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Enantioselective Conjugate Radical Addition to α′-Hydroxy Enones

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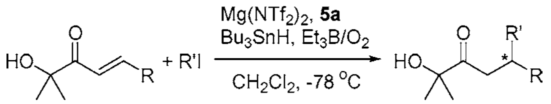
ABSTRACT



Enantioselective conjugate radical addition to α′-hydroxy α,β-unsaturated ketones, compounds containing bidentate donors, has been investigated. It has been found that radical additions to α′-hydroxy α,β-unsaturated ketones in the presence of $Mg(NTf_2)_2$ and bisoxazoline ligand 5a proceeded cleanly, yielding the addition products in high chemical yields and good enantiomeric excesses.

During the past decade, enantioselective radical reactions have been investigated with great interest.[1] Among the various reaction types, conjugate radical addition to α,β-unsaturated carbonyl compounds has attracted a great deal of attention because of its synthetic utility. A majority of these reactions utilize carboxylic acid dervatives. To carry out these reactions, one needs the use of an achiral template such as alkylidene malonates,[2] Evans' oxazolidinones,[3] and the imide group.[4] In all the reported cases, 1,5-coordination (six-membered chelate) of bidentate Lewis acids was used to obtain high enantioselectivities. Recently, the Palomo group has shown the effectiveness of 1,4-coordination (five-membered chelate) using α′-hydroxy enone as an excellent bidentate template for asymmetric construction of C−C bonds in Diels−Alder cycloaddition,[5] Freidel−Crafts alkylation,[6] and the 1,4-addition reaction of carbamate.[7] In the course of our studies on enantioselective radical reactions, we have investigated the use of α′-hydroxy enone as a 1,4-chelating template in the conjugate addition reaction.[8,9]

We initially screened some bisoxazoline ligands with $Mg(ClO_4)_2$ under reductive alkylation conditions with *tert*-butyl iodide and *n*-Bu_3SnH at −78 °C (Table 1). In most cases, the radical reaction of hydroxy enone **1** gave high chemical

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[1] (a) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (b) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251. (c) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2. (d) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions. Concepts, Guidelines and Synthetic Applications*; VCH: Weinheim, 1996. (e) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (f) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

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[3] (a) Sibi, M. P.; Zimmerman, J.; Rheault, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4521. (b) Sibi, M. P.; Manyem, S.; Subramaniam, R. *Tetrahedron* **2003**, *59*, 10575. (c) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. (d) Sibi, M. P.; Ji, J.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (e) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029. (f) Porter, N. A.; Feng, H.; Kavrakova, I. K. *Tetrahedron Lett.* **1999**, *40*, 6713. (g) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702. (h) Wu, J. H.; Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067.

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[5] Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942.

[6] Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154.

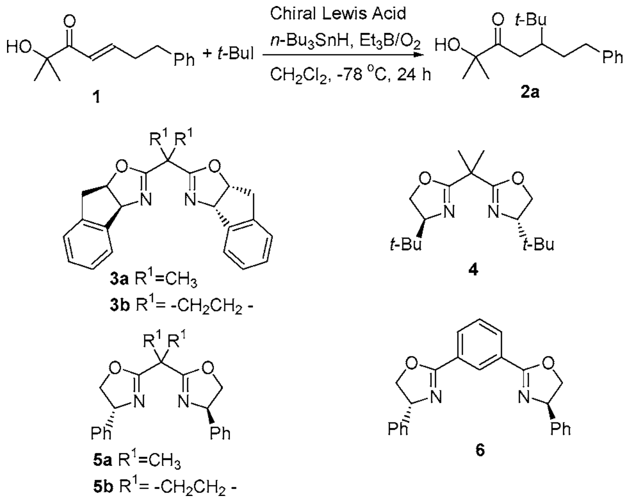
[7] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188.

[8] For the use of a 3,5-dimethylpyrazole template providing five-membered chelation, see: (a) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955. (b) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615.

[9] For selected enantioselective transformations in which a 1,4-coordination of the achiral templates is involved, see: (a) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249. (b) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979. (c) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (d) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419.

