Acyclic Stereocontrol in Radical Reactions. Diastereoselective Radical Addition/ Allylation of *N*-Propenoyloxazolidinone

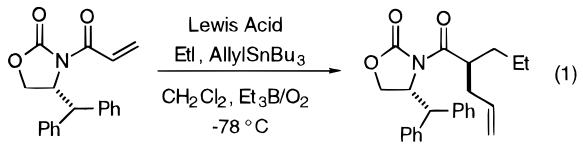
Mukund P. Sibi* and Jianguo Ji

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105-5516

Received May 22, 1996

There has been a steady increase in the use of Lewis acids in radical reactions.[1] The principal function of a Lewis acid in these processes is to control the rotamer population in either the substrate or the reagent, such that high diastereoselectivity is the result.[2] In addition, Lewis acids sometimes accelerate radical additions,[3] and can also serve as radical initiators.[4] Early work on tandem radical addition and trapping experiments using oxazolidine, 2,5-dimethylpyrrolidine, and camphorsultam auxiliaries were reported from the laboratories of Porter,[5] Giese,[6] and Curran.[7,8] The diastereoselectivity in these experiments using alkyl radicals was good to excellent. Recently Porter *et al.*[9] have also reported the use of stoichiometric chiral Lewis acids in achieving high enantioselectivity in tandem addition processes involving *N*-propenoyloxazolidinone. We have recently shown that Lewis acids can be effectively employed for conjugate additions to *N*-enoyloxazolidinones[3] and for ρ-diastereoselective radical allylation.[10] Conjugate addition followed by diastereoselective trapping of the intermediate radical using versatile oxazolidinone auxiliaries with high diastereoselectivity has not been described, but seemed a logical extension of our previous findings.[11] A good understanding of these diastereoselective processes is essential for their successful extension to an enantioselective version. This work describes the Lewis acid-mediated radical addition/trapping of *N*-propenoyloxazolidinone proceeding with high diastereoselectivity. Alkyl radicals as well as radicals containing Lewis basic sites add to *N*-propenoyloxazolidinone with excellent diastereoselectivity in the Lewis acid-mediated process.

Table 1. Lewis Acid-Mediated Diastereoselective Radical Addition to *N*-Propenoyloxazolidinone[a]



entry	Lewis acid (equiv)	isolated yield (%)	ratio β: α[b]
1	–	90	1.0:1.0
2	$BF_3{\cdot}Et_2O$ (2)	90	1.0:1.8
3	ZnI_2 (2)	85	2.2:1.0
4	$ZnCl_2$ (2)	90	4.1:1.0
5	$Zn(OTf)_2$ (2)	85	1.3:1.0
6	$MgBr_2{\cdot}Et_2O$ (2)	93	>100:1[c]
7	$Yb(OTf)_3$ (1)	90	>100:1
8	$Sm(OTf)_3$ (1)	90	>100:1
9	$La(OTf)_3$ (1)	71	>100:1

[a] Typical procedure: see footnote 12. [b] Diastereomeric ratios were determined by ^1H 400 MHz NMR analysis. [c] Absolute stereochemistry was determined to be (*S*) by hydrolysis [see footnote 14].

At the outset we were concerned with three potential problems: (1) low yields, (2) the extent of diastereoselectivity in the tandem process, and (3) telomerization of the starting propenoyloxazolidinone. Our work on Lewis acid-mediated conjugate radical additions[3] in high yields gave us confidence that clean radical addition with negligible polymerization should be possible. The high ρ-diastereoselectivity[10] observed in simple allylation experiments with oxazolidinone auxiliaries supported the assumption that the intermediate radical could be trapped with high selectivity in the tandem process.

Our experiments began with optimization of reaction conditions for the addition of ethyl radical to **1** followed by trapping of the intermediate radical with allyltributylstannane (Table 1, eq 1).[12] The radical reactions were initiated using triethylborane and oxygen. The auxiliary of choice was the oxazolidinone derived from diphenylalanine[13] since it had shown the best characteristics in our earlier work. Some trends emerge. High chemical yields and diastereoselectivity were realized with mag-

(1) 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. (g) Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464. (h) Guindon, Y.; Guerrin, B.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Synlett* **1995**, 449. (i) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945. (j) Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493. (k) Feldman, K. S.; Romaneli, A. L.; Ruckle, R. E., Jr.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100.

