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Enantioselective conjugate radical addition to α′-phenylsulfonyl enones

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ABSTRACT

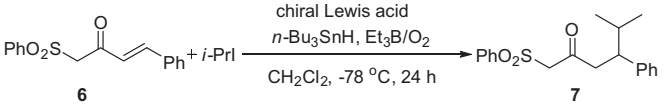
Enantioselective conjugate addition reactions of alkyl radicals to α′-phenylsulfonyl enones are described. A bis-oxazoline-zinc triflate complex proved to be an effective catalyst leading to high enantioselectivities and chemical yields.

Enantioselective conjugate radical addition reactions have been studied to take advantage of the unique features of radical chemistry, in which detachable achiral auxiliaries play an important role in determining the enantioselectivity.[1,2] We have been interested in developing bidentate achiral templates derived from enones and the previously reported enantioselective conjugate radical addition reactions of α′-hydroxy enones[3] and α′-phosphoric enones using chiral Lewis acids.[4,5] In particular, the α′-phosphoric enone template showed a high chemical reactivity and good enantioselectivity with the chiral Lewis acid derived from chiral bis-oxazoline (Box) derivative and zinc(II) triflate.[4] In the course of our studies on enantioselective radical reactions, we investigated the possibility of using an α′-phenylsulfonyl enone template in conjugate radical addition, as the phenylsulfonyl group can be removed under mild conditions[6] or utilized for further transformations.[7] The α′-phenylsulfonyl group has been utilized previously as a highly efficient 1,5-chelating template in the catalytic enantioselective Diels–Alder[8] and Mukaiyama–Michael reactions.[9]

The effect of various Lewis acids along with Box ligands was examined (Table 1). The chiral Lewis acid, derived from $Zn(OTf)_2$ and bis-phenyl Box ligand **5**, gave the highest enantiomeric excess (entry 10). Ligands **1** and **4** were totally ineffective (entries 6 and 9). $Cu(OTf)_2$ was also ineffective (entries 4 and 5) but magnesium salts with ligand **5** gave poor to moderate enantioselectivities (entries 2 and 3). As compared with the previous results obtained with α′-phosphoric enones,[4] a similar trend was observed in terms of the Lewis acid and the ligand. The effect of the solvent was briefly examined as shown in Table 2 and diethyl ether gave the best result (entry 4). The reaction was faster in toluene and gave a high chemical yield, but the enantioselectivity decreased to a small extent (entry 3). Furthermore, the reaction was slow in dichloromethane and THF and the enantioselectivity was moderate (entries 1 and 2). In addition, we briefly examined the catalytic efficiency of the chiral Lewis acid derived from zinc triflate and ligand **5**. The use of 20–30 mol % of the chiral Lewis acid gave the same enantioselectivity for the conjugate addition as compared to the reaction with a stoichiometric amount. Reducing the amount of catalyst to 10 mol % gave almost the same enantioselectivity (80% ee vs 79% ee). The yields were still good. Further lowering of the catalyst loading to 5 mol % resulted in a significant decrease in enantioselectivity (33% ee) as well as in the chemical yield (65%).

To improve the enantioselectivity in the conjugate addition, the effect of structural variation of the α′-phenylsulfonyl enone **8** was studied. As shown in Table 3, structural modification of the sulfonyl groups did not influence the enantioselectivity significantly. *t*-Butylsulfonyl and *p*-toluenesulfonyl groups gave almost the same enantiomeric excess (entries 3 and 4). Furthermore, when the phenylsulfonyl group was changed to bulkier 4-biphenylsulfonyl

Table 1
Effect of Lewis acids and ligands on the conjugate radical addition[a]



Entry	Lewis acid	Ligand	Yield[b] (%)	ee[c] (%)
1	None	None	51 (44)	—
2	$MgBr_2$	(4*R*,5*S*)-**5**	59 (27)	39
3	$Mg(ClO_4)_2$	(4*R*,5*S*)-**5**	66 (23)	52
4	$Cu(OTf)_2$	(*R*)-**2**	51 (33)	0
5	$Cu(OTf)_2$	(4*R*,5*S*)-**5**	57 (18)	4
6	$Zn(OTf)_2$	(*S*)-**1**	65 (27)	0
7	$Zn(OTf)_2$	(*R*)-**2**	68 (12)	13
8	$Zn(OTf)_2$	(*S*)-**3**	66 (13)	6
9	$Zn(OTf)_2$	(*S*)-**4**	63 (27)	0
10	$Zn(OTf)_2$	(4*R*,5*S*)-**5**	75 (10)	71

[a] Typical reaction conditions: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 10.0 equiv of alkyl iodide, 3.0 equiv of Bu_3SnH, and 2.0 equiv of Et_3B were employed.
[b] Isolated yield; yield of recovered **6** in parentheses.
[c] ees were determined using chiral HPLC.