10.1021/ol061634z CCC: $33.50

Table 1. Effect of Lewis Acids and Ligands[a]



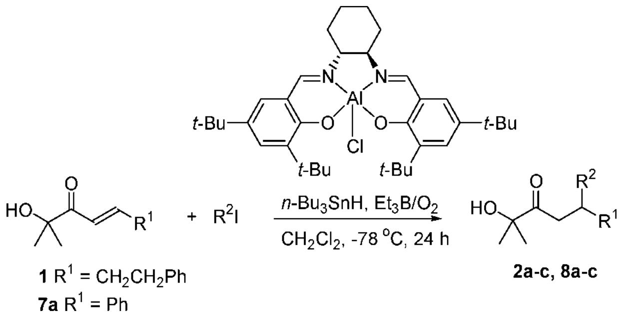
entry	Lewis acid	ligand	compd	yield (%)[b]	ee (%)[c]
1	$Mg(ClO_4)_2$	**3a**	**2a**	87	42
2	$Mg(ClO_4)_2$	**3b**	**2a**	91	5
3	$Mg(ClO_4)_2$	**4**	**2a**	88	45
4	$Mg(ClO_4)_2$	**5a**	**2a**	61	69
5	$Mg(ClO_4)_2$	**5b**	**2a**	66	69
6	$Mg(ClO_4)_2$	**5a**[d]	**2a**	59	61
7	$Cu(OTf)_2$	**5a**	**2a**	26(39)[e]	4
8	$Zn(OTf)_2$	**5a**	**2a**	62	58
9	$Mg(NTf_2)_2$	**5a**	**2a**	66	75
10	$Yb(OTf)_3$	**6**	**2a**	72	5

[a] Typical reaction conditions: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 5.0 equiv of alkyl iodide, 2.0 equiv of Bu_3SnH, and 3.0 equiv of Et_3B were used. [b] Isolated yield. [c] ee's were determined using chiral HPLC. [d] 4 Å molecular sieves were added. [e] Recovered starting material.

yields. In contrast to the previous report,[10] rigid indanol-derived ligand **3a** was not effective (entry 1), and enlarging the bite angle made things worse (ligand **3b**, entry 2). Among the several chiral Lewis acid complexes examined, the best result was obtained with Ph-Box **5a** (entry 4). Addition of 4 Å molecular sieves did not significantly influence either the chemical yield or the enantiomeric excess (entry 6). Further studies using different Lewis acids indicate that the best result was obtained with $Mg(NTf_2)_2$ and Ph-Box **5a** (entry 9).

In addition to C_2-symmetric Box ligands, a commercially available aluminum salen catalyst was briefly tested. As shown in Table 2, the conjugate addition of a *tert*-butyl radical to **1** gave very low enantiomeric excess (entry 1). The addition of isopropyl and *n*-propyl radicals resulted in significantly higher ee's (entries 2 and 3). A similar pattern in which enantioselectivity increased from 3° to 2° to 1° radicals was observed in additions to substrate **7a** (entries 4−6). The aluminum salen catalyst generally gave enantioexcesses that were comparable or variably lower than when the Ph-Box **5a**/$Mg(NTf_2)_2$ catalyst was used (compare results in Table 2 to results in Table 4).

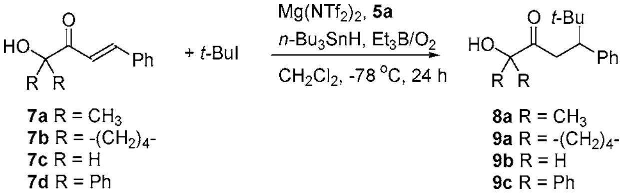
Table 2. Conjugate Addition with Al-Salen[a]



entry	R¹	R²	compd	yield (%)[b]	ee (%)[c]
1	$-CH_2CH_2Ph$	*t*-Bu	**2a**	71	4
2	$-CH_2CH_2Ph$	*i*-Pr	**2b**	82	68
3	$-CH_2CH_2Ph$	*n*-Pr	**2c**	70	72
4	Ph	*t*-Bu	**8a**	79	27
5	Ph	*i*-Pr	**8b**	90	56
6	Ph	n-Pr	**8c**	88	79

[a] Typical reaction conditions: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 5.0 equiv of alkyl iodide, 3.0 equiv of Bu_3SnH, and 5.0 equiv of Et_3B were used. [b] Isolated yield. [c] ee's were determined using chiral HPLC.

Table 3. Effect of Bite Angle on α′-Hydroxyenone[a]



entry	R	compd	yield (%)[b]	ee (%)[c]
1	CH_3	**8a**	90	78
2	$-(CH_2)_4-$	**9a**	75	71
3	H	**9b**	91	73
4	Ph	**9c**	72	2

[a] Typical reaction conditions: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 10.0 equiv of alkyl iodide, 5.0 equiv of Bu_3SnH, and 4.0 equiv of Et_3B were used. [b] Isolated yield. [c] ee's were determined using chiral HPLC.

