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Unprecedented Effects of Achiral Oxazolidinones on Enantioselective Radical-Mediated Conjugate Additions Using a Chiral Zinc Triflate

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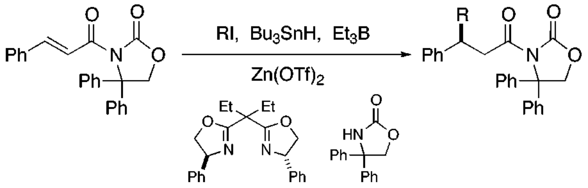
ABSTRACT

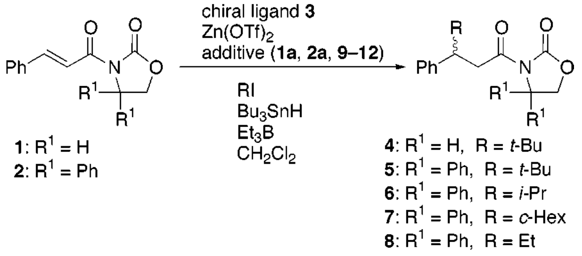


A role of achiral oxazolidinones to enhance the enantioselectivity in reactions of *N*-cinnamoyloxazolidinones with alkyl radicals promoted by a chiral Lewis acid is described. Efficient enantioselective radical-mediated conjugate additions of *N*-cinnamoyloxazolidinone can be realized by use of a chiral zinc triflate generated from a readily prepared chiral bisoxazoline and an achiral oxazolidinone. The NH moiety of achiral oxazolidinones is found to be necessary to enhance the enantioselectivity.

Asymmetric induction in enantioselective radical reactions by use of chiral Lewis acids has been the focus of current investigation in synthetic organic chemistry.[1] Recently, reports on enantioselective radical-mediated conjugate additions to *N*-enoyloxazolidinones catalyzed by chiral Lewis acids generated from chiral bisoxazolines have appeared.[2] Despite this impressive progress, there is no report on an external achiral ligand to increase the enantioselectivity in radical-mediated conjugate additions.[3] We describe here the effects of achiral oxazolidinones on the enantioselectivity in the reactions of *N*-cinnamoyloxazolidinones with alkyl radicals promoted by a chiral Lewis acid.

At first, we examined the reactions of a *tert*-butyl radical to *N*-cinnamoyloxazolidinones **1** and **2** (Scheme 1 and Figure 1). The results are shown in Table 1.[4] The reaction of **1** with *tert*-butyl iodide and tributyltin hydride promoted by a chiral

Scheme 1. Enantioselective Radical-Mediated Conjugate Additions of **1** and **2** in the Presence of Additives



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[1] For recent reviews including enantioselective radical reactions, see: (a) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562−2579. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163−171.

[2] (a) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029−11030. (b) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200−9201. (c) Wu, J. H.; Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067−2070. (d) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800−3801. (e) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417−2428. (f) Mero, C. L.; Porter, N. A. *J. Org. Chem.* **2000**, *65*, 775−781. Other enantioselective radical-mediated conjugate additions, see: (g) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576−3577. (h) Nishida, M.; Hayashi, H.; Nishida, A.; Kawahara, N. *Chem. Commun.* **1996**, 579−580. (i) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955−5958.

10.1021/ol006927l CCC: $20.00

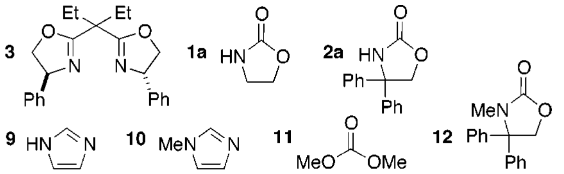

Figure 1. Ligands.

