JOC*Note*

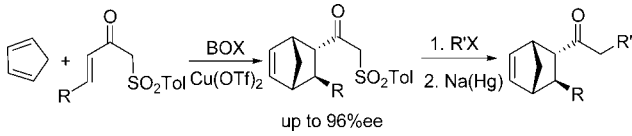
Copper(II)−Bis(oxazoline) Catalyzed Asymmetric Diels−Alder Reaction with α′-Arylsulfonyl Enones as Dienophiles

Santiago Barroso,[†] Gonzalo Blay,*[,†] Lina Al-Midfa,[†] M. Carmen Muñoz,[‡] and José R. Pedro*[,†]

Departament de Química Orgànica, Facultat de Química, Universitat de València, C/Dr. Moliner, 50, E-46100 Burjassot (València), Spain, and Departament de Física Aplicada, Universitat Politècnica de València, E-46071 València, Spain

jose.r.pedro@uv.es; gonzalo.blay@uv.es

Received April 29, 2008



α′-Arylsulfonyl enones are efficient bidentate dienophiles for the Cu(II)-bis(oxazoline) catalyzed enantioselective Diels−Alder reaction with a number of dienes, affording the corresponding products with good to high enantiomeric excesses. The resulting products can be alkylated and the sulfone removed, so α′-arylsulfonyl enones can be regarded as surrogates of simple monodentate enones, which are poor dienophiles with this catalytic system.

The Diels−Alder (D−A) reaction is a powerful organic transformation that constitutes a versatile method for the synthesis of cyclohexene-containing building blocks of great interest for the total synthesis of bioactive natural products.[1] The opportunity to generate up to four stereogenic centers in a stereocontrolled way has stimulated great interest in the development of enantioselective procedures for this transformation.[2−4] The use of chiral Lewis acids has been, by far, the most used tactic for this purpose. The success of this approach depends largely on the fitting of the structure of the Lewis acid to the structure of the dienophile. The dienophiles used in the Diels−Alder reaction are normally categorized in two groups: those that bind to the Lewis acid at one point (monodentate dienophiles) and those that bind at two points (bidentate dienophiles). Earlier studies with monodentate dienophiles have focused mainly on the reaction of unsaturated aldehydes,[3] especially with an α-substituent, and to a lesser extent on the reaction of alkyl acrylates[5] and quinones.[6] The asymmetric Diels−Alder reaction with ketone dienophiles has been only recently reported, despite the prevalence of enantiopure ketones in natural products.[7] However, in most of the examples that use acyclic enones as dienophiles the results are largely dependent on the substituent attached to the carbonyl group, which is poorly amenable to variation. Besides these monodentate dienophiles, a number of effective bidentate dienophiles have been reported. Thus, 3-alkenoyl-1,3-oxazolidin-2-ones (a) have proven to be very efficient substrates with a large number of metal-based catalysts and have become the standard test for new catalyst development.[8] Examples of other chelating dienophiles (Figure 1) include *N*-hydroxyacrylamides (b),[9] α′-hydroxyenones (c),[10] unsaturated α-ketoesters (d),[11] 2-alkylidene-

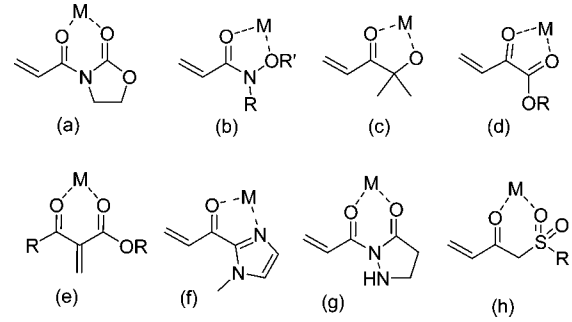


FIGURE 1. Examples of chelating dienophiles.

[†] Universitat de València.
[‡] Universitat Politècnica de València.

