Enantioselective Free Radical Carbon–Carbon Bond Forming Reactions: Chiral Lewis Acid Promoted Acyclic Additions

Jason Hongliu Wu, Rumen Radinov, and Ned A. Porter*

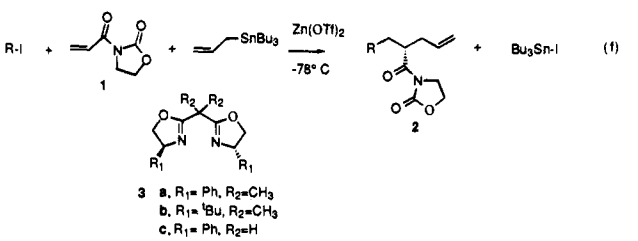
Department of Chemistry, Duke University Durham, North Carolina 27708

Received July 26, 1995

Free radical addition to carbon–carbon double bonds is one of the most important reactions in organic chemistry. Many polymers of commercial interest are formed by free radical addition, and within the last decade, this reaction has been used extensively in organic synthesis. The control of stereochemistry in free radical reactions has been substantially advanced in recent years, and today there is a good understanding of factors that are important in determining the configuration of stereogenic centers formed in diastereoselective free radical additions.[1] Auxiliary groups have been developed that exhibit good control for additions of acyclic radicals, and many "substrate-controlled" reactions have been reported as well. The underlying theme for these developments in stereocontrol has been to fix the configuration of resident chiral groups in the auxiliary or in the substrate relative to the new stereogenic center being formed from the free radical. This strategy, which was modeled on the powerful approaches developed in carbanion and cycloaddition chemistry,[2] works successfully for chiral groups attached to the free radical as well as to the alkene undergoing addition. While many of the problems associated with auxiliary and substrate-controlled diastereoselective free radical reactions have been solved and successful examples of these reaction types are now common,[3] it is of some note that enantioselective free radical reactions, including additions, have been elusive.

Free radical additions are subject to polar effects, and Lewis acids are known to catalyze some polymerizations.[4] Lewis acids have also been used to conformationally fix resident chiral centers through chelation in free radical auxiliary and substrate-controlled reactions.[5] Chiral Lewis acids have been used with modest success in atom transfer reactions of cyclic substrates,[5a] but no examples of substantial control of stereochemistry by chiral Lewis acids have been reported for acyclic radicals in free radical addition reactions. We report here that zinc ion as a Lewis acid, used in conjunction with chiral bidentate ligands, promotes free radical addition to a suitably substituted acrylamide. We further note that the addition reactions of the acrylamide-derived free radical occur with good to excellent enantioselectivity.

The reaction of alkyl iodides, electron-deficient alkenes, and allyltributylstannane has been used extensively to test the efficacy of auxiliary groups in free radical additions.[1] This reaction propagates well at room temperature or above for most alkenes, but the reaction can be sluggish at low temperatures. Indeed, the rate of addition of free radicals to allyltributylstannane is borderline at room temperature, and at low temperatures this step in the chain sequence apparently slows to the extent that chain propagation does not occur for many alkenes.[6] We envisioned the possibility of activating appropriately substituted electron-deficient alkenes by complexation of a chiral Lewis acid promoter. The resulting reactivity difference would provide the possibility for enantioselection since the chiral radical would then propagate preferentially.



(1)

Reaction of **1**[7] (20 mM) in methylene chloride with cyclohexyl iodide and allyltributylstannane at −78 °C in the presence of zinc triflate (1 equiv) and the chiral bidentate ligand **3a**[8] (1 equiv) gives a clean conversion to adduct **2** with isolated yields of between 55 and 90% if triethylborane[9] is used as a low-temperature initiator, see eq 1. *tert*-Butyl iodide has also been used in the addition sequence, and excellent yields of the *tert*-butyl (1:1:1) adduct are obtained under reaction conditions that include zinc triflate and the chiral ligand.[10]

Without the chiral ligand and zinc triflate or without the initiator, the reaction gives only low conversion to adduct **2** at −78 °C. Temperatures above 0 °C and a 5–10-fold excess of allylstannane are required to give (1:1:1) adduct **2** as the major product without the Lewis acid. Lower allylstannane:alkene ratios give substantially more telomeric products that incorporate two or three acrylamides per chain under these conditions.[11]

* To whom correspondence should be addressed: Department of Chemistry, Duke University, Durham, NC 27708. Telephone: (919) 660-1550. FAX: (919) 660-1605. E-mail: porter@chem.duke.edu.

(1) (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) Smadja, W. *Synlett* **1994**, 1.

(2) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 2. (b) Lumtowski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 213. (c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (d) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292.