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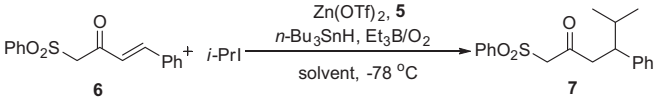
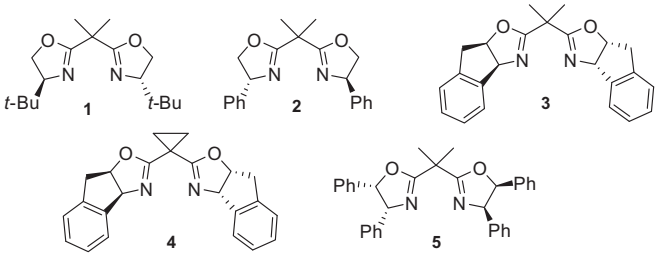
Table 2
Effect of solvent[a]



Entry	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	24	75 (10)	71
2	THF	24	61 (27)	66
3	Toluene	6	96	72
4	Et_2O	12	92	80

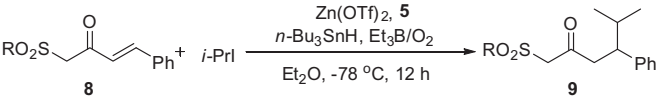
[a] Chiral Lewis acid **5** (30 mol %) used.
[b] Isolated yield; yield of recovered **6** in parentheses.
[c] ees were determined using chiral HPLC.

and mesitylsulfonyl groups, the enantioselectivities dropped to 58% ee and 42% ee, respectively (entries 7 and 8). Although the *t*-butylsulfonyl group was slightly better than the phenylsulfonyl group in terms of the enantioselectivity, α′-phenylsulfonyl enone **6** was utilized to determine the scope of the present method due to the synthetic utility of the phenylsulfonyl group relative to the *t*-butylsulfonyl group.[10]



To determine the scope and limitations of the present method, the reaction was carried out with several structurally different α′-phenylsulfonyl enones using the chiral Lewis acid (20 mol %) derived from $Zn(OTf)_2$ and ligand **5** in diethyl ether at −78 °C for 12 h. As shown in Table 4, conjugate addition reactions of **10** with several alkyl iodides proceeded cleanly, yielding the addition products **11** in high yields. The enantioselectivities of the products ranged from 73% to 95% ee, the highest being achieved when **10** (R = Me) was reacted with cyclohexyl iodide (entry 6). The size of the alkyl radical did not have a large impact on the level of enantioselectivity in the conjugate addition. Although the enantioselectivities were not always very high, this method accommodates primary, secondary, and tertiary alkyl radicals.

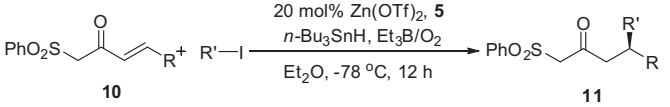
Table 3
Modification of the α′-phenylsulfonyl enone[a]



Entry	R	Yield[b] (%)	ee (%)
1	Ph	92	80
2	CH_3	71	61
3	*t*-Bu	87	85
4	*p*-Tolyl	88	84
5	4-Chlorophenyl	58 (33)	60
6	4-*t*-Butylphenyl	91	72
7	4-Biphenyl	87	58
8	Mesityl	76	42
9	Naphthyl	84	69

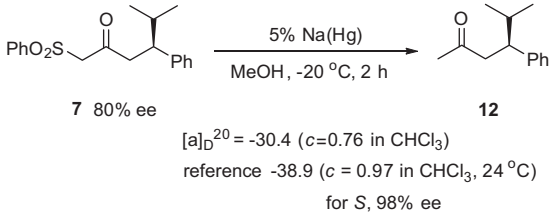
[a] Typical reaction conditions: 1.0 equiv of substrate, 0.2 equiv of chiral Lewis acid, 10.0 equiv of alkyl iodide, 3.0 equiv of Bu_3SnH, and 2.0 equiv of Et_3B were used.
[b] Isolated yield; recovered starting material in parentheses.