(1) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667.
(2) For examples on the use of chiral auxiliaries, see:(a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261–4263. (c) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397–1401.
(3) For general reviews and accounts on catalytic asymmetric Diels−Alder reactions, see: (a) Harada, T.; Kusukawa, T. *Synlett* **2007**, 1823–1835. (b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A. Eds.; Wiley-VCH: New York, 2002. (c) *Lewis Acids in Organic Synthesis*; Yamamoto, H. Ed.; Wiley-VCH: New York, 2000; Vols. 1 and 2. (d) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: Berlin, 1999; Vol. 3.
(4) For some examples of asymmetric organocatalytic Diels−Alder reaction, see: (a) Kano, T.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2006**, *8*, 2687–2689. (b) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229–2232. (c) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627. (d) Wilson, R. M.; Jen, W. S.; Mac Millan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616–11617. (e) Kim, K. H.; Lee, K. S.; Lee, D.-W.; Ko, D.-H.; Ha, D.-C. *Tetrahedron Lett.* **2005**, *46*, 5991–5994. (f) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141–4144. (g) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (h) Northrup, A. B.; Mac Millan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460.
(5) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992–9993.
(6) (a) Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6043–6046. (b) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800–4802. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390. (d) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559–1562.
(7) (a) Singh, R. S.; Adachi, S.; Tanaka, F.; Yamauchi, T.; Inui, C.; Harada, T. *J. Org. Chem.* **2008**, *73*, 212–218. (b) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498–1499. (c) Rickerby, J.; Vallet, M.; Bernardinelli, G.; Viton, F.; Kündig, E. P. *Chem. Eur. J.* **2007**, *13*, 3354–3368. (d) Futatsugi, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1484–1487. (e) Singh, R. S.; Harada, T. *Eur. J. Org. Chem.* **2005**, 3433–3435. (f) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979–3982. (g) Hawkins, J. M.; Nambu, M.; Loren, S. *Org. Lett.* **2003**, *5*, 4293–4295.
(8) (a) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594. (b) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7553. (c) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460–6461.
(9) (a) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735–1738. (b) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1731–1734.

10.1021/jo8009227 CCC: $40.75 © 2008 American Chemical Society
Published on Web 07/23/2008

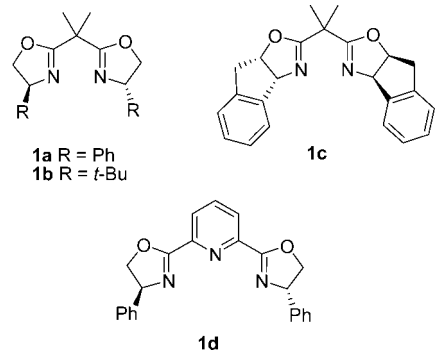


FIGURE 2. Structure of bis(oxazoline) ligands used in this study.

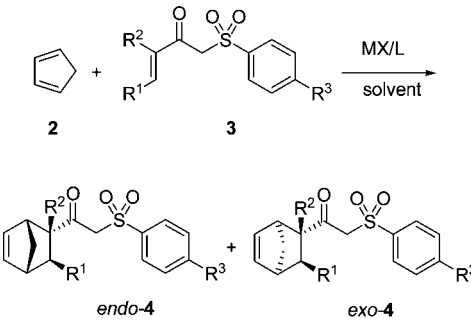
1,3-dicarbonyl compounds (e),[12] acrylimides (f),[13] or 2-acylimidazoles (g),[14] which upon combination with the Lewis acid form tight templates that give rise to highly ordered transition structures responsible for the enantioselectivity. In some of these cases, the resulting D−A product can be transformed into a ketone upon removal of the bidentate template, normally with the use of a nucleophilic organometallic reagent. Wada and co-worker have introduced the use of α′-phenylsulfonyl enones (h) as heterodienes in hetero-D−A reactions catalyzed by TADDOL−Ti(IV) complexes.[15] The β-sulfonyl ketone acts as a bidentate ligand for the chiral titanium reagent. These authors have also described the enantioselective D−A reaction of these substrates with cyclopentadiene to afford the cycloadduct in high optical purity, although no other diene was explored.[16] Because β-sulfonyl ketones can be alkylated[17] and the sulfonyl group reductively removed,[18] this kind of dienophiles can be regarded as alkyl enone equivalents.