(3) (a) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309. (b) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791. (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) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (e) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007. (f) Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412. (g) Bullard, M.; Zeitz, H.-G.; Giese, B. *Synlett* **1991**, 423. (h) Damm, W.; Dickhaut, J.; Wetterich, F.; Giese, B. *Tetrahedron Lett.* **1993**, *34*, 431. (i) Renaud, P.; Bourquard, T.; Gerster, M.; Moufid, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1601.

(4) Zubov, V. P.; Valuev, L. I.; Kabanov, V. A.; Kargin, V. A. *J. Polym. Sci., Part A-1* **1971**, *9*, 833.

(5) (a) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K. Sato, F. *J. Org. Chem.* **1995**, *60*, 3576. (b) Guindon, Y.; Guerin, B.; Chabot, C.; Mackintosh, N.; Ogilve, W. W. *Synlett* **1995**, 449. (c) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945. (d) Murakata, M.; Tsutsui, H.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1995**, 481. (e) Renaud, P.; Gerster, M. *J. Am. Chem. Soc.* **1995**, *117*, 6607. (f) Feldman, K. S.; Romaneli, A. L.; Ruckle, R. E., Jr.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100. (g) 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. (h) Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. *J. Org. Chem.* **1994**, *59*, 3547. (i) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421. (j) Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464. (k) Guindon, Y.; Lavallee, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701. (l) Renaud, P.; Ribezzo, M.; *J. Am. Chem. Soc.* **1991**, *113*, 7803. (m) Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493.

(6) Curran, D. P.; van Elburg, P. A.; Giese, B.; Gilges, S. *Tetrahedron Lett.* **1990**, *31*, 2861.

(7) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 30.

(8) (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (d) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.

(9) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.

(10) The chiral ligand can be readily recovered by flash chromatography.

(11) We will report on the higher telomers of **2** elsewhere. Radinov, R.; Mero, C.; Porter, N. *Tetrahedron Lett.*, in press.

0002-7863/95/1517-11029$09.00/0

Table 1. Reactions of Alkene **1** with Alkyl Iodides, $Zn(OTf)_2$ and Allyltributylstannane[a]

entry	R (equiv of RI)[b]	ligand (L*)	**1**:M:L* [c]	solvent	isolated yield (%)	*R*:*S*	ee
1	c-hexyl (10)	**a** (*S,S*)	1:1:1	CH_2Cl_2	62	25:75	50
2	c-hexyl (10)	**a** (*S,S*)	1:1:1	ether	90	18:82	64
3	c-hexyl (10)	**a** (*S,S*)	1:2:2	ether	61	10:90	80
4	c-hexyl (1.5)	**a** (*R,R*)	1:1:1.2	*d*	62	84:16	68
5	c-hexyl (1.5)	**a** (*R,R*)	1:2:2.4	*d*	92	86:14	72
6	*tert*-butyl (5)	**a** (*S,S*)	1:1:1.2	*d*	78	6:94	88
7	*tert*-butyl (5)	**a** (*R,R*)	1:1:1.2	*d*	92	95:5	90
8	*tert*-butyl (5)	**a** (*R,R*)	1:2:2.1	ether	55	94:6	88
9	c-hexyl (10)	**b** (*S,S*)	1:1:1	CH_2Cl_2	60	50:50	0
10	c-hexyl (10)	**c** (*S,S*)	1:1:1	CH_2Cl_2	63	33:67	34

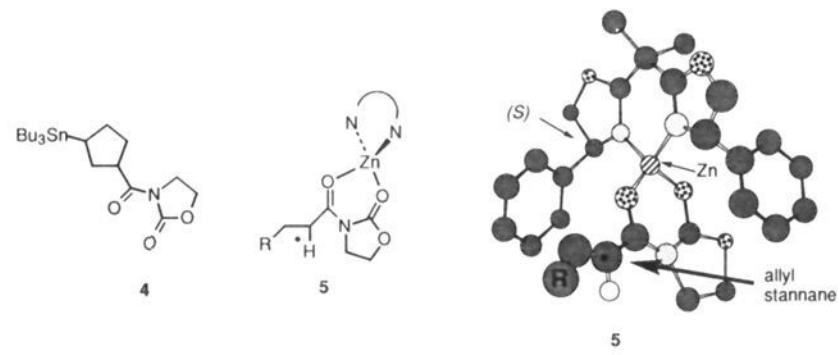
[a] Reaction at −78 °C initiated by triethylborane with 20 mM **1**, 1.5−10-fold equivalents of alkyl iodide and allyltributylstannane. [b] Equivalents of RI and allylstannane used. [c] M = $Zn(OTf)_2$. [d] Pentane/CH_2Cl_2 solvent mixture, 40:60.