Lewis acid generated from $Zn(OTf)_2$ and **3** by use of triethylborane as a radical initiator at −78 °C gave **4** in 88% chemical yield,[5] but the enantiomeric excess (ee) was only 9% with *S* configuration predominating (entry 1). After several attempts, we discovered that achiral oxazolidinones **1a** and **2a**, which are the intermediates in the synthesis of **1** or **2**, played a significant role in inducing high enantioselectivity. The enantioselectivities were increased to 41 and 52% ee, respectively, by adding **1a** and **2a** at the beginning of the reaction (entries 2 and 3). When *N*-cinnamoyldiphenyloxazolidinone (**2**) was used as a substrate,[6] the effects of **2a** were outstanding. Surprisingly, the degree of asymmetric induction in the reaction with assistance by **2a** dramatically reached 88% ee with the opposite facial selectivity (*R* configuration) (entry 5), while the reaction without **2a** gave **5** with *S* configuration in only 3% ee (entry 4).[7]

Table 1. Enantioselective Radical-Mediated Conjugate Additions of *tert*-Butyl Radical to **1** or **2** in the Presence of $Zn(OTf)_2$ and **3**[a]

entry	substrate	additive	yield (%)[b]	ee (%)[4]	config[4]
1	**1**	none	88	9	*S*
2	**1**	**1a**	86	41	*S*
3	**1**	**2a**	78	52	*S*
4	**2**	none	80	3	*S*
5	**2**	**2a**	96	88	*R*

[a] Stoichiometric amounts of catalysts were used (catalyst:substrate = 1:1). $Zn(OTf)_2$:**3**:additive = 1:1:1. All reactions were carried out by use of 2 equiv each of *t*-BuI, Bu_3SnH, and Et_3B for a substrate in CH_2Cl_2 at −78 °C. [b] Isolated yield.

The effects of achiral oxazolidinones mentioned above are of interest, because the zinc without external ligands has a satisfactory coordination sphere (a six-coordination: bidentate ligands **2** and **3** and two OTf ligands). Thus, the influence of various additives on the reaction of **2** were examined. The reactions were performed using isopropyl iodide, because the ee of the product **6** could be determined directly by HPLC using a chiral column.[8] As shown in Table 2, the reaction using **2a** as an additive gave the best result (entry 2: 82% ee, *R*). Other additives, **9**−**12**, did not increase the degree of ee (13−29% ee, *S*). It is noted that *N*-methyldiphenyloxazolidinone (**12**) as a structural analogue of **2a** was not effective (29% ee, *S*). These results demonstrate that the NH moiety of oxazolidinone is responsible for high asymmetric induction.

Table 2. Enantioselective Radical-Mediated Conjugate Additions of Isopropyl Radical to **2** in the Presence of **3** and $Zn(OTf)_2$[a]

entry	additive	yield (%)[b]	ee (%)[8]	config[8]
1	none	72	32	*S*
2	**2a**	86	82	*R*
3	**9**	74	13	*S*
4	**10**	89	14	*S*
5	**11**	95	28	*S*
6	**12**	98	29	*S*

[a] Stoichiometric amounts of catalysts were used (catalyst: **2** = 1:1). $Zn(OTf)_2$:**3**:additive = 1:1:1. All reactions were carried out by use of 2 equiv each of *i*-PrI, Bu_3SnH, and Et_3B for **2** in CH_2Cl_2 at −78 °C. [b] Isolated yield.

The difference in function between **2a** and **12** in a solution of $Zn(OTf)_2$ led us to study the complexes spectroscopically [^{1}H NMR (500 MHz) spectra at −30 °C][9] (Figure 2).[10] When 2 equiv of **2** was added to a CD_2Cl_2 solution of a 1:1:1 mixture of **3**, $Zn(OTf)_2$, and **12**, the pattern of the CH_2 signal

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(3) For a recent review on nonchiral additives in the enantioselective reactions, see: (a) Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570−1577 and references therein. For selected recent reports on the use of achiral ligands in the enantioselective reactions catalyzed by chiral Lewis acids, see: (b) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535−4538. (c) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083−4084. (d) Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron Lett.* **1996**, *37*, 3027−3030. (e) Desimoni, G.; Faita, G.; Invernizzi, A. G.; Righetti, P. *Tetrahedron* **1997**, *53*, 7671−7688. We recently reported the enantioselective radical-mediated allylations catalyzed by chiral aluminum reagents and high enantioselectivities were also obtained by use of a chiral aluminum containing Et_2O, see: (f) Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713−11714. (g) Murakata, M.; Jono, T.; Hoshino, O. *Tetrahedron: Asymmetry* **1998**, *9*, 2087−2092.