In connection with our recent research on enantioselective catalytic D−A reactions[19] we became interested in exploring effective new catalysts and expanding the substrate scope for the D−A reaction with α′-arylsulfonyl enones.

Because metal complexes with bis(oxazoline) (BOX)[20] ligands have found successful application in a large number of enantioselective reactions with bidentate substrates, we decided to explore this kind of ligand in our research (Figure 2). Also, while our work was near to completion, Kim et al. reported a catalytic enantioselective Mukaiyama−Michael reaction of 2-(trimethylsilyloxy)furan with α′-phenylsulfonyl enones catalyzed by Cu−BOX complexes.[21]

The reaction between compound **3a** (R^1 = Ph, R^2 = H, R^3 = Me) and cyclopentadiene (**2**) was used for the optimization of the reaction conditions (Scheme 1, Table 1).

SCHEME 1. Diels−Alder Reaction between Cyclopentadiene (2) and Compounds 3



A screening of different BOX ligands and metal salts in dichloromethane (DM) as solvent showed that the combination of $Cu(OTf)_2$ and (*S*)-PhBOX (**1a**) gave the best results, affording the expected D−A product **4a** with a 91:9 *endo*:*exo* ratio, 95% ee (for the major *endo* product) and full conversion after 5 h at 0 °C (Table 1, entry 1). However, the (*S*)-*t*-BuBOX (**1b**), (*R*)-InBOX (**1c**) and (*S*)-PhPyBOX (**1d**) ligands slowed down the reaction and provided the corresponding product with lower diastereo- and enantioselectivity (entries 2−4). From the other metal salts tested, only zinc triflate afforded results similar to those of copper triflate, although the reaction was considerably slower and the product was obtained with slightly lower ee (entry 7). Several solvents were also screened with the complex **1a**−$Cu(OTf)_2$. In all the cases the reaction took place with lower stereoselectivity than in dichloromethane. Interestingly, toluene gave a slightly better diastereoselectivity while it provided the product with slightly lower ee (entry 9). By combining both solvents it was possible to maximize both the diastereo- and enantioselectivity of the reaction (entries 12−14).

Next, we studied the substrate scope of the reaction with different α′-arylsulfonyl enones under the optimized conditions. Both the substituent on the double bond and on the arylsulfonyl group were amenable to variation; the results are shown in Table 2.

In general, variations on the arylsulfonyl group had little effect on the reaction outcome (entries 1−3), although the *p*-chlorophenylsulfonyl enone **3c** gave the product with the best ee. The reaction was also successful with tosylsulfonyl enones bearing different substitution on the β-carbon of the double bond. Thus high enantiomeric excesses (above 95%) and good diastereoselectivities were obtained with β-aryl-substituted compounds, regardless of the electronic features of the aryl *p*-substituent (entries 4−6). The dienophile also tolerates a methyl group attached to the double bond (entry 8) and even a bulky *tert*-butyl group (entry 10), although in this case the reaction had to be carried out at room temperature. Compound **3g**, which has a monosubstituted double bond, reacted rapidly to give the D−A product **4g** with good diastereo- and enantioselectivity (96%) but with low yield. The high reactivity of these enones probably gave rise to side reactions that lowered the yield (entry 7). A second conjugated double bond as in dienone **3j** was also tolerated (entry 11). Compound **3k**, which bears a methyl group attached to the α-carbon of the double bond, reacted with cyclopentadiene to give the corresponding D−A product with high enantioselectivity, although as a 1:1 diastereomeric mixture (entry 12). The reaction could even be performed with a trisubstituted alkene **3l** with good results (entry 13). Also, the amount of catalyst could be reduced as low as