(2) For discussion on acyclic diastereoselection in radical reactions see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995. (b) Giese, B. *Radical in Organic Synthesis. Formation of Carbon-Carbon Bond*; Pergamon: Oxford, 1986. (c) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (d) Smadja, W. *Synlett* **1994**, 1. (e) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, 143. (f) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.

(3) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779.

(4) (a) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421. (b) Nishida, M.; Nishida, A.; Kawahara, N. *Synlett* **1995**, 1045.

(5) (a) Porter, N. A.; Carter, R. L.; Mero, C. L.; Roepel, M. G.; Curran, D. P. *Tetrahedron* **1996**, *52*, 4181. (b) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. (c) Porter, N. A.; Rosenstein, I. J.; Breyer, R. A.; Bruhnke, J. D.; Wu, W.-X.; McPhail, A. T. *J. Am. Chem. Soc.* **1992**, *114*, 7664. (d) Radinov, R.; Mero, C. L.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1995**, *36*, 8183.

(6) (a) Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *J. Am. Chem. Soc.* **1990**, *112*, 6741. (b) Bulliard, M.; Zeitz, H.-G.; Giese, B. *Synlett* **1991**, 423.

(7) (a) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (b) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007. (c) Curran, D. P.; Shen, W.; Zhang, J.; Gieb, S. J.; Lin, C.-H. *Heterocycles* **1994**, *37*, 1773.

(8) For selected examples of tandem radical additions from other laboratories see: (a) Mizuno, K.; Ikeda, M.; Toda, S.; Otsuji, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1288. (b) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003. (c) Garner, P. P.; Cox, P. B.; Klippenstein, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4183.

(9) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029.

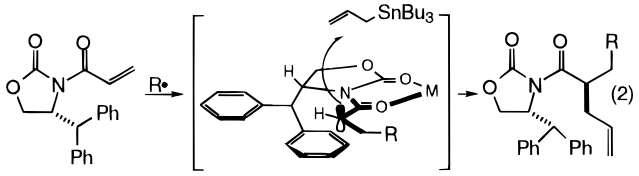
(10) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190.

(11) (a) Use of an oxazolidinone auxiliary for addition/trapping with insignificant diastereoselectivity has been reported by Crich and Davies: Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205. (b) While this manuscript was under preparation, another report on radical addition to *N*-enoyloxazolidinones with low selectivity was reported: Wu, M.-J.; Fu, C.-L.; Duh, T.-H.; Yeh, J.-Y. *Synthesis* **1996**, 462.

(12) Typical procedure: under N_2, to a flask containing **1** (0.5 mmol), $MgBr_2{\cdot}Et_2O$ (258 mg, 1.0 mmol), and CH_2Cl_2 (5 mL) were added ethyl iodide (2.5 mmol) and allyl tributyltin (1 mmol) at −78 °C. Et_3B (1 M, in hexane) (1.0 mL, 1 mmol) was then added. A 5 mL amount of O_2 was finally added via syringe over 2 h.

S0022-3263(96)00947-4 CCC: $12.00

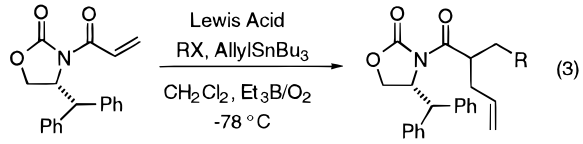
nesium and rare earth Lewis acids (Table 1, entries 6−9). Use of zinc and boron Lewis acids led to high yields but low diastereoselectivity (Table 1, entries 2−5). The absolute stereochemistry of the newly formed chiral center was established to have the *S* configuration.[14] These results indicate that effective Lewis acids coordinate with the two carbonyl groups of the enoyloxazolidinone (eq 2). With the two carbonyls locked in the *syn*



configuration, the radical site also adopts a *syn* configuration for steric reasons. Allylstannane addition to the intermediate radical then takes place from the face opposite to the bulky oxazolidinone 4- substituent.