(4) The ee of **4** was determined directly by HPLC using a chiral column (Chiralcel OD). The ee of **5** was determined by a chiral HPLC analysis of benzyl 4,4-dimethyl-3-phenylpentanoate, which was obtained by hydolysis of **5** followed by esterification [LiOH−H_2O_2, 93%; $(COCl)_2$, DMF, then Et_3N, $PhCH_2OH$, 96%] (Chiralcel OJ). The absolute configurations of **4** and **5** were determined by chemical correlation with (*S*)-4,4-dimethyl-3-phenylpentanoic acid, see: Imajo, S.; Kuritani, H.; Shingu, K.; Nakagawa, M. *J. Org. Chem.* **1979**, *44*, 3587−3589. See the Supporting Information for details.

(5) The chiral ligand **3** {$[\alpha]^{25}_D$ −180.4 (*c* 1.1, EtOH), mp 63−64 °C (Et_2O−petroleum ether)} was prepared by a similar method to that described in the literature, see: (a) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544. (b) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728−729.

(6) For substituted *N*-enoyloxazolidinones as substrates in enantioselective radical reactions, *N*-enoyldimethyloxazolidinones are known, see ref 2b.

(7) The reaction of **2** assisted by an achiral ligand was initially carried out by use of **2a**, because employment of **2a** in the reaction of **1** gave a slightly higher ee than that of **1a** (entry 2 vs 3 in Table 1) However, an unsubstituted achiral oxazolidinone **1a** was also effective: the reaction of **2** with isopropyl iodide using **1a** as an additive gave **6** in 84% ee (*R*) with 91% yield. Although clarification of the role of C-4 substituent on achiral oxazolidinone remains, the use of **2a** was expected to facilitate ^{1}H NMR analysis of the zinc complexes since the CH_2 signals of **2a** would be simpler than those of **1a** (Figure 2).

(8) A chiral column (Chiralcel OD) was used. The absolute configuration of **6** was determined by chemical correlation with (*S*)-4-methyl-3-phenylpentanoic acid, see: Lardicci, L.; Salvadori, P.; Caporusso, A. M.; Menicagli, R.; Belgodere, E. *Gazz. Chim. Ital.* **1972**, *102*, 64−84, and also ref 2b. See the Supporting Information for details.

(9) When the measurements were carried out at −78 °C, these signals became too broad to allow the spectra to be analyzed.

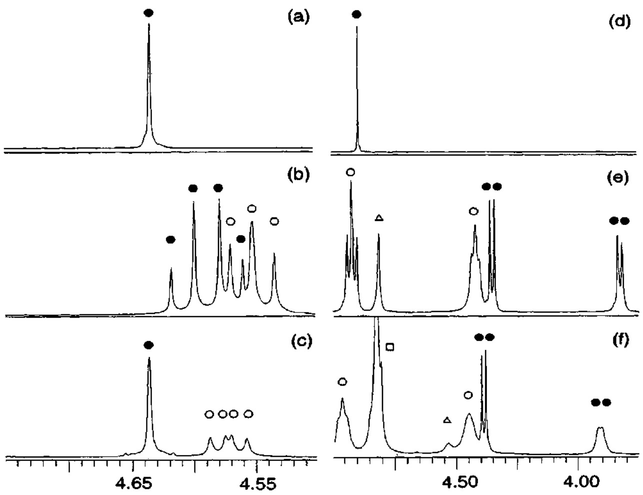

Figure 2. ^{1}H NMR (500 MHz) spectra: (a) **12**; (b) Zn(OTf)$_2$−**3** and **12**; (c) Zn(OTf)$_2$−**3** and **12** with 2 equiv of **2**; (d) **2a**; (e) Zn(OTf)$_2$−**3** and **2a**; (f) Zn(OTf)$_2$−**3** and **2a** with 2.5 equiv of **2**. ●: **12** or **2a**. ○: **3**. □: **2**. △: water (contamination).

