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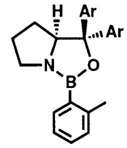
Triflimide Activation of a Chiral Oxazaborolidine Leads to a More General Catalytic System for Enantioselective Diels−Alder Addition

Do Hyun Ryu and E. J. Corey*

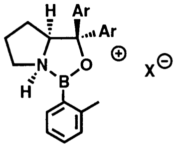
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138

Received March 31, 2003; E-mail: corey@chemistry.harvard.edu

Protonation of chiral proline-derived oxazaborolidines such as **1a** and **1b** by triflic acid generates chiral boron Lewis acids (**2a** and **2b**) that are of great utility as catalysts for enantioselective Diels−Alder reactions of a wide variety of dienes and dienophiles.[1−3] These reactions were demonstrated not only to be highly enantioselective for many cases but also to follow the absolute stereochemistry predicted by a well-defined mechanistic model.[4,5] Although the reactions were first described for α-substituted α,β-enals and a variety of acyclic and cyclic dienes,[1] subsequent studies demonstrated a broader range with regard to the dieneophile component, including α,β-unsaturated esters, lactones, and ketones.[2] Unfortunately, the catalysts **2a** and **2b** decompose at an appreciable rate at or above 0 °C, limiting the range of application. We therefore sought a modification of these catalysts that would increase their stability and allow effective application to a wider group of mutually less reactive dienes and dienophiles. It was gratifying that a simple change of the counterion from triflate ($CF_3SO_3^-$) to triflimide, $(CF_3SO_2)_2N^-$, as illustrated by **3a** and **3b** had a remarkably beneficial effect on catalyst stability, with no loss of potency.



1 { (a) Ar = C_6H_5
(b) Ar = 3,5-dimethylphenyl

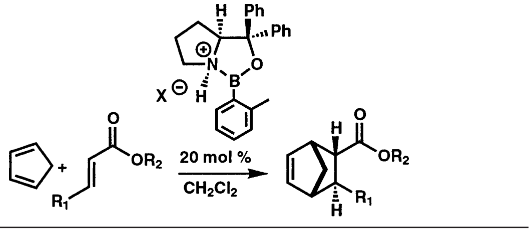


2 { (a) Ar = C_6H_5, X = CF_3SO_3
(b) Ar = 3,5-dimethylphenyl,
X = CF_3SO_3

3 { (a) Ar = C_6H_5, X = $(CF_3SO_2)_2N$
(b) Ar = 3,5-dimethylphenyl,
X = $(CF_3SO_2)_2N$

Treatment of **1a** with an equivalent of the strong acid[6] triflimide ($(CF_3SO_2)_2NH$, Aldrich Co.) results in the protonation of **1a** at nitrogen (as observed previously with triflic acid[1,2]) to form the very strong chiral Lewis acid **3a**. ^1H NMR analysis of a 1:1 mixture of **1a** and triflimide in CD_2Cl_2 in the temperature range −80 to 23 °C shows the formation of three new species with several protons shifted downfield relative to **1a**. We believe these to be (a) the trivalent boron cation **3a** (largest downfield shift) and (b) two diastereomeric tetracoordinated boron species in which the two counterions of **3a** are bonded. The ratio of **3a** to the tetracoordinated boron species was found to be ca. 1:1.2. In the ^1H NMR spectrum of **3a**, the methine $N{-}C_\alpha{-}H$ proton appears as a doublet of triplets at δ 5.44, in contrast to a doublet of doublets at δ 4.59 for the $N{-}C_\alpha{-}H$ methine proton in **1a** (each in CD_2Cl_2 at 0 °C). The corresponding methine $N{-}C_\alpha{-}H$ peaks in the ^1H NMR spectra of the two tetracoordinated diastereomers corresponding to **3a** are centered at δ 4.90 and 5.01.[7]