To improve the enantioselectivity in the conjugate addition, we modified the structure of the α′-hydroxy enone **7** to cause slight differences in coordination angles. As shown in Table 3, the structural variations did not result in improved selectivity. Interestingly, the diphenyl-substituted enone **7d** gave a nearly racemic product.

To study the scope and limitation of the present method, additional experiments using $Mg(NTf_2)_2$ and Ph-Box **5a** were performed. As shown in Table 4, conjugate addition reactions to enone substrates **1**, **7**, and **10** with several alkyl iodides proceeded cleanly, yielding the addition products in high yields (entries 1−12). The ee's of the products ranged from 66 to 86%. Reaction using a stoichiometric amount of the chiral Lewis acid gave a higher chemical yield but nearly the same enantioselectivity (compare entry 6 with 9). The

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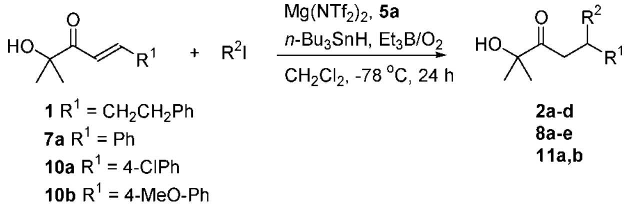
(10) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800.

Table 4. Enantioselective Conjugate Addition Reactions with Various Radical Precursors[a]



entry	R^1	R^2	compd	yield (%)[b]	ee (%)[c]
1	$-CH_2CH_2Ph$	*t*-Bu	**2a**	66	75
2	$-CH_2CH_2Ph$	*i*-Pr	**2b**	85	68
3	$-CH_2CH_2Ph$	*n*-Pr	**2c**	63(17)[d]	72
4	$-CH_2CH_2Ph$	Et	**2d**	87	72
5	Ph	*t*-Bu	**8a**	90	78
6	Ph	*i*-Pr	**8b**	78	78
7	Ph	*n*-Pr	**8c**[e]	68	86
8	Ph	Et	**8d**	82	80
9	Ph	*i*-Pr	**8b**[f]	96	70
10	Ph	*c*-Hexyl	**8e**	77	67
11	4-Cl−Ph	*t*-Bu	**11a**	76	81
12	4-MeO−Ph	*t*-Bu	**11b**	66	66

[a] Typical reaction conditions: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 10.0 equiv of alkyl iodide, 4.0 equiv of Bu_3SnH, and 3.0 equiv of Et_3B were used. [b] Isolated yield. [c] ee's were determined using chiral HPLC. [d] Recovered starting material. [e] Reaction time: 48 h. [f] 1.0 equiv of Lewis acid was used. Reaction time: 12 h.

electronic nature of the aryl substituent in the substrate had an interesting impact. *tert*-Butyl radical addition to the electron-poor 4-chloro-substituted enone gave higher selectivity (entry 11, 81% ee) in contrast to the electron-rich 4-methoxy-substituted enone (entry 12, 66% ee). The size of the radical precursor did not have a large impact on the level of selectivity in the conjugate addition (compare entries 1−4 and 5−10), in contrast to the results with the aluminum salen catalyst (see Table 2). Although the ee's in the conjugate addition are not very high, the method nicely accommodates primary, secondary, and tertiary alkyl radicals.

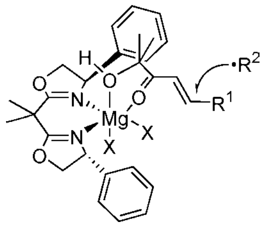


Figure 1. Cis octahedral transition state.

Compound **8b** was converted to a known compound which established its stereochemistry as *R*.[10] A tentative model which accommodates the observed face selectivity is shown in Figure 1. In this model, Mg occupies the center of an octahedral geometry. The Box ligand occupies two equatorial sites, with the carbonyl of the substrate occupying an equatorial site and the bulkier quaternary alcohol moiety occupying an axial position. In this organization, the phenyl group of the ligand provides the blocking leading to good enantioselectivity. Formation of the minor enantiomer could arise either from imperfect face shielding in this complex or from some reaction proceeding via one or more alternative magnesium complexes.

In summary, the α′-hydroxy enone template was introduced to achieve an enantioselective conjugate radical addition process. Several alkyl radicals worked well, yielding the conjugate addition products with high chemical yields and good enantioselectivities.

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Supporting Information Available: Characterization data for compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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