(10) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942–13493.
(11) Zhou, J.; Tang, Y. *Org. Biomol. Chem.* **2004**, *2*, 429–433.
(12) Yamauchi, M.; Aoki, T.; Li, M.-Z.; Honda, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 3113–3118.
(13) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349–2352.
(14) (a) Evans, D. A.; Fandrick, K. R.; Song, H. J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041. (b) Boersma, A. J.; Feringa, B. L.; Roelfes, G. *Org. Lett.* **2007**, *9*, 3647–3650. (c) Ishihara, K.; Fushimi, M. *Org. Lett.* **2006**, *8*, 1921–1924.
(15) (a) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637–1640. (b) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205–1220.
(16) Wada, E.; Pei, W.; Kanemasa, S. *Chem. Lett.* **1994**, 2345–2348.
(17) Nenajdenko, V. G.; Krasovskiy, A. L.; Balenkova, E. S. *Tetrahedron* **2007**, *63*, 12481–12539.
(18) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547–10658.
(19) (a) Barroso, S.; Blay, G.; Pedro, J. R. *Org. Lett.* **2007**, *9*, 1983–1986. (b) Barroso, S.; Blay, G.; Cardona, L.; Pedro, J. R. *Synlett* **2007**, 2659–2661.
(20) For a review on BOX catalyzed reactions, see: (a) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651.
(21) Yang, H.; Kim, S. *Synlett* **2008**, 555–560.

TABLE 1. Screening of Ligands, Metal Salts and Solvents for the Diels−Alder reaction of 3a (R^1 = Ph, R^2 = H, R^3 = Me) and cyclopentadiene (2) according to Scheme 1[a]

entry	MX	L	solvent	*t* (h)	conv (%)[b]	*endo*:*exo*[b]	ee *endo* (%)[c]
1	$Cu(OTf)_2$	**1a**	DM	5	100	91:9	95
2	$Cu(OTf)_2$	**1b**	DM	70	29	76:24	−7[d]
3	$Cu(OTf)_2$	**1c**	DM	70	94	89:11	42
4	$Cu(OTf)_2$	**1d**	DM	24	9	82:18	−34[d]
5	$Cu(SbF_6)_2$	**1a**	DM	22	100	86:14	56
6[e]	$Mg(OTf)_2$	**1a**	DM	24	64	80:20	73
7	$Zn(OTf)_2$	**1a**	DM	20	100	87:13	93
8[e]	$Cu(OTf)_2$	**1a**	THF	24	20	79:21	69
9	$Cu(OTf)_2$	**1a**	Tol	20	84	95:5	91
10	$Cu(OTf)_2$	**1a**	MeCN	20	10	76:24	−8[d]
11	$Cu(OTf)_2$	**1a**	$MeNO_2$	5	100	80:20	61
12	$Cu(OTf)_2$	**1a**	DM/Tol (1:1)	4	100	93:7	95
13	$Cu(OTf)_2$	**1a**	DM/Tol (1:2)	3	100	94:6	94
14[f]	$Cu(OTf)_2$	**1a**	DM/Tol (1:1)	24	100	95:5	96

[a] **3a** (0.25 mmol), **2** (1.8 mmol), MX (0.025 mmol), L (0.025 mmol), solvent (1.6 mL), 0 °C, unless otherwise stated. [b] Determined by ^{1}H NMR. [c] Determined by HPLC. [d] The opposite enantiomer was obtained. [e] Room temperature. [f] −20 °C.

TABLE 2. Diels−Alder Reaction of Compounds 3 and Cyclopentadiene (2) According to Scheme 1[a]