of **12** became nearly identical to that of the free **12**.[11] This finding and the results from asymmetric reactions (entries 1 and 6 in Table 2) indicate that the coordination of **12** to a zinc center is weak enough to allow competition between **12** and **2**; therefore, the asymmetric reaction mainly proceeded by way of the complex dissociated with **12**, so that the sense and degree of asymmetric induction in the presence of **12** were similar to those in the absence of an additive. On the other hand, the CH$_2$ signals of **2a** became broad, but the chemical shifts were almost unchanged, even when 2.5 equiv of **2** was added to a solution of the chiral zinc complex containing **2a**, indicating that **2a** could coordinate tightly to the zinc center in the presence of **2**. Thus, it is reasonable to assume that addition of **2a** and **2** gives rise to a newly formed ternary chiral zinc complex.[12]

The tight coordination of **2a** to the chiral zinc triflate in the presence of **2** permitted an efficient substoichiometric reactions, and the ternary complex containing **2a** was found to afford radical adducts **5**−**8** in higher ee's generally than the complex without **2a**.[13] The results are shown in Table 3.[14] The ee values were similar to those attained with a stoichiometric amount. Although a slight loss of selectivity was observed in the reactions of a primary radical, acceptable ee's were obtained (entries 9 and 10).[15] It is also noted that the sense of asymmetric induction of all reactions with **2a** was identical. Apparently, employment of the ternary complex provides a reliable method, which allows the synthesis of radical adducts in good to high ee's with predictable absolute configuration.[16]

Table 3. Enantioselective Radical-Mediated Conjugate Additions of Radicals to **2** in the Presence of Zn(OTf)$_2$ and **3**[a]

entry	R−I	chiral LA (equiv)	additive	yield (%)[b]	ee (%)[4,8,14]	config[4,8,14]
1	*i*-Pr	0.5	none	85	24	*S*
2	*i*-Pr	0.5	**2a**	87	84	*R*
3	*i*-Pr	0.25	**2a**	92	80	*R*
4	*t*-Bu	0.25	**2a**	72	83	*R*
5	c-Hex	1.0	none	80	4	*R*
6	c-Hex	1.0	**2a**	83	81	*R*
7	c-Hex	0.25	**2a**	86	84	*R*
8	Et	1.0	none	73	5	*R*
9	Et	1.0	**2a**	92	71	*S*
10	Et	0.25	**2a**	91	72	*S*

[a] Stoichiometric (catalyst: **2** = 1:1) and substoichiometric (catalyst:**2** = 1:2 or 1:4) amounts of catalyst were used. Zn(OTf)$_2$:**3**:**2a** = 1:1:1. All reactions were carried out by use of 2 equiv each of alkyl iodide and Bu$_3$SnH for **2**, and Et$_3$B (2−4 equiv for catalyst) in CH$_2$Cl$_2$ at −78 °C. See ref 13. [b] Isolated yield.

In conclusion, efficient enantioselective conjugate additions by use of a chiral zinc complex containing an achiral oxazolidinone have been developed. Moreover, our finding that an achiral oxazolidinone having an NH moiety can coordinate to a chiral zinc triflate in the presence of a substrate so that enantioselectivity of the radical addition is enhanced dramatically is unprecedented. Although effects of achiral ligands on the enantioselectivity are known in other areas of asymmetric catalysis, the results mentioned here

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[10] Chemical shifts are referenced to methylene chloride. Zn(OTf)$_2$ was obtained from Aldrich Chemical Co. and used without further purification. CD$_2$Cl$_2$ was distilled under argon from CaH$_2$ prior to use. Solutions for the measurements were prepared under an argon atmosphere. [**2a**] = [**12**] = [Zn(OTf)$_2$] = [**3**] = 50 mM, which is identical to the concentration of a solution used in the present asymmetric reactions. Chemical shift of the CH$_2$ signal of **12**: (a) δ 4.63 as a singlet; (b) δ 4.57 and 4.61, two sets of a doublet, J = 9.2 Hz; (c) δ 4.64 as a singlet. Chemical shift of the CH$_2$ signal of **2a**: (d) δ 4.89 as a singlet; (e) δ 3.82 and 4.35, two sets of a doublet, J = 8.9 Hz; (f) δ 3.91 and 4.39, two sets of a doublet, J = 8.6 Hz. See the Supporting Information for details.

