Lewis Acid-Mediated Intermolecular β-Selective Radical Additions to *N*-Enoyloxazolidinones

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Conjugate addition to α,β-unsaturated systems is a fundamental process in organic chemistry.[1] A multitude of chiral auxiliaries have been described which provide good to excellent diastereoselectivity in anionic conjugate additions to acyclic α,β-unsaturated systems.[2] In contrast, however, only a handful of reports describe the diastereoselective conjugate additions of radicals to acyclic systems.[3] Curran's fairly complex auxiliary (derived from Kemp's triacid) has provided excellent levels of diastereoselectivity,[4] and a few examples of diastereoselective intramolecular β-radical additions have also been reported.[5] However, a general solution to the problem of acyclic diastereoselection in β-radical additions has remained elusive.[6] We report here that record levels of diastereoselectivity can be obtained in β-radical addition using a simple, readily available, and easily removable oxazolidinone auxiliary in conjunction with Lewis acid additives.

Oxazolidinone auxiliaries have found surprisingly limited application in radical reactions.[7] This may be due to a lack of appropriate rotamer control with *N*-acyloxazolidinones.[8] High stereoselectivity requires a dominant reactive rotamer in which one face is effectively blocked, but in ground state conformer **3**, the R group is too far away for effective face shielding. We hypothesized that a chelating Lewis acid additive could enforce predominant reaction via rotamer **1**, so that with an appropriate R group in the auxiliary, facial shielding in the β-addition of radicals should be possible. The increasing application of Lewis acids in radical reactions[9] and the excellent diastereofacial control in Lewis acid-mediated Diels–Alder reactions of *N*-enoyloxazolidinones[8] (involving a type **1** rotamer) supported our approach.

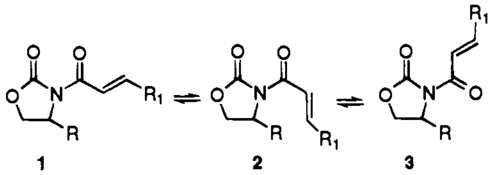
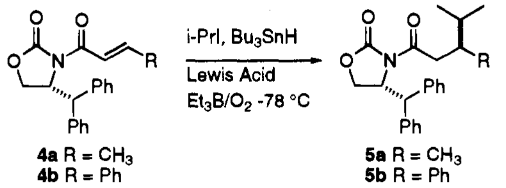


Table 1. Effect of Lewis Acids on β-Diastereoselectivity



entry	substrate	Lewis acid[a]	solvent	% yield[b]	ratio[c]
1	**4a**	none	CH_2Cl_2/hex	60[d]	1.3:1
2	**4a**	BF_3OEt_2	CH_2Cl_2/hex	80 (5)	1.3:1
3	**4a**	$ZnCl_2$	CH_2Cl_2/hex/THF	30[e]	1.3:1
4	**4a**	$SnCl_4$	CH_2Cl_2/hex	30 (60)	3:1
5	**4a**	$Zn(OTf)_2$	CH_2Cl_2/hex/ether	50 (20)	3:1
6	**4a**	Et_2AlCl	CH_2Cl_2/hex	70 (20)	4:1
7	**4a**	$MeAlCl_2$	CH_2Cl_2/hex	<20 (80)	5:1
8	**4a**	$ZnCl_2$	CH_2Cl_2/hex/ether	90	5:1
9	**4a**	$MgBr_2$	CH_2Cl_2/hex/ether	90	6:1
10	**4a**	$MgBr_2$	CH_2Cl_2/hex/THF	90	6:1
11	**4a**	$La(OTf)_3$	CH_2Cl_2/hex/THF	80	7:1
12	**4a**	$Sc(OTf)_3$	CH_2Cl_2/hex/THF	90	15:1
13	**4a**	$Sm(OTf)_3$	CH_2Cl_2/hex/THF	90	18:1
14	**4a**	$Yb(OTf)_3$	CH_2Cl_2/hex/THF	93[g]	25:1
15[f]	**4a**	$Yb(OTf)_3$	CH_2Cl_2/hex/THF	90	25:1
16	**4b**	$ZnCl_2$	CH_2Cl_2/hex/ether	70	9:1
17	**4b**	$La(OTf)_3$	CH_2Cl_2/hex/THF	80	12:1
18	**4b**	$MgBr_2$	CH_2Cl_2/hex/ether	90	20:1
19	**4b**	$Yb(OTf)_3$	CH_2Cl_2/hex/THF	89[g]	45:1

[a] Two equivalents of Lewis acid was used in all reactions. [b] NMR yields, except when purified yields are indicated. Yields in parentheses are for the alkene reduction product. [c] Diastereomer ratios were determined by ^{1}H NMR (400 MHz). [d] 30% starting material was recovered. [e] 60% starting material was recovered. [f] 2-Bromopropane was used instead of 2-iodopropane. [g] Purified yield.