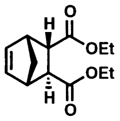
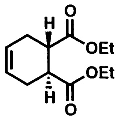
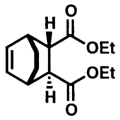
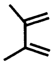
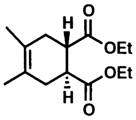
Table 1. Comparison of Diels−Alder Catalysts **2a** and **3a**



R_1	R_2	X	concn	temp (°C), time (h)	% yield, ee (endo/exo)
Me	Et	TfO	0.25	4, 72	46; >98 (endo) (91:9)
Me	Et	Tf_2N	0.25	20, 16	94; 97 (endo) (89:11)
Ph	CF_3CH_2	TfO	1.0	4, 72	27; 95 (endo) (85:15); 94 (exo)
Ph	CF_3CH_2	Tf_2N	1.0	20, 16	79; 93 (endo) (83:17); 96 (exo)
Ph[a]	CF_3CH_2	−	0.25	20, 16	86; 0 (endo) (88:12); 0 (exo)

[a] $EtAlCl_2$ (20 mol %) was used as a Lewis acid catalyst.

Table 2. Diels−Alder Reactions of Diethyl Fumarate, 20 mol % **3a** or **3b** as Catalyst, and Less Reactive Dienes

Diene	Product	Catalyst	Sol.	Temp. (°C), Time (h)	% Yield; ee
		3a	$PhCH_3$	-60, 2	99; >99
		3b	CH_2Cl_2	20, 40	79; 88
		3b	$PhCH_3/CH_2Cl_2$	20, 16	92; 93
		3b	CH_2Cl_2	20, 40	80; 96
		3a	$PhCH_3$	20, 40	90; 98
		3b	$PhCH_3$	20, 16	99; 98

The greater thermal stability and superior catalytic efficacy of the triflimidate **3a** as compared to the triflate **2a** was first revealed by the experimental results summarized in Table 1. As mentioned above, although catalyst **2a** is too unstable to be used above 4 °C, catalyst **3a** functions well at 25 °C.

The experimental data summarized in Table 2 show that the triflimide catalysts **3a** and **3b** produce excellent results using diethyl fumarate as a test dienophile with a variety of less reactive dienes, in contrast to the corresponding triflates **2a** and **2b** (data not shown). The same group of dienes, including the least reactive, 1,3-butadiene, react with the less reactive test dienophile trifluoroethyl acrylate to give uniformly outstanding results with catalyst **3a** or

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Table 3. Diels–Alder Reactions of Trifluoroethyl Acrylate, 20 mol % **3a** or **3b**, and Less Reactive Dienes

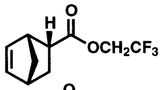
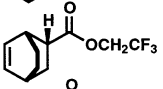
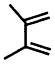
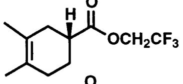
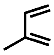
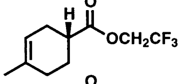
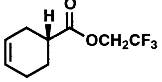
Diene	Product	Catalyst	Sol.	Temp. (°C), Time (h)	% Yield; ee (*endo:exo*)
		3a	$PhCH_3$	-60, 2	97; >99 (98:2)
		3a	$PhCH_3$	20, 40	81; 98 (>99:1)
		3a	$PhCH_3$	20, 16	98; 98
		3a	$PhCH_3$	0, 8	99; 98
		3a 3b	$PhCH_3$ neat	20, 40 20, 24	78; 88 96; 95

Table 4. Diels–Alder Reactions of α,*β*-Enones with 2,3-Dimethylbutadiene in the Presence of 20 mol % **3a** and **3b**