entry	3	R^1	R^2	R^3	*t* (h)	4, yield (%)[b]	*endo*:*exo*[c]	ee (%)[d]
1	**a**	Ph	H	Me	4	**4a**,97	93:7	95/nd
2	**b**	Ph	H	OMe	2	**4b**,92	93:7	95/nd
3	**c**	Ph	H	Cl	0.7	**4c**,96	93:7	97/98
4	**d**	4-$MeOC_6H_4$	H	Me	5	**4d**,95	96:4	95/nd
5	**e**	4-BrC_6H_4	H	Me	1	**4e**,93	92:8	95/94
6	**f**	4-$NO_2C_6H_4$	H	Me	1	**4f**,90	90:10	95/95
7	**g**	H	H	Me	0.1	**4g**,50	92:8	96/nd
8	**h**	Me	H	Me	0.3	**4h**,93	92:8	91/nd
9[e]	**h**	Me	H	Me	5	**4h**,85	92:8	92/nd
10[f]	**i**	*t*-Bu	H	Me	5	**4i**,99	43:57	90/83
11	**j**	PhCH=CH-	H	Me	24	**4j**,86	94:6	92/nd
12	**k**	H	Me	Me	0.3	**4k**,65	49:51	94/90
13[f]	**l**	Me	Me	Me	9	**4l**,93	50:50	96/88

[a] **3** (0.25 mmol), **2** (1.8 mmol), $Cu(OTf)_2$ (0.025 mmol), **1a**(0.025 mmol), 1:1 DM/Tol (1.6 mL), 0 °C unless if otherwise stated. [b] Isolated product after flash chromatography. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. [e] **3h** (1.0 mmol), **2** (6.0 mmol), $Cu(OTf)_2$ (0.025 mmol), **1a** (0.025 mmol), 1:1 DM/Tol (6.0 mL), 0 °C. [f] Room temperature.

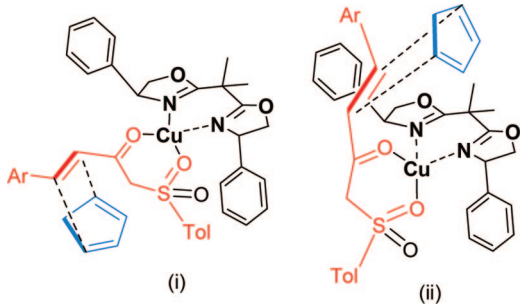


FIGURE 3. Stereochemical models for the Diels−Alder reaction.

2.5 mol % and the reaction scaled up at least four times without noticeable effect on the yield and stereoselectivity (Table 2, entry 9).

Finally, we tested the reaction with other dienes using compounds **3g** and **3h** as dienophiles (Table 3). 1,3-Cyclohexadiene and **3g** gave the expected product **4m** (entry 1) with high enantioselectivity (96% ee) as only one diastereomer (*endo*:*exo* >99:1). Compound **3g** reacted with isoprene to give compound **4n** with high regioselectivity and moderate ee (entry 2), similar to that obtained in the reaction with 2,3-dimethylbutadiene (entry 3). Significantly, the more reactive 2-trimethylsilyloxy-1,3-butadiene reacted with compound **3h** to give the corresponding cyclohexanone **4p** with high ee and good yield (67% after hydrolysis of the trimethylsilyl enol ether).

The absolute stereochemistry of *endo*-**4d** (Table 2, entry 4) was elucidated by X-ray crystallographic analysis (see Supporting Information), and for the rest of the products it was assigned on the assumption of a uniform reaction mechanism. To explain the stereochemical course of the reaction, we propose two possible models similar to those reported previously for other Cu(II)−BOX catalyzed reactions in which the dienophile would coordinate the Cu(II) atom in a bidentate fashion through the carbonyl and sulfone oxygen atoms (Figure 3). In the first model, this would lead to a distorted square planar complex (i) in which the α-*si* face of the double bond in the *s-trans* conformation of the enone would be available for the *endo* approach of the diene.[21] Alternatively, a species with tetrahedral geometry (ii) and the enone having the *s-cis* conformation would account for the same stereochemical outcome.[22] Although the square planar geometry is normally more favorable for the Cu(II) complexes, in this case the tetrahedral complex could be stabilized by a $\pi-\pi$ interaction between the enone double bond and the phenyl group of the bis(oxazoline).[23,24]

Scheme 2 shows some examples of transformation of the Diels−Alder product **4h**. The active methylene of the ketosulfones can be alkylated with a variety of alkylating agents and the sulfone group reductively removed to provide the corresponding ketones **6** and **8**, with good yields for the two steps and without loss of optical purity.

