Chiral Lewis Acid Catalysis in Radical Reactions: Enantioselective Conjugate Radical Additions

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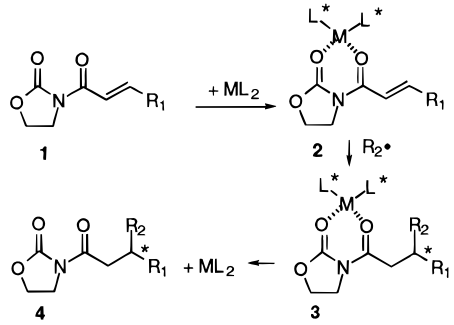
Development of new methods for the preparation of enantiomerically pure compounds is an important goal for synthesis. There are numerous examples of enantioselective Diels−Alder, aldol, and other reactions that are directed by chiral Lewis acids[1,2] but there are only a few reports of enantioselective radical reactions.[3] The first example of a chiral Lewis acid-mediated radical carbon−carbon bond-forming reaction proceeding with high enantioselectivity was recently reported.[4] In this example, the radical was complexed to the chiral Lewis acid prior to trapping with allyltributylstannane.

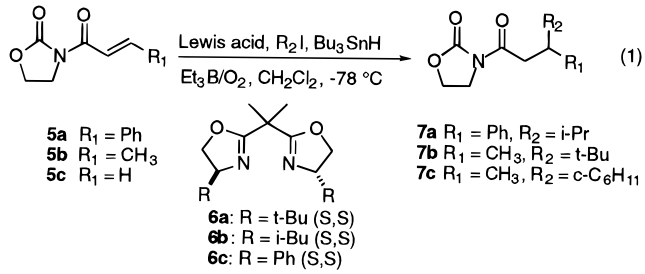
This communication describes radical additions in which chiral Lewis acids are complexed to alkene radical traps which undergo enantioselective attack at the β centers. A general solution to the problem of acyclic diastereoselection in β-radical additions has been elusive[5] until recently, when record levels of diastereoselectivity were observed by the use of an oxazolidinone auxiliary in conjunction with Lewis acid additives.[6] The current report provides the first examples of acyclic enantioselection in β-radical additions promoted by substoichiometric chiral Lewis acid.[7]

Several issues must be addressed for the development of a successful protocol in the Lewis acid-catalyzed enantioselective radical addition to enoates **1**[6,7] (Scheme 1): (1) the Lewis acid/ligand complex ML_2 (M = Lewis acid and L = chiral ligand) should bind with the substrate **1** strongly, (2) the conformation of the chelated complex **2** must be controlled (*s-cis* vs *s-trans* rotamer of the enoate), (3) the ligand must provide facial bias for radical addition through steric interactions, and (4) the Lewis acid−product complex should dissociate to continue the catalytic cycle.

Scheme 1



The results of the addition of alkyl radicals to **5** in the presence of Lewis acids and chiral ligands **6** (eq 1)[8,9] are shown in Table 1. Several combinations of Lewis acids and ligands were initially evaluated.[10] Of these, magnesium and zinc Lewis acids gave the best results. Excellent chemical yields and high enantioselectivities were obtained for both **5a** and **5b** using stoichiometric Lewis acid and ligand (Table 1, entries 3, 5, 10, 13, and 14). In general, aliphatic substituted ligand(**6a** or **6b**)−Mg Lewis acid combinations gave high enantioselectivity (entries 3, 5, 13, and 14), whereas the phenyl-substituted ligand **6c** gave high selectivity in combination with zinc triflate (entries 8−10). Reactions with the crotonate substrate **5b** were more selective with the zinc Lewis acid−phenyl-substituted ligand **6c** than reactions of the cinnamate (compare entry 8 with 9). In reactions carried out under identical conditions, addition of *tert*-butyl radical gives product with higher selectivity than does that of cyclohexyl radical (entries 9 and 10).



