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Highly Enantioselective Diels−Alder Reactions of Maleimides Catalyzed by Activated Chiral Oxazaborolidines

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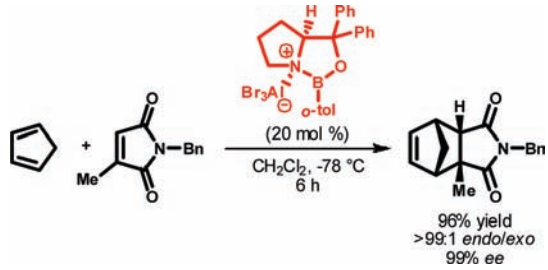
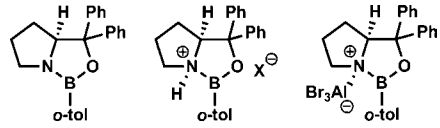
ABSTRACT



Diels−Alder reactions of various combinations of maleimides and 1,3-dienes with cationic oxazaborolidines as catalysts have been shown to be highly efficient and enantioselective.

A series of studies in these laboratories have demonstrated that activation of oxazaborolidine **1** by protonation,[1] methylation[2] or complexation with aluminum bromide[3] generates cationic species (Figure 1) which are very effective as catalysts for asymmetric cycloaddition reactions, particularly Diels−Alder processes. A wide range of dienes and dienophiles have been employed and excellent levels of diastereoselectivity and enantioselectivity have been achieved.[4]



1 **2a**: X = OTf; **2b**: X = NTf_2 **3**

Figure 1. Chiral oxazaborolidine and its activated derivatives.

With the goal of expanding the dienophile scope of Diels−Alder reactions promoted by activated oxazaborolidines, we recognized that maleimides as dienophiles would lead to useful compounds. Although maleimides have been successfully utilized as the dienophile component for *diastereoselective* Diels−Alder reactions with a number of chiral dienes,[5] development of general catalytic enantioselective variants has remained elusive. In 1994, we reported the first catalytic asymmetric Diels−Alder reaction of maleimides using a diazaluminolidine-based catalyst[6] and applied this method for the enantioselective total synthesis of gracilins B and C.[7] Although a high level of enantioselectivity was

(1) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808–3809.
(2) Canales, E.; Corey, E. J. *Org. Lett.* **2008**, *10*, 3271–3273.
(3) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498–1499.
(4) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117, Also see: Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667.
(5) (a) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630–7640. (b) Menezes, R. F.; Zezza, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3295–3298, and the references therein.
(6) Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089–12090.
(7) Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616–9617.

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achieved, the range of these reactions appeared restricted to reactive dienes and maleimides bearing a bulky aromatic *N*-substituent. Recently Tan and co-workers reported a method for catalytic enantioselective Diels−Alder reaction of maleimides with 3-hydroxy-2-pyrones promoted by an amino alcohol-based organocatalyst.[8]

These earlier studies were carried out with only C_{2v}-symmetrical maleimides as dienophile. The objective of the present work was the development of a general catalytic asymmetric Diels−Alder reaction with both symmetrical and unsymmetrical components. The previously proposed stereochemical models[4] via pretransition state assemblies analogous to **4** (Figure 2) predicted that position selectivity, enantioselectivity, and diastereoselectivity were likely.

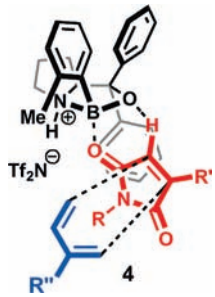
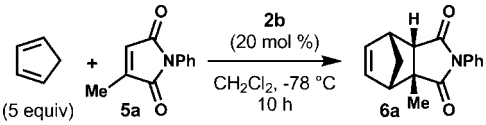


Figure 2. Expected pretransition state assembly for the Diels−Alder reaction of maleimides.

