Pergamon

Tetrahedron Letters, Vol. 38, No. 12, pp. 2067-2070, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00295-5

Substrate Steric Effects in Enantioselective Lewis Acid Promoted Free Radical Reactions

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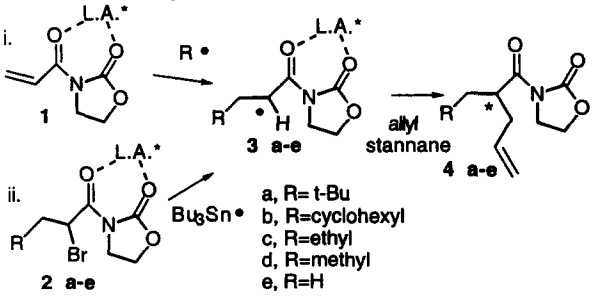
Summary: *High to moderate levels of stereoselectivity are observed in chiral Lewis acid promoted allyl transfer reactions of radicals substituted α to oxazolidinones. Similar selectivity patterns are observed for reactions in which such radicals are generated by addition to an acrylimide or by reactions in which the same radical is generated from the corresponding bromide. A good correlation is obtained for selectivity vs. the Taft steric parameter for the alkyl group attached to the radical center.* © 1997 Elsevier Science Ltd.

Recent reports indicate that radical-molecule reactions can be achieved with high diastereoselectivity[1] and enantioselectivity.[2] Chiral auxiliary control of radical addition and atom transfer reactions is well established and recently, examples of addition reactions promoted by chiral Lewis acids (L.A.*) have been reported to proceed with significant control of configuration in newly-formed stereogenic centers. Lewis acid promoted addition reactions have been reported in which a chiral Lewis acid complexes to a radical undergoing addition to an alkene trap, see Scheme 1a. More recently, addition of radicals to alkenes complexed to chiral Lewis acids (see Scheme 1b) have been achieved[3] with enantiomeric excesses of over 95% at "catalyst" levels of 10%.[4] These successful examples of enantioselective radical transformations utilize complexes of acyl oxazolidinones, bisoxazoline chiral ligands such as **5**[5] and magnesium and zinc Lewis acids.

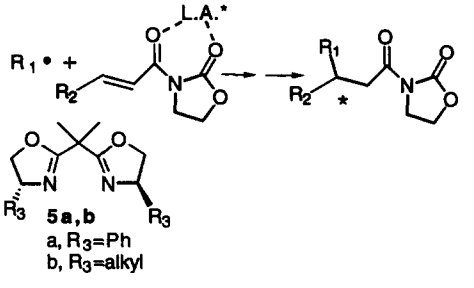
While enantioselective radical transformations have been recently established, mechanistic studies on the nature of these processes are needed to provide a fundamental understanding of the factors that are important in determining selectivity. We report here a comparison of enantioselectivity in reactions in which a radical complexed to a chiral Lewis acid is generated by two independent routes as

Scheme 1. Lewis Acid Promoted Enantioselective Radical Additions

a.) Lewis acid complexed to radical



b.) Lewis acid complexed to alkene



outlined in Scheme 1a (routes i. and ii.). These studies show that the steric bulk of the R-CH_2- group attached to the radical **3** is important in determining the selectivity of the subsequent allyl transfer reaction.

The bromides **2a-d** were prepared by standard methods.[6] Reaction of **2** [7] (20 mM) in methylene chloride/pentane with allyltributylstannane at -78° C in the presence of zinc triflate and the chiral bidentate ligand **5a**[8] gives a clean conversion to the adduct **4**[6] with isolated yields of between 60 and 90% if triethylborane[9] is used as a low temperature initiator (see Table 1). Analysis of the starting bromide by chiral HPLC after partial reaction indicates that no kinetic resolution occurs during the reaction. Alkyl iodides have also been used with alkene **1** in the addition sequence to give the same products **4** (with the same predominant enantiomer) under comparable reaction conditions. Without the chiral ligand and zinc triflate or without the initiator, the reaction gives only low conversion to the adduct **4** at –78°C. Bisoxazoline **5a** with the *R,R* configuration gives products **4a,b** with *R* configuration while **4c,d** are formed with *S* configuration because of a change in group priorities.