Starting with ligands of identical absolute configuration, reactions with ligands possessing alkyl substituents (**6a** and **6b**) [*S,S*-ligand gives *R* product] gave opposite enantioselectivity to that observed in reactions with ligand **6c** [*S,S*-ligand gives *S* product] containing an aryl substituent (compare entries 3−5 with 6 and 7; entries 9 and 12 with 13). *Since all of the ligands are derived from amino acid precursors, these experiments constitute a simple method for the preparation of either enantiomeric product by the use of "natural" precursors.*

The catalytic nature of the reaction was also examined using the best ligand−Lewis acid combinations (Table 2). For example, isopropyl radical addition to **5a** proceeds equally well with 50 mol % of the catalyst as with stoichiometric amounts (compare entry 1 with 2). Further reduction of the catalyst load to 20 mol % for reaction with **5a** resulted in only a small

(1) (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(2) (a) Evans, D. A.; Murray, J. A.; Matt, P. v.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798. (b) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (c) Corey, E. J.; Imai, N.; Zhang, H-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

(3) (a) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576. (b) Murakata, M.; Tsutsui, H.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1995**, 481.

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

(5) 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) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res*. **1991**, *24*, 296. (c) Smadja, W. *Synlett* **1994**, 1. For early work on conjugate radical addition, see: (d) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007.

(6) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779 and references cited therein.

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

(8) The starting materials **5** and **8** and the ligands were prepared using literature procedures.

(9) Bisoxazolines have been used as a ligand for a variety of reactions. For a review, see: Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

(10) Combinations of different bisoxazolines (for **6** R = -CH_2Ph, -$CHPh_2$, -$CH_2C_6H_{11}$, 2-naphthyl, etc.) with Lewis acids ($ZnCl_2$, $MeAlCl_2$, rare earth triflates) were also evaluated in the conjugate radical addition with limited success or with no improvement over **6a**−**c**.

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Table 1. Enantioselective Conjugate Radical Additions using Stoichiometric Chiral Lewis Acid[a]

entry	substrate	product	ligand[b]	Lewis acid[c]	yield (%)[d]	ee (%)[e]
1	**5a**	**7a**	*SS*-**6a**	$Zn(OTf)_2$	61	37 (*R*)
2	**5a**	**7a**	*SS*-**6a**	$Mg(OTf)_2$	61	45 (*R*)
3	**5a**	**7a**	*SS*-**6a**	$MgBr_2$	92	77 (*R*)
4	**5a**	**7a**	*SS*-**6a**	MgI_2	88	61 (*R*)
5	**5a**	**7a**	*SS*-**6b**	MgI_2	88	82 (*R*)
6	**5a**	**7a**	*SS*-**6c**	MgI_2	88	47 (*S*)
7	**5a**	**7a**	*RR*-**6c**	$MgBr_2$	84	32 (*R*)
8	**5a**	**7a**	*SS*-**6c**	$Zn(OTf)_2$	88	61 (*S*)
9	**5b**	**7c**	*RR*-**6c**	$Zn(OTf)_2$	66	72 (*R*)
10	**5b**	**7b**	*RR*-**6c**	$Zn(OTf)_2$	90	82 (*R*)
11	**5b**	**7b**	*RR*-**6c**	$Mg(OTf)_2$	60	55 (*R*)
12	**5b**	**7b**	*RR*-**6c**	$Mg(ClO_4)_2$	71	64 (*R*)
13	**5b**	**7b**	*SS*-**6a**	$MgBr_2$	78	82 (*R*)
14	**5b**	**7b**	*SS*-**6b**	MgI_2	88	74 (*R*)

[a] For standard experimental conditions, see supporting information. [b] One equivalent of the ligand was used. [c] One equivalent of the Lewis acid was used. [d] Yields are for column or preparative TLC purified material. [e] Enantiomeric excess was determined by chiral HPLC analysis. The absolute stereochemistry of the product was determined by independent synthesis, X-ray analysis of a derivative, or hydrolysis (see supporting information for details).

Table 2. Enantioselective Radical Additions using Catalytic Chiral Lewis Acid[a]