Initial studies focused on a reaction between cyclopentadiene with 2-methyl-*N*-phenylmaleimide **5a** in the presence of 20 mol % catalyst **2b** (Scheme 1).[9] In a typical procedure,

Scheme 1. Asymmetric Diels-Alder Reaction of 2-Methyl-*N*-phenylmaleimide with Cyclopentadiene[a]



92% (84%)[a]
>99:1 *endo*/*exo*
93% *ee* (>99% *ee*)[a]

[a] Values in parentheses correspond to the sample obtained after single recrystallization.

slow addition of 5.0 equivalents of cyclopentadiene over two hours to a solution of **2b** and **5a** in dichloromethane (final concentration is 0.5 M with respect to **5a**) at −78 °C and further reaction at this temperature for 8 h afforded the *endo*-product **6a** in 92% yield as a single diastereomer in 93% *ee*. The absolute stereochemistry of the product was determined by comparison of optical rotation with the value reported previously for a sample of known absolute configuration.[10] The absolute stereochemistry of **6a** is consistent with the model shown in Figure 2. Enantiopurity could be improved to >99% *ee* after a single recrystallization from hexanes/EtOAc. Further studies established that the same reaction promoted by the $AlBr_3$-activated catalyst **3**[11] provided *endo*-product **6a** with even higher selectivity (98% *ee*) than with catalyst **2b** (see Table 1, entry 2).

Encouraged by the preliminary results, we decided to study the substrate scope of this reaction both in terms of maleimide and diene. We first examined the viability of various unsymmetrical maleimides with different steric and electronic properties (Table 1). In general, 2-bromo-substituted maleimides were found to be more reactive than the corresponding 2-methyl-substituted analogs. *Endo*-products were obtained exclusively in all cases with excellent *ee*. This method is not limited to maleimides with bulky *N*-aromatic substituent: Diels−Alder reaction of *N*-benzyl and *N*-ethyl maleimides provided products with 93−99% *ee* (entry 3, 5−6).

After demonstrating success with various maleimides and cyclopentadiene as the diene, we turned our attention to other dienes with the results summarized in Table 2. Reactions with less reactive dienes such as cyclohexadiene or isoprene provided the corresponding products **7** and **8** in high yield and *ee* (entries 1−5), using in some of these cases higher reaction temperatures or longer reaction times. Although the product derived from isoprene and *N*-phenylmaleimide (**8a**) was obtained with high *ee* (entry 5), the corresponding reaction with *N*-benzylmaleimide (to form **8b**) was only moderately enantioselective, even with $AlBr_3$-activated catalyst **3** (entry 6 and 7). On the other hand, reactive dienes such as 2-triisopropylsilyloxy-1,3-butadiene reacted efficiently with *N*-phenylmaleimide **5f** in the presence of 20 mol % catalyst **3** to produce the Diels−Alder product **9a** in high yield and excellent *ee* (entry 8).

Methylcyclopentadiene, obtained by thermal cracking of the dimer as a 1:1 mixture of 1- and 2-methyl isomers, was also used as diene for reaction with *N*-phenylmaleimide **5f**

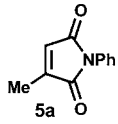
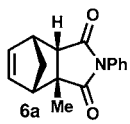
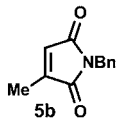
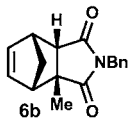
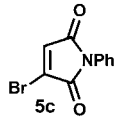
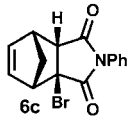
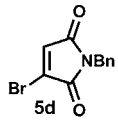
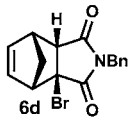
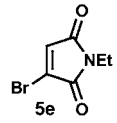
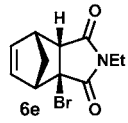
(8) Soh, J. Y.-T.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 6904–6905.