[11] By addition of **2**, the chemical shift of the NCH$_3$ signal of **12** in a solution containing Zn(OTf)$_2$ and **3** also came close to that of free **12**. Chemical shift of the NCH$_3$ signal of **12**: δ 2.58 (free **12**), δ 2.38 (a chiral zinc complex containing **12**), δ 2.51 (a chiral zinc complex containing **12** and **2**).

[12] Although the precise structures of the complexes are not interpreted at this time, at least one OTf counteranion might dissociate in the complex combined both with **2a** and **2**. For reports of OTf as a dissociate anion or an auxiliary ligand in the chiral Lewis acids, see: (a) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481−7484. (b) Yao, S.; Johannsen, M.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2345−2349. (c) Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron* **1998**, *54*, 15721−15730. (d) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943 and references therein. Also see refs 2a−c, 2e,f, and 2i.

[13] In some cases **2a** enhances chemical yields; however, it is not excluded that operations of the isolation and purification of the products cause a loss to chemical yields, especially workup (MeCN−hexane) to remove organotin compounds.

[14] The ee's of **7** and **8** were determined directly by HPLC using a chiral column (Chiralcel OD). The absolute configuration of **7** was determined by converting it to (*R*)-3-cyclohexyl-3-phenyl-1-propanal. For the antipode, see: Ahlbrecht, H.; Enders, D.; Santowski, L.; Zimmermann, G. *Chem. Ber.* **1989**, *122*, 1995−2004. The absolute configuration of **8** was determined by chemical correlation with (*R*)-3-phenylpentanoic acid, see: Lardicci, L.; Menicagli, R.; Salvadori, P. *Gazz. Chim. Ital.* **1968**, *98*, 738−759, and also ref 2i. For the antipode, see: Soai, K.; Machida, H.; Yokota, N. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1909−1914. See the Supporting Information for details.

[15] As the pioneering work, one example of the enantioselective radical-mediated conjugate addition of ethyl radical has been known to give 39% ee, see: ref 2i.

should provide new insights into the formation of a chiral zinc triflate. Studies to elucidate the precise mechanism of the asymmetric induction and further improve the enantioselectivity are in progress.

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Supporting Information Available: Experimental procedures, spectral data for the compounds, determination of the absolute configurations, and ^{1}H NMR spectral data for the chiral zinc complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **General procedure of the substoichiometric enantioselective conjugate additions:** A mixture of 98% Zn(OTf)$_2$ (0.2 mmol), **3** (0.2 mmol), and **2a** (0.2 mmol) in CH$_2$Cl$_2$ (2 mL) was stirred for 1 h at rt to become a clear solution. The resulting clear solution was cooled to −78 °C. A solution of **2** (0.4 or 0.8 mmol) in CH$_2$Cl$_2$ (2 mL) was added, and the mixture was stirred for 30 min at −78 °C. Alkyl iodide (0.8 or 1.6 mmol), Bu$_3$SnH (0.8 or 1.6 mmol), and a solution of triethylborane in hexane (1 N, 0.4 mmol) were added successively, and the mixture was allowed to stand for 12 h at the same temperature. The reactions were monitored by analytical thin-layer chromatographic (TLC) methods (silica gel). When TLC analysis showed the starting material, an additional portion of a solution of triethylborane (0.4 mmol) was added, and the mixture was stirred for an additional 12 h at −78 °C. After the reaction was complete (TLC, benzene), AcOH (0.4−0.8 mL) was added at −78 °C and the mixture was stirred for 1 h. H$_2$O was added, and the mixture was extracted with CH$_2$Cl$_2$ (20 mL × 2). The organic layer was washed with saturated aqueous NaHCO$_3$ and brine successively and dried over MgSO$_4$. After filtration, the solvent was removed under reduced pressure. The residue was taken up in MeCN. The mixture was washed with hexane. Concentration followed by purification through column chromatography (hexane−AcOEt) gave **5**−**8**.