Table 1 gives results for addition of isopropyl radical (generated from 2-iodopropane and Bu_3SnH, with triethylboron/oxygen as initiator) to the crotonate and cinnamate derivatives **4a**,**b**. The required starting materials **4a**,**b** were prepared by standard acylation of 4-(diphenylmethyl)-2-oxazolidinone, a new chiral auxiliary introduced by our group.[10] In the absence of Lewis acid additive, a 1.3:1 diastereomeric mixture of **5a** was formed in 60% chemical yield, accompanied by starting material (entry 1).[11]

A variety of Lewis acids varying in strength and coordinating ability were then evaluated.[12] Some highlights emerge. *Record levels of acyclic diastereoselection in β-radical additions using simple chiral auxiliaries are observed* (entries 14, 19) with *diastereoselectivity comparable to or better than that obtained with reactions under ionic conditions.*[13] Maximum yields and selectivity are achieved using lanthanide Lewis acids (entries

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[1] Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.

[2] Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771 and references cited therein.

[3] (a) Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464. (b) Rück, K.; Kunz, H. *Synthesis* **1993**, 1018.

[4] Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007.

[5] (a) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455. (b) Nishida, M.; Hayashi, H.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1995**, *36*, 269.

[6] For discussion on acyclic diastereoselection in radical reactions, see: (a) Giese, B. *Radical in Organic Synthesis. Formation of Carbon–Carbon Bond*; Pergamon: Oxford, 1986. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (c) Smadja, W. *Synlett* **1994**, 1. (d) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, 143. (e) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.

[7] For an example on the use of oxazolidinones in ρ-diastereoselective reactions, see: Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.*, submitted for publication.

[8] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

[9] For selected recent examples on the use of Lewis acids in radical reactions, see: (a) Renaud, P.; Gerster, M. *J. Am. Chem. Soc.* **1995**, *117*, 6607. (b) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259. (c) Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. *J. Org. Chem.* **1994**, *59*, 3547. (d) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576. (e) Murakata, M.; Tsutsui, H.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1995**, 481. (f) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701.

[10] (a) Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J.; Christensen, J. W. *Tetrahedron Lett.*, submitted for publication. (b) Sibi, M. P.; Deshpande, P. K.; Ji, J. *Tetrahedron Lett.*, submitted for publication.

[11] No regioisomeric product, i.e., the product arising from addition to the α-carbon, was detected in the reaction.

[12] Typical reaction procedure: To a solution of **4a** (0.1 mmol, 1 equiv) in CH_2Cl_2 (2 mL) under N_2 was added the Lewis acid additive (2 equiv), the solvent additive (1 mL, either THF, Et_2O, or CH_2Cl_2, depending on the solubility of the Lewis acid), 2-iodopropane (10 equiv), Bu_3SnH (5 equiv), and triethylboron/hexane (1.0 M, 1 mL, 10 equiv) at −78 °C, and 1 mL increments of oxygen were added by syringe at 0, 1, and 2 h. After completion followed by workup, the crude reaction mixture was analyzed by 400 MHz NMR.

[13] For conjugate addition using oxazolidinone auxiliaries, see: Nicolás, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766.

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Table 2. Effect of Stoichiometry and Additives in Yb(OTf)$_3$ Catalyzed Reactions of **4a**[a]

entry	equiv[b]	solvent/additive	% yield[c]	ratio[d]
1	2.0	CH_2Cl_2/hex/THF	90	25:1
2	1.0	CH_2Cl_2/hex/THF	90	25:1
3	0.3	CH_2Cl_2/hex/THF	90	20:1
4	2.0	THF/hex	90	15:1
5	2.0	CH_2Cl_2/hex/ether	90	9:1
6	2.0	CH_2Cl_2/hex	50 (40)	1.3:1
7	2.0	toluene/hex/THF	90	11:1
8	2.0	CH_2Cl_2/hex/THF/H_2O[e]	90	20:1
9	2.0	CH_2Cl_2/hex/THF/H_2O[f]	60[g]	1.7:1

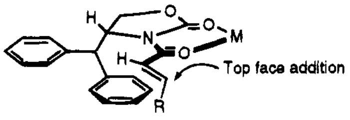
[a] Reaction of **4a** with *i*-PrI/Bu_3SnH at −78 °C using Et_3B/O_2 as the initiator. [b] Molar equivalents of Yb(OTf)$_3$ relative to substrate. [c] Yield in parentheses is for the alkene reduction product. [d] Diastereomer ratios were determined by ^{1}H NMR (400 MHz). [e] Ten equivalents of water (relative to substrate) was added. [f] Thirty equivalents of water (relative to substrate) was added. [g] 30% starting material was recovered.

11, 13, 14, 17, and 19), with ytterbium[14] giving the highest diastereoselectivity. *The β-substituent of the enoyl group had a significant impact on the diastereoselectivity of the radical addition.* Under identical reaction conditions, isopropyl radical addition to **4b** gave 45:1 selectivity, as compared to 25:1 for **4a** (entry 14 vs 19). Several other trends are also noteworthy. Nonchelating Lewis acid gave diminished stereoselectivity (entry 2). Lewis acids greatly increased the chemical yield of the reaction (compare entry 1 with entries 8−15),[9d] and the yield and selectivity were as high with 2-bromopropane as with 2-iodopropane (entry 15 vs 14). Strong conventional Lewis acids not only gave inferior diastereoselectivity but also gave significant amounts of the reduction product (entries 2, 4−7).