(9) Twenty mol percent catalyst was used typically for faster reaction. It is possible to reduce the catalyst loading to 10 mol % without affecting the reaction yield and enantioselectivity. However, in these cases reactions must be carried out in more concentrated solution (1.0 M instead of 0.5 M).

(10) Adams, D. J.; Blake, A. J.; Cooke, P. A.; Gill, C. D.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4603–4615. Also see Supporting Information.

(11) *Typical experimental procedure:* A 0.25 M solution of oxazaborolidine **1** in toluene (0.5 mL; 0.125 mmol) was placed in a 10 mL oven- and flame-dried Schlenk tube and the solvent was removed under reduced pressure. Then 0.2 mL of abs. CH_2Cl_2 was added and the resulting clear solution was cooled to −25 °C (dry ice/iso-propanol) under positive nitrogen pressure. A solution of $AlBr_3$ (0.1 mL of 1.0M in CH_2Br_2; 0.1 mmol) was added, and the reaction mixture was stirred at −25 °C for 25 min. The resulting green solution was cooled to −78 °C (dry ice/iso-propanol), and a solution of maleimide **5a** (94 mg; 0.5 mmol) in 0.4 mL abs. CH_2Cl_2 was added. At this point, cyclopentadiene (0.21 mL; 2.5 mmol) was added down the wall of the flask over a period of two hours and stirred at −78 °C. The reaction was monitored by TLC and judged to be complete within 8 h. Triethylamine (0.1 mL) was added to the reaction mixture followed Et_2O (2 mL), allowed to warm to ambient temperature and filtered through a Celite pad. The filtrate was concentrated in vacuo and the residue purified by silica gel column chromatography using hexanes/EtOAc (5:1 to 3:1) to obtain, as a white crystalline solid, the desired product **6a** (117 mg, 0.46 mmol, 92% yield; mp 124−125 °C). For further details about determination of enantiomeric purity by HPLC-analysis, see Supporting Information.

Table 1. Catalytic Enantioselective Diels-Alder Reactions of Cyclopentadiene with Various Maleimides[a]

entry	dienophile	product	cat.	temp (°C), time (h)	yield, *ee* (%)[b]
1	 5a	 6a	**2b**	-78, 10	92, 93
2			**3**	-78, 8	92, 98
3	 5b	 6b	**3**	-78, 6	96, 99
4	 5c	 6c	**2b**	-78, 2	99, >99
5	 5d	 6d	**2b**	-78, 2	98, 99
6	 5e	 6e	**3**	-95, 2.5	98, 93

[a] Reactions were carried out using 20 mol % catalyst and 5 equiv of cyclopentadiene at 0.5 M in CH_2Cl_2 with respect to the dienophiles. [b] In all cases, *endo*-products were obtained in >99:1 *dr*. Enantiomeric excesses were determined by HPLC or GC using chiral column (see Supporting Information). Absolute configuration of products **6b**−**e** were assigned in analogy to **6a**.

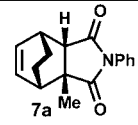
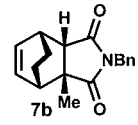
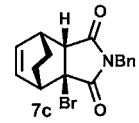
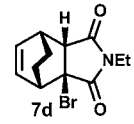
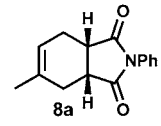
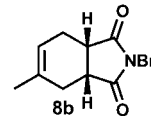
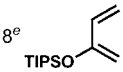
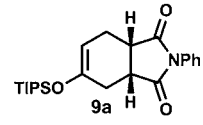
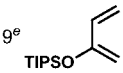
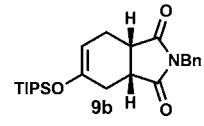
in the presence of catalyst **2b** (Scheme 2).[12] Although two position isomeric[13] *endo*-products (**10** and **11**) were formed from the methylcyclopentadiene mixture in a 6:1 ratio with high enantiomeric excess, they were easily separated by chromatography on silica gel.