The results for tandem additions using primary, secondary, tertiary, cycloalkyl, α-alkoxy alkyl, and acyl radicals are tabulated in Table 2 (eq 3). Several interesting trends emerged. Reactions with alkyl radicals proceeded with >100:1 diastereoselectivity, regardless of the degree of substitution (Table 2, entries 1−4). The range of radical precursors employed to evaluate new methodologies is generally limited to alkyl radicals. For radical processes to become more synthetically useful, the use of radicals containing heteroatoms is essential. The selective addition of functionalized radicals would make products more useful as precursors for the synthesis natural products. Functionalized radicals possessing Lewis basic sites could also be used successfully in the addition/allylation experiments. Addition of acyl radicals[15] generated from acyl halides followed by allyl trapping proceeded with excellent selectivity (Table 2, entries 7 and 8).[16] Surprisingly, the use of acyl selenides as radical precursors gave small amounts of the starting compound along with polymeric material, but none of the tandem addition product. The diastereoselectivity in the reaction involving methoxymethyl addition was more

Table 2. Diastereoselective Addition/Allylation Using Different Radical Precursors[a]



1 3

entry	RX	Lewis acid (eq)	prod.	yield (%)[b]	ratio[c]
1	MeI	$MgBr_2$ (2)	**3a**	82	>100:1
2	i-PrI	$MgBr_2$ (2)	**3b**	85	>100:1
3	t-BuI	$MgBr_2$ (2)	**3c**	94	>100:1
4	$C_6H_{11}I$	$MgBr_2$ (2)	**3d**	93	>100:1
5	$MeOCH_2Br$	$MgBr_2$ (2)	**3e**	50	1.8:1
6	$MeOCH_2Br$	$Yb(OTf)_3$ (1)	**3e**	70	58:1
7	MeCOBr	$MgBr_2$ (2)	**3f**	55	50:1
8	PhCOBr	$MgBr_2$ (2)	**3g**	90	50:1

[a] For typical procedure see footnote 12. [b] Yields are for isolated products. [c] Diastereomeric ratios were determined by ^1H 400 MHz NMR analysis. The absolute stereochemistry at the newly formed center has not been established.

complex. Whereas ytterbium triflate gave 58:1 selectivity, magnesium bromide gave only a 1.8:1 mixture (entries 5 and 6). The higher selectivity with ytterbium triflate may reflect its higher coordinating ability. It is evident that functionalized radicals possessing Lewis basic sites can be used successfully, but that appropriate matching of the Lewis acid may be critical.

In conclusion, we have shown that Lewis acid-mediated tandem additions proceed with high levels of diastereoselectivity. The use of simple as well as functionalized radicals in these tandem addition processes has also been established. Further studies regarding the dependence of diastereoselectivity on the Lewis acid-radical precursor combination, extension of the methodology to more complex systems, and applications of these reactions in natural product synthesis are currently underway in our laboratory.

Acknowledgment. We thank NSF (OSR-9452892), National Institutes of Health, SC Johnson&Wax, and FMC Lithium for financial support of our research programs. Partial support for this work was provided by the NSF's Instrumentation and Laboratory Improvement Program through grant no. USE-9152532 and by NRICGP (95-37501-2300) for upgrade of the NMR data acquisition system.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**3** (7 pages).

JO960947C

(13) For the preparation of the oxazolidinone derived from diphenylalanine see: Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J.; Christensen, J. W. *Tetrahedron Lett.* **1995**, *36*, 8961.

(14) The absolute stereochemistry of the product was established by hydrolysis ($LiOH/H_2O_2$, H_2O/THF, 0 °C to rt). **2** gave (*S*)-2-propyl-4-pentenoic acid $[\alpha]^{26}_D$ −6.10° (*c* = 0.725, $CHCl_3$). [lit.: $[\alpha]^{25}_D$ −5.50° (*c* = 0.975, $CHCl_3$)] (lit.: Hauck, R.-S.; Nau, H. *Toxicol. Lett.* **1989**, *49*, 41. Porubek, D. J.; Barnes, H.; Theodore, L. J.; Baillie, T. A. *Chem. Res. Toxicol.* **1988**, *1*, 343). All the other compounds were assumed to provide similar absolute stereochemistry at the newly formed center.

(15) For examples of acyl radical additions to enoates see: Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429.

(16) The addition of acyl and alkoxyalkyl radicals to **1** in the absence of Lewis acids gave very low diastereoselectivity.