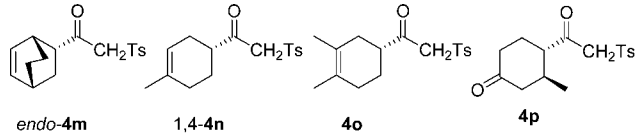
In summary, we have shown that α′-arylsulfonyl enones are efficient dienophiles for the asymmetric Cu(II)-BOX catalyzed Diels−Alder reaction with reactive dienes. The success of the reaction lies in the bidentate character of these compounds that allows for a two binding point coordination with the catalyst. Because the resulting products can be alkylated and the sulfone group removed, the α′-aryl sulfonyl enones can be used as bidentate surrogates of simple monodentate enones in enantioselective Cu-BOX catalyzed D−A reactions.

(22) (a) Pandey, M. K.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2006**, *47*, 897–900. (b) Rasappan, R.; Hager, M.; Gissibi, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099–6102. (c) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127–6130.

(23) The metal geometry in the Ph-BOX−Cu(II) complexes is controversial; see: (a) Thourhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen; K, A. *Chem. Eur. J.* **2002**, *8*, 1888–1898. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

(24) For mechanistics aspects of the D−A reaction, see: (a) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3262–3265.

TABLE 3. Diels–Alder Reaction of Some Dienes with Compounds 3g and 3j[a]

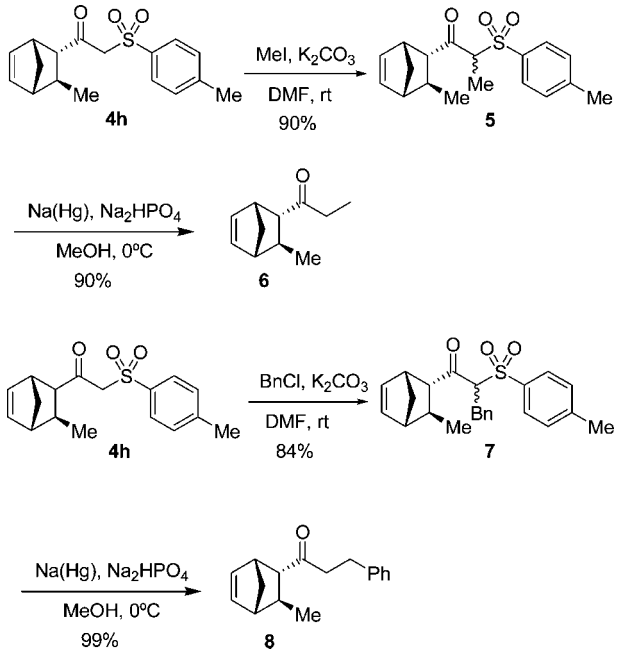


endo-**4m** 1,4-**4n** **4o** **4p**

entry	diene	**3**	*t* (h)	**4**, yield (%)[b]	isomeric ratio	ee (%)[c]
1	1,3-cyclohexadiene	**3g**	8	**4m**, 45	>99:1[d]	96/nd
2	2-methyl-1,3-butadiene (isoprene)	**3g**	21	**4n**, 35	96:4[e]	79/69
3	2,3-dimethyl-1,4-butadiene	**3g**	24	**4o**, 56		76
4	2-trimethylsilyloxy-1,4-butadiene	**3h**	0.5	**4p**, 67[f]		92[f]

[a] **3** (0.25 mmol), diene (1.8 mmol), $Cu(OTf)_2$ (0.025 mmol), **1a** (0.025 mmol), 1:1 DM/Tol (1.6 mL), 0 °C. [b] Isolated product after flash chromatography. [c] Determined by HPLC. [d] *endo*/*exo*. [e] 1,4-/1,3- regioisomers. [f] Yield and ee after hydrolysis

SCHEME 2. Modification of the Diels–Alder Products



Experimental Section[25]