Encouraged by the excellent results obtained with cationic oxazaborolidines as catalysts for Diels−Alder reactions of

(12) *Experimental procedure for the Diels−Alder reaction of* **5f** *and methylcyclopentadiene:* A 0.25M solution of oxazaborolidine **1** in toluene (0.5 mL; 0.125 mmol) was placed in a 10 mL oven- and flame-dried Schlenk tube and the solvent was removed under reduced pressure. Then 0.3 mL of abs. toluene was added and the resulting clear solution was cooled to −25 °C (dry ice/iso-propanol) under positive nitrogen pressure. A solution of Tf_2NH (0.2 mL of 0.5M in abs. toluene; 0.1 mmol) was added, and the resulting solution was stirred at −25 °C for 25 min. The reaction mixture was cooled to −78 °C (dry ice/iso-propanol), and methylcyclopentadiene (∼1:1 mixture of 1- and 2-methyl isomers; 0.5 mL; 5.0 mmol) was slowly added down the wall of the flask over 15 min. At this point a solution of maleimide **5f** (87 mg; 0.5 mmol) in 0.3 mL abs. toluene and 0.2 mL abs. CH_2Cl_2 was added over a period of two hours. The reaction was monitored by TLC and judged to be complete within 2 h; reaction mixture was diluted with Et_2O (2 mL), brought to ambient temperature and filtered through a Celite pad. The filtrate was concentrated to a colorless oil. 1H-NMR analysis of the crude product revealed a 6:1 ratio of **10** and **11**. Purification by silica gel column chromatography using hexanes/EtOAc (5:1 to 4:1 to 3:1) afforded, as colorless crystals, **10** (mp 141−143 °C) and **11** (mp 193−195 °C). For further details about determination of enantiomeric purity by HPLC-analysis, see Supporting Information.

(13) For a recent report on asymmetric Diels-Alder reactions of substituted cyclopentadiene see: Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9536–9537.

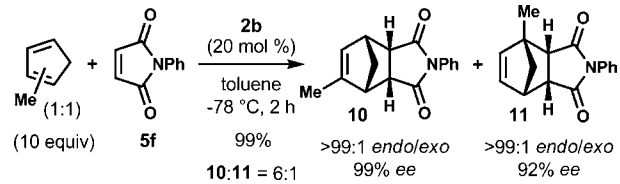
Table 2. Catalytic Enantioselective Diels−Alder Reactions of an Assortment of Dienes and Maleimides[a]

entry	diene	product	cat.	temp (°C), time (h)	yield, *ee* (%)[b]
1		 7a	**3**	-20, 90	88, 90
2[c]		 7b	**3**	4, 24	96, 97
3[d]		 7c	**3**	-30, 3	92, 98
4[d]		 7d	**3**	-40, 12	93, 96
5		 8a	**2b**	-78, 16	97, 92
6		 8b	**2b**	-78, 15	97, 76
7			**3**	-78, 7	96, 77
8[e]		 9a	**3**	-78, 6	94, >99
9[e]		 9b	**3**	-78, 12	96, 80

[a] Reactions were carried out with 20 mol % catalyst and 5 equiv of diene at 0.5 M in CH_2Cl_2 with respect to the dienophiles except where noted. [b] When applicable, *endo*-products were obtained in >99:1 *dr*. Enantiomeric excesses were determined by HPLC or GC using chiral column (see Supporting Information). Absolute configuration of the products were assigned in analogy to **6a**. [c] Reaction was carried out neat. [d] Reaction was carried out at 1.0 M concentration. [e] Diene (1.5 equiv) was used.

