. M.; Alezra, V.; Viton, F.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4481. (d) Cavill, J. L.; Peters, J.-U.; Tomkinson, N. C. O. *Chem. Commun.* **2003**, 728.

(3) *exo*-Selective Diels−Alder reactions of acrylic esters and amides: (i) Chiral substrates: (a) Lamy-Schelkens, H.; Ghosez, L. *Tetrahedron Lett.* **1989**, *30*, 5891. (b) Avenoza, A.; Bueno, M. P.; Cativiela, C.; Mayoral, J. A. *Tetrahedron: Asymmetry* **1992**, *3*, 343. (c) Fraile, J. M.; García, J. I.; Gracia, D.; Mayoral, J. A.; Pires, E. *J. Org. Chem.* **1996**, *61*, 9479. (d) Kawamura, M.; Kudo, K. *Chirality* **2002**, *14*, 727. (ii) Chiral Lewis acids: (e) Sagasser, I.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 261. (f) Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron* **2002**, *58*, 2929. (iii) Catalytic antibody: (g) Gouverneur, V. E.; Houk, K. N.; de Pascual-Teresa, B.; Beno, B.; Janda, K. D.; Lerner, R. A. *Science* **1993**, *262*, 204. See, also: (h) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D.; Waltermire, B. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 6438.

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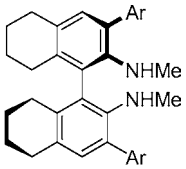
developing a hitherto difficult *exo*-selective asymmetric Diels−Alder reaction using a certain chiral organocatalyst.[5,6] Here, we wish to report the realization of such a cycloaddition reaction catalyzed by chiral binaphthyl-modified diamine salts (Figure 1).

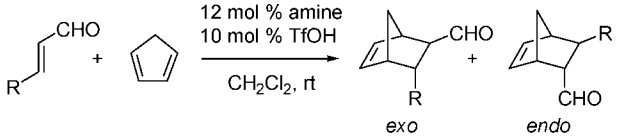


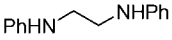
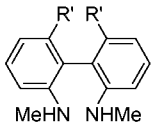
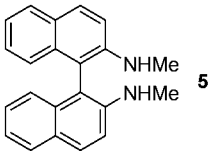
(*R*)-**1**: Ar = Ph
(*R*)-**2**: Ar = 4-*t*-BuPh

Figure 1. Binaphthyl-based diamines.

To find an appropriate amine salt catalyst for the *exo*-selective Diels−Alder reaction, we first examined the chemical behavior of *N*-methylaniline derivatives as secondary amines due to their ease of preparation and further structural modification. In addition, introduction of both electron-donating (methyl) and electron-withdrawing (phenyl) substituents on nitrogen atom is expected to accelerate the formation and hydrolysis of an iminium salt as a reactive intermediate, respectively.[2d,5] Thus, the Diels−Alder reaction of cyclopentadiene with cinnamaldehyde was carried out in the presence of catalytic secondary amine (12 mol %) and catalytic trifluoromethanesulfonic acid (10 mol %) in dichloromethane at room temperature, and the results are summarized in Table 1. With *N*-methylaniline catalyst, the desired *exo* adduct was obtained as a major product (*exo*/*endo* = 2.2:1) in 75% yield (entry 1). In contrast, the parent aniline showed none of the reactivity (entry 2), and use of *N*-methylbenzylamine as an aliphatic secondary amine produced the cycloadducts in only 20% yield with slightly higher *exo* selectivity (entry 3). These findings prompted us to investigate the substituent effect of other secondary amines with an *N*-alkylaniline core. Although neither the introduction of ortho substituents on the aromatic ring of *N*-methylaniline nor the use of *N*,*N*′-diphenylethylenediamine affected the diastereoselectivity (entries 4−7), the improved selectivity was achievable with biphenyldiamine **3** (entry 8). Furthermore, axially chiral diamines **4** and **5** exhibited better *exo* selectivity than **3** (entries 9 and 10). Similar high *exo* selectivity is also observed in the Diels−Alder reaction between cyclopentadiene and other α,*β*-unsaturated aldehydes with binaphthyldiamine catalyst **5** (entries 11−13).