Procedure for Catalytic Enantioselective D–A Reaction. $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) contained in a dry Schlenk tube was heated at 90 °C under vacuum for 1 h. After this time (*S*)-PhBOX **1a** (8.4 mg, 0.025 mmol), dichloromethane (0.8 mL), and toluene (0.8 mL) were added under nitrogen atmosphere, and the mixture was stirred for 1 h at room temperature. Then, the α′-arylsulfonyl enone **3a** (75.0 mg, 0.25 mmol) was added, and the mixture was stirred for 0.5 h. After this time, the solution was cooled to 0 °C and freshly distilled cyclopentadiene (**2**, 0.15 mL, 1.8 mmol) was added. After 4 h, the reaction mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel eluting with hexane–EtOAc (9:1) to give **4a** (89.0 mg, 97%). Assay of enantiomeric excess: chiral HPLC analysis (Chiralpak AD-H, 15% isopropanol–85% hexane, 1.0 mL/min); e*xo* (both enantiomers) t_R = 15.8 min, major *endo* (2*S*,3*S*)-(+) t_R = 17.6 min, minor *endo* (2*R*,3*R*)-(−) t_R = 22.5 min. e*ndo*-**4a** (ee 95%, de 94%): mp 120–123 °C; $[\alpha]^{25}_D$ +121.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (2H, d, *J* = 8.3 Hz), 7.31 (4H, m), 7.21 (3H, m), 6.36 (1H, dd, *J* = 3.2 Hz, *J* = 5.6 Hz), 5.92 (1H, dd, *J* = 2.7 Hz, *J* = 5.7 Hz), 4.31 (1H, d, *J* = 13.7 Hz), 4.07 (1H, d, *J* = 13.7 Hz), 3.44 (1H, dd, *J* = 3.4 Hz, *J* = 5.0 Hz), 3.39 (1H, s), 3.10 (1H, dd, *J* = 1.3 Hz, *J* = 4.9 Hz), 2.99 (1H, d, *J* = 1.5 Hz), 2.43 (3H, s), 1.85 (1H, d, *J* = 8.7 Hz), 1.60 (1H, ddd, *J* = 1.6 Hz, *J* = 3.3 Hz, *J* = 8.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 198.0 (s), 145.2 (s), 143.1 (s), 139.5 (d), 135.7 (s), 132.7 (d), 129.8 (d), 128.5 (d), 128.3 (d), 127.4 (d), 126.2 (d), 65.8 (t), 60.9 (d), 49.0 (d), 47.4 (t), 46.5 (d), 45.6 (d), 21.6 (q); MS(FAB) *m*/*z* (%): 367 (M^++1, 4), 301 (100), 155 (24); HRMS 367.1371, $C_{22}H_{23}O_3S$ required 367.1362. *exo*-**4a** (significant peaks, taken from an *endo*/*exo* mixture): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (1H, dd, *J* = 2.9 Hz, *J* = 5.6 Hz), 4.22 (1H, d, *J* = 13.6 Hz), 3.54 (1H, dd, *J* = 3.4 Hz, *J* = 5.7 Hz), 3.15 (1H, d, *J* = 1.3 Hz), 1.49 (1H, ddd, *J* = 1.6 Hz, *J* = 3.3 Hz, *J* = 8.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.4 (s), 141.9 (s), 136.4 (d), 136.3 (d), 128.2 (d), 127.86 (d), 126.6 (d), 66.6 (t), 59.6 (d), 49.3 (d), 47.6 (t), 47.3 (d), 46.3 (d).

Acknowledgment. Financial support from the Ministerio de Educación y Ciencia and FEDER (CTQ 2006-14199) is gratefully acknowledged. S.B. thanks the Universitat de València for a predoctoral grant (V segles program).

Supporting Information Available: General experimental methods, characterization data for all new compounds, copies of ^{1}H and ^{13}C NMR spectra and chromatograms for compounds **3**, **4**, **6**, and **8** and synthetic intermediates for compounds **3**, ORTEP plot and crystallographic information file (CIF) for compound **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8009227

(25) For a description of the general experimental methods, see Supporting Information.