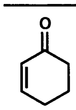
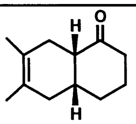
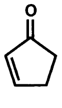
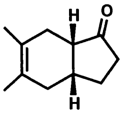
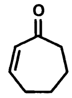
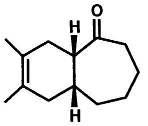
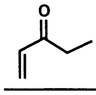
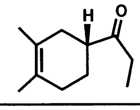
Dienophile	Product	Catalyst	Sol.	Temp. (°C), Time (h)	% Yield; ee
		3a 3b 3b	$PhCH_3$ neat neat	20, 16 4, 24 -20, 88	99; 64 99; 77 96; 85
		3b	neat	-20, 72	99; 76
		3b	neat	0, 96	67; 81
		3a	neat	-20, 88	87; 80

Table 5. Reaction of 2,5-Dimethyl-1,4-benzoquinone, **3a** (20 mol %), and Various Dienes[10]

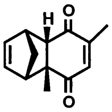
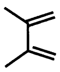
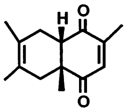
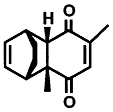
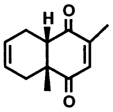
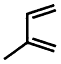
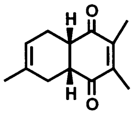
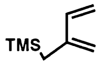
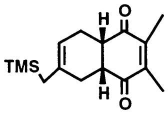
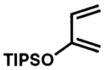
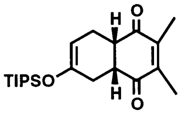
Diene	Product	Sol.	Temp. (°C), Time (h)	% Yield; ee
		CH_2Cl_2	-95, 2	99; >99
		CH_2Cl_2	-95, 2	99; >99
		CH_2Cl_2	-78, 16	99; >99
		CH_2Cl_2	-78, 48	97; 91

Table 6. Reaction of 2,3-Dimethyl-1,4-benzoquinone, **3a** (20 mol %), and Acyclic Dienes[10]

Diene	Product	Sol.	Temp. (°C), Time (h)	% Yield; ee
		$PhCH_3$ $PhCH_3$ CH_2Cl_2	-20, .5 -78, .5 -95, 2	95; 70 94; 88 99; 90
		$PhCH_3$	-78, .5	96; >99
		$PhCH_3$ CH_2Cl_2	-92, 2 -95, 2	80; >99 98; >99

3b, as documented by the results summarized in Table 3. In the experiments with **3a** or **3b** and the reactive component cyclopentadiene, the reaction proceeded rapidly at −60 °C with both fumarate and acrylate esters, and so this lower temperature could conveniently be used (first entry, Tables 2 and 3).

As recently reported,[2] the triflate catalysts **2a** and **2b** effect highly enantioselective Diels–Alder reaction between cyclopentadiene and a collection of cyclic α,*β*-enones or α,*β*-unsaturated lactones. However, these same dienophiles (which have only marginal reactivity) resist catalytic reaction with less reactive dienes, e.g., 2,3-dimethylbutadiene. In contrast, the use of catalysts **3a** and **3b** and various α,*β*-enones gave much better results with 2,3-dimethylbutadiene as test diene, as summarized in Table 4.

Until recently, the important quinone–diene subset of Diels–Alder additions was not amenable to enantioselective catalysis. The initial advances came with the use of Mikami's BINOL–$Cl_2Ti(O\textit{i}\text{-}Pr)_2$ mixture, a catalyst of unknown structure, which gave adducts with a very limited set of reactants, specifically with benzoquinone or naphthoquinone and two 1-substituted butadienes (ca. 85% ee).[8,9] We now report that the use of catalysts **3a** and **3b** results in outstanding enantioselectivities and yields with a range of 1,4-benzoquinones and dienes. Table 5 displays the results of experiments with 2,5-dimethyl-1,4-benzoquinone and dienes of varying reactivity, which are uniformly excellent. Complementary data are shown in Table 6 for the reaction of 2,3-dimethyl-1,4-benzoquinone with three acyclic dienes, for which the results were very satisfactory.