The newly created stereocenter in the major diastereomers of **5a,b** had the *S* configuration shown.[15] Although the selectivity differs dramatically depending on Lewis acid, the same sense of stereoinduction is found with and without Lewis acid additive (entry 1).[16] To compare the utility of the auxiliary derived from diphenylalaninol, we have also tested isopropyl radical addition to the crotonate derived from 4-(phenylmethyl)-2-oxazolidinone (Evans's auxiliary).[17] A 3:1 diastereomeric mixture resulted with Yb(OTf)$_3$ as a Lewis acid and a 0.9:1 ratio without added Lewis acid.

Having established that excellent diastereoselectivities are achievable using Yb(OTf)$_3$, we examined the effect of stoichiometry and solvent on the addition of isopropyl radical to **4a** (Table 2). Several entries in the table are noteworthy. The addition reaction works equally well with substoichiometric amount of the Lewis acid reagent (entries 1−3), with negligible reduction in stereoselectivity. The addition of an ethereal solvent is essential for obtaining high diastereoselectivity (entries 1−6), and replacement of THF with ether led to lower selectivity (entry 1 vs 6).[18] Replacement of CH_2Cl_2 with toluene reduced the selectivity (entry 1 vs 7). *Limited amounts of water did not lead to diminished yield or selectivity* (entries 1, 8, and 9).[14,19] This is a tremendous practical advantage relative to organometallic or conventional Lewis acid-mediated reactions, since careful drying of reagents, solvents, and apparatus is unnecessary. Large excesses of water, however, did suppress both the yield and the stereoselectivity (entry 9).

The high yields and diastereoselectivity observed in the β-radical addition can be explained by a chelation model. Upon Lewis acid chelation, the orientations of the two carbonyls are fixed, as needed for selectivity, and chelation also activates the enoyl fragment toward radical conjugate addition.[9d] The activating effect of Lewis acids explains the facile conjugate addition in high chemical yields (Table 1, entry 1 vs 8−14). Radical addition to the chelated substrate then takes place from the face opposite the bulky diphenylmethyl substituent. Replacement of the diphenylmethyl group by the smaller benzyl group (Evans's auxiliary) leads to less effective facial shielding. The subtleties of the dependence of stereoselectivity on the specific Lewis acid are still not fully understood (Table 1, entries 8−14). For the lanthanides, the selectivity pattern of La < Sm < Yb suggests that reducing the ionic radius improves the selectivity. The significantly higher selectivity observed for cinnamate **4b** as compared to crotonate **4a** (Table 1, entry 14 vs 19) is puzzling. This observation, combined with the decreased selectivity in the presence of toluene (Table 2, entry 1 vs 7), indicates that factors other than steric effects alone may play a role in determining the levels of selectivity. Experiments to understand the variation in selectivity with Lewis acids and the β-substituent, extension to other radicals and auxiliaries, and examination of tandem β- and α-selectivities, are underway.



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Supporting Information Available: Experimental procedures and characterization data for compounds **4** and **5** and NMR spectra of mixtures of **5a**/**5b** to support the reported diastereomer ratios (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(14) Yb(OTf)$_3$ was purchased from Aldrich and contained 1% water by mass. Use of anhydrous Yb(OTf)$_3$ did not lead to improvement in selectivity.

(15) The absolute stereochemistries of the products were established by hydrolysis (LiOH, H_2O_2): **5a** gave (*S*)-3,4-dimethylpentanoic acid, $[\alpha]^{26}_D = -10.72$ (c = 0.55, benzene) {lit. $[\alpha]^{21}_D = -6.95$ (c = 1.18, benzene): Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235}; **5b** gave (*S*)-4-methyl-3-phenylpentanoic acid, $[\alpha]^{26}_D = -33.6$ (c = 3.77, $CHCl_3$). {lit:$[\alpha]^{25}_D = -34.44$ (c = 4.06, $CHCl_3$); Lardicci, L.; Salvadori, P.; Caporusso, A. M.; Menicagli, R.; Belgodere, E. *Gazz. Chim. Ital.* **1972**, *102*, 64}.

(16) The Bu_3SnI generated in situ in the reaction may conceivably serve as a Lewis acid. See: Sibi, M. P.; Ji, J. *J. Am. Chem., Soc.* submitted for publication.

(17) Gage J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77.

(18) The ytterbium triflate had limited solubility in the absence of ethereal solvents. Rare earth Lewis acids have high coordination numbers and are probably coordinated by the ethereal solvents in addition to the substrate.

(19) Unlike most conventional Lewis acids, lanthanide triflates are stable in water. See: Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.