Table 1. *exo*-Selective Diels−Alder Reaction of Cyclopentadiene with α,*β*-Unsaturated Aldehydes Catalyzed by Amine−TfOH Salts[a]



entry	amine	R	conditions [°C, h]	% yield[b] (*exo*/*endo*)[c]
1	PhNHMe	Ph	rt, 20	75 (2.2/1)
2	$PhNH_2$	Ph	rt, 20	0
3	$PhCH_2NHMe$	Ph	rt, 20	20 (2.6/1)
4	2-MePhNHMe	Ph	rt, 10	30 (2.8/1)
5	2-*t*-BuPhNHMe	Ph	rt, 10	15 (2.1/1)
6	2,6-Me_2PhNHMe	Ph	rt, 10	18 (2.4/1)
7		Ph	rt, 16	47 (2.3/1)
8	 R′ = H **3**	Ph	rt, 10	86 (5.8/1)
9	R′ = Me **4**	Ph	rt, 23	83 (8.0/1)
10	 **5**	Ph	rt, 20	99 (9.2/1)
11		H	-40, 30	80 (9.4/1)
12		Me	-20, 20	99 (12/1)
13		EtO_2C	-40, 20	93 (9.2/1)

[a] The reaction of cyclopentadiene (3 equiv) with the α,*β*-unsaturated aldehyde in CH_2Cl_2 was carried out in the presence of 12 mol % of amine and 10 mol % of TfOH. [b] Isolated yield. [c] Determined by ^1H NMR.

With this information, we set out to design enantiopure binaphthyldiamine catalysts for the *exo*-selective asymmetric Diels−Alder reaction. Attempted use of enantiopure (*R*)-**5**, however, resulted in formation of the cycloadduct with low enantioselectivity in the Diels−Alder reaction of cyclopentadiene with cinnamaldehyde (Table 2, entry 1). We then screened octahydrobinaphthyldiamine catalysts as novel binaphthyl-modified chiral diamines, which were readily prepared as follows (Scheme 1): Axially chiral diamine (*R*)-**6**[7] was converted to diamine (*R*)-**8** in two steps by ethoxycarbonylation and subsequent reduction. Careful bromination of (*R*)-**8** with NBS in THF yielded (*R*)-**9**, which was treated by Suzuki−Miyaura coupling with phenylboronic acid and 4-*tert*-butylphenylboronic acid to furnish (*R*)-**1** and (*R*)-**2**, respectively.

Selected results are summarized in Table 2. Although octahydrobinaphthyl diamine (*R*)-**8** exhibited lower reactivity and enantioselectivity (entry 2), the introduction of phenyl groups at 3,3′-positions of octahydrobinaphthyl moiety

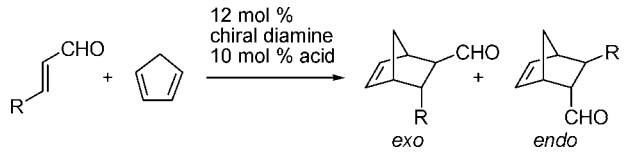
(4) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.

(5) Chiral amine salt catalyzed enantioselective Diels−Alder reactions: (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (b) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (c) Kim, K. H.; Lee, S.; Lee, D.-W.; Ko, D.-H.; Ha, D.-C. *Tetrahedron Lett.* **2005**, *46*, 5991. (d) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141, and ref 2b.

(6) Other organocatalytic Diels−Alder reactions: (a) Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7403. (b) Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F., III. *Terahedron Lett.* **2002**, *43*, 3817. (c) Braddock, D. C.; MacGilp, I. D.; Perry, B. G. *Synlett* **2003**, *1121*, and ref 2d.

(7) Shi, M.; Wang, C.-J. *Chirality* **2002**, *14*, 412.

Table 2. *exo*-Selective Asymmetric Diels−Alder Reaction of Cyclopentadiene with α,β-Unsaturated Aldehydes Catalyzed by Chiral Diamine Salts[a]