Analysis of adducts **2** by chiral capillary gas chromatography[12] indicates substantial enantiomeric enrichment of the product of the addition sequence under some reaction conditions. Product enantiomer ratios as high as 95:5 are obtained (90% enantiomeric excess, Table 1, entry 7) with enantioselectivity depending critically on the chiral ligand, the solvent, the Lewis acid, and the radical undergoing the addition reaction. Use of ligand **3b** gives racemic product (entry 9) while **3c** gives product with somewhat lower enantioselectivity (entry 10) than reactions utilizing **3a**. Selectivities obtained are lower when the ligand and zinc ion equivalents are reduced compared to **1**. Excess ligand and zinc ion improve the selectivity in the reaction of cyclohexyl radicals (entries 2 and 3) while this effect is not as substantial for additions of *tert*-butyl radicals. Zinc chloride and magnesium triflate chiral complexes give racemic products under conditions identical with those used for zinc triflate although these Lewis acids appear to promote the addition sequence. Scandium triflate gives low selectivity (<10%) when used under our best conditions. It is of some synthetic interest that the reaction proceeds well with only 1.5 equiv of alkyl iodide and allyltributylstannane (Table 1, entries 4 and 5) compared to the alkene, if zinc triflate and **3a** are present.

Reaction of alkene **1** in methylene chloride at temperatures above 0 °C with Lewis acid, allylstannane, and chiral ligand gives a complex product mixture that includes product **4**, a (3 + 2) adduct of allylstannane and **1**.[13] This cycloaddition becomes important at above room temperature even in the presence of cyclohexyl iodide and radical initiator.

Chiral (1:1:1) adduct **2** is hydrolyzed with LiOOH under standard conditions,[7] and the product acid is converted to the corresponding methyl ester with diazomethane. Analysis of this methyl ester by chiral capillary gas chromatography indicates that the major enantiomer formed in the addition sequence has the *S* configuration if ligand **3a** or **3c** have the *S,S* configuration.[14]

The Lewis acid complexation of alkene **1** with zinc triflate and ligand **3a** may activate the alkene toward addition by nucleophilic radicals such as cyclohexyl and *tert*-butyl, but the stereoselective step in the sequence is, nevertheless, the subsequent addition−fragmentation reaction of the intermediate radical **5** with allyltributylstannane. It therefore seems likely that the bis(oxazoline), the sole source of chirality in the reaction, and zinc ion are associated with the radical at the stage



of the allyl addition reaction. A model similar to that proposed for Lewis acid catalyzed Diels−Alder reactions[15] can be used to rationalize the configuration of product **2**. Both the chiral *S,S* bis(oxazoline) and the acryloyl oxazolidinone are bidentate ligands which are coordinated to a central tetrahedral zinc ion[16] in a 1:1:1 complex in this model. Chelation of the bis(oxazoline) ensures a C_2 symmetric conformation. The *Z,Z* conformation of the acryloyl oxazolidinone is fixed by chelation of the carbonyls; the *s-cis* conformation of the α-amidyl radical is preferred for steric reasons.[1] In this model, the back face of the prostereogenic radical is protected from reaction by one of the phenyls of the ligand while the other phenyl of the ligand is remote from the open face of the radical. Addition occurs to the front face of the radical shown in the model, the *S* product being formed in reactions utilizing the *S,S* ligand.

The enantioselective addition allyl transfer sequence of **1** utilizing zinc triflate and chiral ligand **3** may prove to be useful as a guide for the development of catalytic enantioselective free radical carbon−carbon bond forming reactions.[17] Furthermore, it may be useful in its own right as a practical route to chiral organic substructures.

Acknowledgment. Support for this research from the NSF and the NIH (HL-17921) is gratefully acknowledged. We also thank Dr. Mark Burk for helpful discussions. J.H.W. thanks the Wellcome Foundation for a fellowship.

Supporting Information Available: Typical reaction conditions, NMR spectra of key compounds, and gas chromatograms from analyses on chiral GC columns (13 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.

JA9525014

(12) A 20-m Chiraldex GTA column is used. Chromatography conditions for the chiral adduct from **1**: for the cyclohexyl radical adduct, 145 °C, *R* elutes first; for the *tert*-butyl radical adduct, 104 °C, *R* elutes first; for the methyl ester, 85 °C, *R* elutes first.

(13) To be published: Rakus, K.; Wu, J. H.; Radinov, R.; Porter, N. For a similar reaction of allyltributylstannane, see: Herndon, J. W.; Wu, C.; Harp, J. J.; Kreutzer, K. A. *Synlett* **1991**, 1.

(14) This was confirmed for the cyclohexyl adduct by independent synthesis of the methyl ester by allylation of the appropriate enolate derived from Oppolzer's sultam (Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, 5603). Saponification gave the *S* acid. Independent synthesis of the *tert*-butyl adduct was achieved by radical addition using a chiral oxazolidine auxiliary; see ref 3c.

(15) (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (b) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460.

(16) See, for example: Bolm, C.; Weichhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.

(17) Survey reactions of a variety of Lewis acids, several ligands similar in structure to **3**, and alkenes similar in structure to **1** are being carried out under a variety of conditions of initiation and will be reported in due course.