Table 4
Addition of alkyl radicals to α′-phenylsulfonyl enone[a]



Entry	R	R′	Yield[b] (%)	ee (%)
1	Ph	Et	72	90
2	Ph	*c*-Hexyl	89	74
3	Ph	*t*-Bu	94	78
4	Me	Et	83	77
5	Me	*i*-Pr	94	86
6	Me	*c*-Hexyl	91	95
7	Me	*t*-Bu	88	78
8	CH_2CH_2Ph	Et	92	91
9	CH_2CH_2Ph	*i*-Pr	91	77
10	CH_2CH_2Ph	*t*-Bu	85	73

[a] Typical reaction conditions: 1.0 equiv of substrate, 0.2 equiv of chiral Lewis acid, 10.0 equiv of alkyl iodide, 3.0 equiv of *n*-Bu_3SnH, and 2.0 equiv of Et_3B were used.
[b] Isolated yield.



Scheme 1. Absolute configuration.

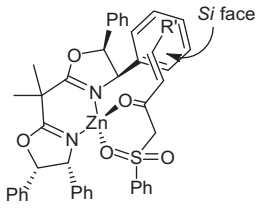


Figure 1. Tetrahedral model for the catalyst-substrate complex.

The absolute stereochemistry was determined by converting **7** into known compound **12**.[11] Treatment of **7** with sodium amalgam in MeOH at −20 °C for 2 h afforded **12** in 75% yield (Scheme 1).[12] On the basis of the previously reported optical rotation, the stereochemistry was assigned as *S*.[11] Figure 1 shows a tentative model which accommodates the observed facial selectivity, where Zn^{2+} occupies the center of the tetrahedral transition state.[13] Two coordination sites are occupied by two nitrogen atoms of the Box ligand, and the remaining two sites accommodate the oxygen atoms of the α′-phenylsulfonyl enone template. Due to the presence of a phenyl group at the 4-position in the ligand, the alkyl radical would approach from the *Si* face of the double bond. Furthermore, it is assumed that the *s-cis*-conformation of α′-phenylsulfonyl enones could result from π–π stabilization of the transition state.[14]

In summary, the α′-phenylsulfonyl enone template has been introduced to achieve an enantioselective conjugate radical addition process. Several alkyl radicals worked well, yielding the conjugate addition products in high yields and good enantioselectivities.

Acknowledgments

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10. *Typical procedure*: Box ligand **5** (11 mg, 0.02 mmol) and $Zn(OTf)_2$ (7 mg, 0.02 mmol) were dissolved in Et_2O (1.0 mL) under N_2. After being stirred at room temperature for 45 min, an Et_2O solution (2 mL) of α′-phenylsulfonyl enone **6** (28 mg, 0.10 mmol) was added via cannula. The mixture was stirred for 30 min, the reaction mixture was cooled down to −78 °C and then isopropyl iodide (100 μL, 1.0 mmol), tributyltin hydride (83 μL, 0.30 mmol), and triethylborane (200 μL, 0.20 mmol) were added sequentially. After the reaction was stirred at −78 °C under a balloon of air for 12 h, the solvent was evaporated and the residue was filtered through a short column of KF/silica gel (1/9 w/w) to remove organotin residue. The filtrate was concentrated and subjected to silica gel column chromatography to give **7** (30.5 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 1.74–1.80 (m, 1H), 2.74–2.80 (m, 1H), 2.97 (dd, J = 17.2, 4.4 Hz, 1H), 3.15 (dd, J = 17.2, 10.3 Hz, 1H), 3.77 (d, J = 13.3 Hz, 1H), 3.92 (d, J = 13.3 Hz, 1H), 7.06 (d, J = 6.9 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 7.19–7.22 (m, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.52 (t, J = 7.8 Hz, 2H), 7.51–7.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 21.0, 33.3, 48.1, 48.4, 67.4, 126.7, 128.4, 128.5, 128.6, 129.4, 134.3, 138.3, 142.9, 197.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{23}O_3S$: 331.1371; found: 331.1368. The enantiomeric excess was determined by HPLC analysis (Chiralcel IA, hexane/*i*-PrOH, 85/15, *S*-isomer (major): t_R = 8.4 min and *R*-isomer (minor): t_R = 9.2 min; $[\alpha]_D^{20}$ −30.4 (c 0.76 in $CHCl_3$).
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