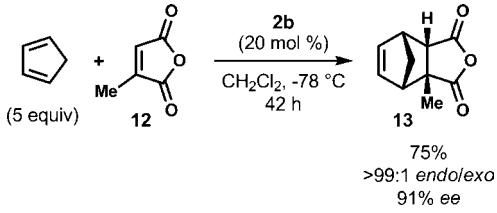
maleimides, we investigated briefly the possibility that unsymmetrical maleic anhydrides might also participate in

Scheme 2. Enantioselective Diels−Alder Reaction of Methyl-cyclopentadienes with *N*-Phenylmaleimide **5f**



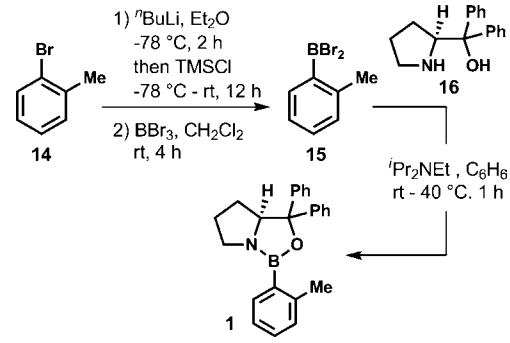
enantioselective [4 + 2] additions. We are unware of previous examples of enantioselective Diels−Alder reactions with maleic anhydride-type substrates. Indeed the reaction of citraconic anhydride **12** with cyclopentadiene and 20 mol % of catalyst **2b** in dichloromethane afforded the *endo*-product **13** in 75% yield[14] and 91% *ee* (Scheme 3).[15]

Scheme 3. Enantioselective Diels−Alder Reaction of Citraconic Anhydride **12** with Cyclopentadiene



Finally, we have developed an alternative method for the preparation of oxazaborolidine **1**, which involves the reaction of easily accessible dibromo(*o*-tolyl)borane **15** with (*S*)-1,1-diphenylpyrrolidinemethanol **16** in the presence of 2 equiv of Hünig's base in benzene (Scheme 4).[16] Simple filtration of the resulting HBr salt with exclusion of air and moisture gave rapid access to **1**. This new method is superior to the standard azeotropic condensation reaction between **16** and *o*-tolylboroxine[17] because it is faster, simpler and leads to pure **1**.[18] Precatalyst **1** synthesized via this new method was used for the enantioselective Diels−Alder reactions reported in this paper.

Scheme 4. New Method for the Preparation of Precatalyst **1**



In summary, cationic oxazaborolidines are extremely efficient catalysts for enantioselective Diels−Alder reactions of maleimides and 1,3-dienes. The scope of the method is broad and the reactions are generally enantiocontrolled and diastereoselective.

Acknowledgment. We thank Dr. Nathan Wallock of Sigma-Aldrich Co. for a gift of the precatalyst **1** and triflimide.

Supporting Information Available: Experimental procedures, and spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Reaction was slow and interrupted before completion (approximately 80% conversion).

(15) For determination of enantiomeric purity and absolute configuration, see Supporting Information.

(16) *Experimental procedure for the preparation of* **1**: (*S*)-1,1-Diphenylpyrrolidinemethanol **15** (697 mg; 2.75 mmol) was placed in a 25 mL oven- and flame-dried round bottom flask together with 2.5 mL abs. benzene and Hünig's base (0.96 mL; 5.50 mmol) under nitrogen. A solution of dibromo(*o*-tolyl)borane **14** (720 mg; 2.75 mmol) in 2.5 mL abs. benzene was added via syringe over 30 min at rt. After the addition was complete, the resulting white suspension was heated at 40 °C for 1 h. The reaction mixture was cooled to ambient temperature and the precipitate was filtered through a sintered glass funnel under nitrogen. The filtrate was concentrated under reduced pressure to a pale yellow oil, which was taken in abs. toluene to make a 0.25M solution of **1** and used subsequently for Diels-Alder experiments. Also see Supporting Information.

(17) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992–9993.

(18) Also see: Chein, R. J.; Yeung, Y.-Y.; Corey, E. J. *Org. Lett.* **2009**, *11*, 1611–1614.