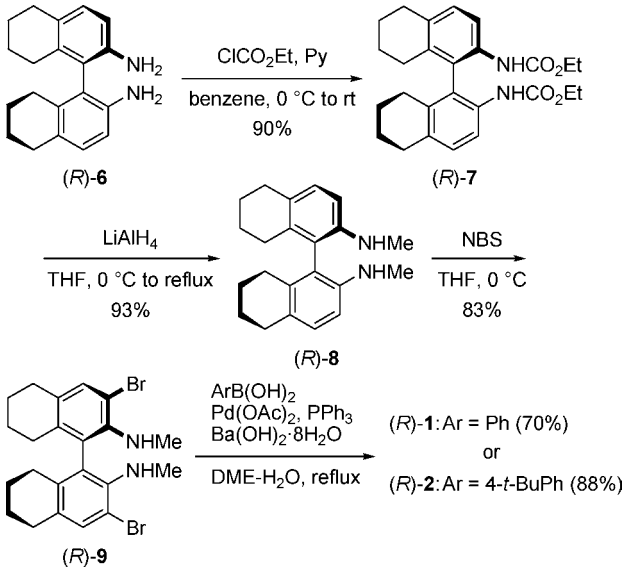
entry	chiral diamine	R	conditions (°C, h)	% yield[b] (*exo*/*endo*)[c]	% ee[d] *exo*	(config)[e] *endo*
1	(*R*)-**5**	Ph	rt, 20	99 (9.2/1)	9 (*R*)	15 (*R*)
2	(*R*)-**8**	Ph	rt, 23	61 (8.2/1)	38 (*S*)	27 (*R*)
3	(*R*)-**1**	Ph	rt, 36	90 (5.6/1)	53 (*R*)	39 (*R*)
4	(*R*)-**2**	Ph	rt, 20	87 (6.5/1)	72 (*R*)	68 (*R*)
5[f]	(*R*)-**2**	Ph	rt, 9	89 (8.6/1)	79 (*R*)	71 (*R*)
6[f]	(*R*)-**2**	Ph	0, 50	80 (9.5/1)	86 (*R*)	79 (*R*)
7[f,g]	(*R*)-**2**	Ph	0, 55	93 (11/1)	87 (*R*)	86 (*R*)
8[f,g,h]	(*R*)-**2**	Ph	−20, 160	80 (13/1)	92 (*R*)	91 (*R*)
9[f,g,h]	(*R*)-**2**	Me	−20, 160	72 (>20/1)	88 (*S*)	
10[f,g]	(*R*)-**2**	EtO_2C	−60, 144	90 (5.5/1)	83	56

[a] Unless otherwise noted, the reaction of cyclopentadiene (3 equiv) with the α,β-unsaturated aldehyde in CH_2Cl_2 was carried out in the presence of 12 mol % of chiral diamine and 10 mol % of TfOH. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by GC analysis using a chiral capillary column or HPLC analysis using a chiral column. Details are given in the Supporting Information. [e] The absolute configuration at the 2-position was determined by comparison of the sign of optical rotation with reported values. See ref 2b. [f] α,α,α-Trifluorotoluene was used as a solvent. [g] *p*-TsOH·H_2O was used as an acid. [h] Additional cyclopentadiene (2 equiv) was added twice after 48 and 96 h.

enhanced the enantioselectivity (entry 3). In particular, sterically more congested diamine (*R*)-**2** showedgood levels of *exo*- and enantioselectivity (entry 4). We then optimized the reaction conditions using diamine (*R*)-**2**. The use of α,α,α-trifluorotoluene[8] as solvent in place of dichloromethane resulted in faster reaction rate and higher stereoselectivities (entry 5). Lowering the reaction temperature also increased both the *exo*- and enantioselectivity at the expense of the reaction rate (entry 6). Among several Brønsted acids, *p*-toluenesulfonic acid was found to be more effective for the reaction than trifluoromethanesulfonic acid (entry 7). Finally, the reaction could be performed at −20 °C under the optimized conditions to give the desired *exo* cycloadduct

(8) α,α,α-Trifluorotoluene is known as a useful alternative to dichloromethane; see: Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.

Scheme 1



with excellent *exo*- and enantioselectivity (entry 8). This reaction system was also applicable to other α,β-unsaturated aldehydes (entries 9 and 10). Unfortunately, however, this reaction system was only suitable for a combination of α,β-unsaturated aldehydes and cyclopentadiene. For example, the reactions of α,β-unsaturated aldehydes with other dienes such as 1,3-cyclohexadiene and 1,3-pentadiene gave only traces of cycloadducts.

In summary, we have developed the highly *exo*-selective Diels−Alder reaction of cyclopentadiene with α,β-unsaturated aldehydes catalyzed by the binaphthyl-modified diamine salt. With the novel axially chiral diamine, an asymmetric variant of this process has also been realized. Further work aimed at the elucidation of the mechanism and broadening the scope of this reaction is currently in progress.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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