It is noteworthy that every one of the 24 examples of catalytic enantioselective Diels–Alder reactions which are displayed in Tables 1–6 affords with high predominance the enantiomer which is predicted for catalysts **3a** and **3b** from the mechanistic model.[1–5,10]

The results of the quinone Diels–Alder reactions summarized in Tables 5 and 6 prompted the further study of such reactions between unsymmetrical dienes and dienophiles, which involve position (or "regio-") selectivity as well as enantioselectivity. The use of 2,5-dimethyl-1,4-benzoquinone as the dienophile was of special interest since the expected coordination of catalyst to this quinone to the carbonyl lone pair anti to methyl would activate both C═C subunits of the quinone, leading to both possible adducts, as shown in Figure 1. In fact, as shown for two test cases in Table 7, both possible position isomers (6- and 7-) are formed, even though the dienes have differing terminal π-nucleophilicities. These results raised the question of whether there is any possibility of controlling position selectivity as well as enantioselectivity in catalytic quinone Diels–Alder reactions with two unsymmetrical components. We were pleased to discover a simple, rational, and highly promising solution to this general problem which utilized 3-iodo-2,5-dimethyl-1,4-benzoquinone as a synthetic equivalent of 2,5-dimethyl-1,4-benzoquinone.

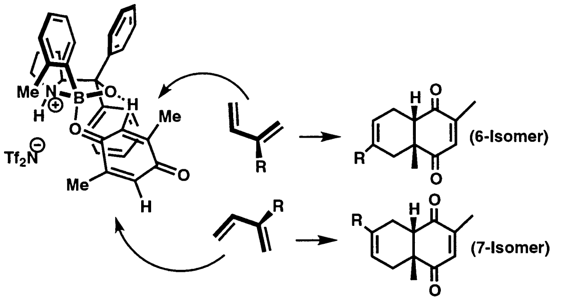


Figure 1. Two modes of reaction of a 2-substituted 1,3-butadiene with 2,5-dimethylbenzoquinone and catalyst **3a**.

Table 7. Enantioselective Diels−Alder Reactions of 2,5-Dimethyl-1,4-benzoquinone, **3a** (20 mol %), and Two Unsymmetrical Dienes

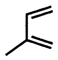
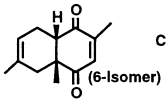
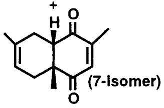
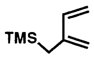
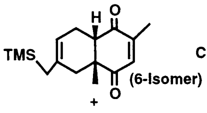
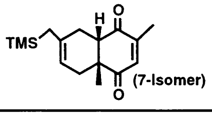
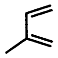
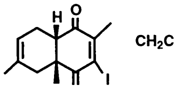
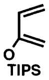
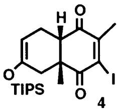
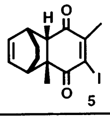
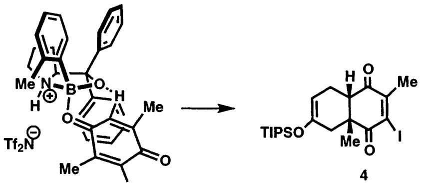
Diene	Product	Sol.	Temp. (°C), Time (h)	% Yield; ee (6-Isomer : 7-Isomer)
	 (6-Isomer)	CH_2Cl_2	-95, 2	99; >99 (6-Isomer) (62 : 38)
	+  (7-Isomer)			93 ee (7-Isomer)
TMS 	 (6-Isomer)	CH_2Cl_2	-95, 2	98; 92 (6-Isomer) (48 : 52)
	+  (7-Isomer)			>99 ee (7-Isomer)

Table 8. Enantioselective Reactions of 3-Iodo-2,5-dimethyl-1,4-benzoquinone, **3a** (20 mol %), and Two Unsymmetrical Dienes[10]

Diene	Product	Sol.	Temp. (°C), Time (h)	% Yield; ee (6-Isomer : 7-Isomer)
	 (6-isomer)	CH_2Cl_2	-78, 16	99; >99 (6-Isomer) (93 : 7); >99 (7-Isomer)
	 4	CH_2Cl_2	-78, 16	99; >99
	 5	CH_2Cl_2	-78, 16	99; >99