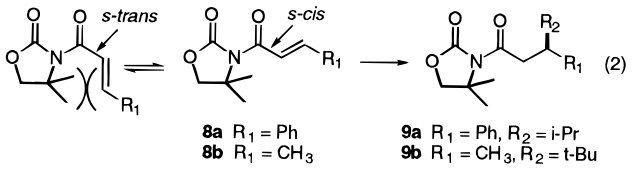
entry	substrate	product	Lewis acid/ligand	LA[b] (equiv)	yield (%)[c]	ee (%)[d]
1	**5a**	**7a**	MgI_2/**6b**	1.0	88	82
2	**5a**	**7a**	MgI_2/**6b**	0.5	86	79
3	**5a**	**7a**	MgI_2/**6b**	0.2	86	67
4	**5a**	**7a**	MgI_2/**6b**	0.05	57	40
5	**5b**	**7b**	MgI_2/**6b**	1.0	88	74
6	**5b**	**7b**	MgI_2/**6b**	0.2	73	66
7	**5b**	**7b**	$Zn(OTf)_2$/**6c**	1.0	90	82
8	**5b**	**7b**	$Zn(OTf)_2$/**6c**	0.2	71	70

[a] For experimental conditions, see supporting information. [b] A 1:1 ratio of Lewis acid to ligand was used. [c] Yields are for column or preparative TLC purified material. [d] Enantiomeric excess was determined by chiral HPLC analysis.

decrease of enantioselectivity (entry 3). A similar trend was also observed for reactions with **5b** (compare entry 5 with 6 and 7 with 8). It is interesting to note that measurable enantioselectivity was obtained for **5a** with 5 mol % of the catalyst (entry 4). The chemical yields for reactions with <10 mol % catalyst loading were generally lower and the reaction took a longer time for completion.

Radical additions to **8a** and **8b** were examined, and the product configuration was established (eq 2). Addition of isopropyl radical to **8a** gave **9a** [1 equiv of $MgBr_2$, ligand (*R,R*)-**6c**] in 90% chemical yield and 52% ee with the product possessing *R* configuration (compared to 32% ee (*R*) with substrate **5a**). Similarly **8b** gave **9b** [1 equiv of $Zn(OTf)_2$, ligand (*R,R*)-**6c**] in 72% ee with *R* absolute configuration (compared to 82% ee (*R*) with substrate **5b**). Since **8a** and **8b** cannot adopt an *s-trans* conformation due to steric constraints[11] and these substrates provide products of the same absolute configurations as **5a** and **5b**, these results suggest that all of these substrates react via a transition state derived from the *s-cis* rotamer.

(11) Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436.



A tetrahedral zinc model was used to explain the enantioselectivities observed in the allylation of radicals derived from **5c** using zinc Lewis acid−**6c** combinations.[4] The interpretation of the results on β selectivity reported here are not as straightforward, and two models are minimally required since aryl and alkyl substituents on **6** give products having different configurations. Studies with **8** suggest a transition state having *s-cis* alkene conformation, but the issues of complex geometry and one-point or two-point binding of substrate are unresolved. If one assumes two-point binding of **5** in the transition state, then the results of addition to complexes that include ligands bearing aryl substituents such as **6c** can be understood based on a planar (or equivalent) arrangement of ligand **6c** and substrate **5**. This could be achieved within a four-, five-, or six-coordinate complex of the Lewis acid, substrate, and counterions (i.e., halide, triflate).[12]

The results of addition to complexes that include ligands bearing alkyl substitutents (**6a** or **6b**) can be understood based on a tetrahedral (or equivalent) arrangement of ligand and substrate. In either case, radical addition takes place via a transition state resulting from attack on the less-hindered alkene face giving the product with the observed absolute configuration.[13] We suggest that a ligand−substrate complex derived from ligands **6a** and **6b** is more crowded than one formed from **6c** due to the increased size of the alkyl substituents compared to the planar aryl groups, and for this reason, the geometry of the complex is ligand-dependent. Experiments to improve and gain a better insight into the enantioselective process are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for compounds **5**−**9** (13 pages) are included. See any current masthead for ordering and Internet access instructions.

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(12) Four-coordinate planar, five-coordinate square pyramidal, or octahedral with axial counterions, shown as structure **10**, can provide "planar" equivalent complexes of substrate and ligand.

(13) Four-coordinate tetrahedral, five-coordinate square pyramidal or trigonal bipyramidal (shown as structure **11**), or octahedral with counterions adopting a *cis* arrangement all can provide "tetrahedral" equivalent complexes of substrate and ligand. For the octahedral complex, the counterions adopt one of the two possible axial−equatorial arrangements due to steric constraints. Support for this model comes from Corey's work on Diels−Alder cycloadditions (ref 2c). Also see: Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron Lett.* **1996**, *37*, 3027.