As shown in Table 8, the reactions of 3-iodo-2,5-dimethyl-1,4-benzoquinone with isoprene and 2-triisopropylsilyloxy-1,3-butadiene are highly enantio- and position-selective. The reason for this is that the iodine substituent in the quinone deactivates the C=C subunit to which it is attached (C=C protection) and also blocks catalyst coordination to the carbonyl lone pair which is syn to it. In consequence, there is only one carbonyl lone pair in 3-iodo-2,5-dimethyl-1,4-benzoquinone that is sterically accessible for coordination with catalyst **3a**. The structure and absolute configuration of the adducts **4** (from 2-triisopropylsilyloxy-1,3-butadiene and 3-iodo-2,5-dimethyl-1,4-benzoquinone) and also **5** were determined unequivocally by X-ray crystallographic analysis[10] and agree with the predictions of the mechanistic model,[1−5] as summarized in Figure 2 for **4**.



4

Figure 2. Pre-transition-state assembly for the reaction of **3a**, 3-iodo-2,5-dimethyl-1,4-benzoquionone, and 2-triisopropylsilyloxy-1,3-butadiene.

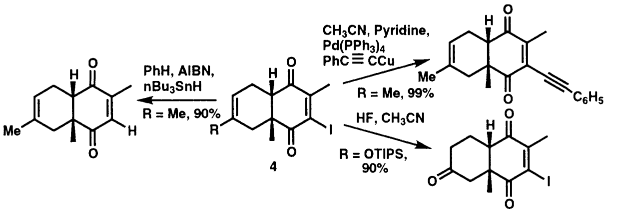


Figure 3. Representative transformation of iodo-substituted quinone−Diels−Alder adducts.

The adduct **4** can serve as a versatile synthetic intermediate thanks to the presence of the iodine function. Figure 3 shows just three of the many useful transformations which are possible from this interesting chiral Diels−Alder adduct. The use of iodo- or bromo-substituted unsymmetrical quinones in the Diels−Alder reaction opens a range of significant new possibilities for this important process.

The studies reported herein with **3a** and **3b** show that these thermally stable and powerful chiral Lewis acids are highly promising for many enantioselective Diels−Alder reactions that were previously beyond the reach of synthetic chemists. They provide further support for the previously proposed[1−5] predictive mechanistic model.

Acknowledgment. We are grateful to Pfizer, Inc. for a generous grant.

Supporting Information Available: Detailed data regarding absolute configuration, analysis, and characterization of the products described herein (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808−3809.

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

(3) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.

(4) For α,β-enals, this model[1] involves formyl C−H- -O hydrogen-bonding and π−π attractive interaction between the coordinated α,β-enal and the proximate C-aryl substituent in **3**. See: Corey E. J.; Lee, T. W. *J. Chem. Soc., Chem. Commun.* **2001**, 1321−1329.

(5) For α,β-unsaturated esters, lactones, and ketones with an α-C−H unit, the model[2] involves α-C−H- -O hydrogen-bonding and π−π attractive interaction between the coordinated dienophile and the proximate C-aryl substituent in **3**.

(6) See: Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; Des Marteau, D. D.; Yagupolski, L. M.; Yagupolski, Y. L.; Ignat'ev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3047−3057.

(7) Since the catalysts **3a** and **3b** and the corresponding tetracoordinated boron species are in kinetically rapid equilibrium, all can serve as Diels−Alder catalysts by complexing with a dienophile.

(8) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643−646. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820. (c) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373−2376.

(9) The Mikami catalyst has been found to afford much better results with achiral 1,4-quinone monoketals as substrates. See: Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559−1562.

(10) Detailed data regarding absolute configuration, analysis, and characterization of these products are presented in the Supporting Information.

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