Table 1. Product Enantiomeric Excess for Reactions of R-I/1 or 2 a-d with Allyl Stannane in the Presence of Zinc Triflate and Bisoxazoline 5a at -78°C.[a,b]

entry	Precursor	Lewis acid eq.	R=methyl	R=ethyl	R=c-hexyl	R=t-butyl
1	**1**	0.2	22	30	34	54
2	**1**	0.6	56	62	76	84
3	**1**	1.0	61	69	78	90
4	**1**	2.0	67	75	80	90
5	**2**	0.2	16	22	26	52
6	**2**	0.6	25	36	43	64
7	**2**	1.0	42	50	58	74
8	**2**	2.0	46	53	64	76

a. See Scheme 1 for a description of the transformation. b. Yields of isolated products were from 60-90%.

Selectivity generally increases with increasing Lewis acid equivalents (entries 1 to 4) and the addition/trapping sequence (route i.) generally gives higher product enantiomeric excess than the corresponding reactions starting from the bromide precursor (*cf.* entries 1-4 with entries 5-8). Furthermore, product selectivity correlates with the R group, t-Bu>c-hexyl>ethyl>methyl. The data in Table 1 may be analyzed by plotting log (*R/S*)[10] vs. the modified Taft steric parameter E'_S[11] for the group R-CH_2- attached to the radical center in **3**. This analysis gives good correlations for all reactions carried out by the same route and with the same equivalents of Lewis acid (see Figure 1). Product enantioselectivity at a given level of Lewis acid depends on the precursor, routes i. or ii., while selectivity for both routes responds to substituent steric effects in an analogous way. This suggests that the same reactive intermediate, **3**, is involved in both processes while the extent to which this intermediate participates in the reaction depends on the precursor.

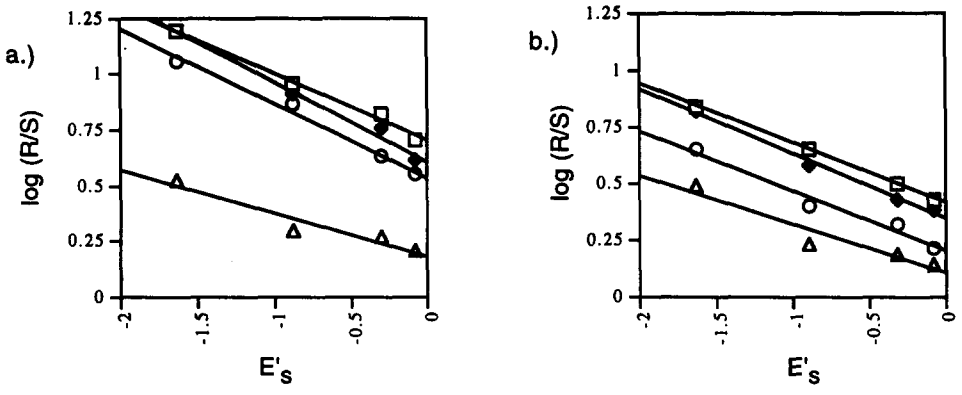


Figure 1. a.) Plot of log(R/S) of product **4** starting from **1** vs. E'_s for group R-CH_2- attached to radical **3.** b.) Plot of log(R/S) of product **4** starting from **2** vs. E'_s for group R-CH_2- attached to radical **3.** Open triangles=0.2 eq. Lewis acid to alkene, open circles=0.6 eq., filled diamonds=1.0 eq., open squares=2.0 eq.

A mechanism consistent with these observations suggests that an equilibrium between the reactant alkene **1** or bromide **2** and Lewis acid precedes formation of the radical **3** (by addition or bromine atom transfer). The alkene **1** is apparently a better Lewis base than the bromides **2a-d**. Furthermore, the data suggest that a non-selective (background) conversion to product competes with the Lewis acid promoted reaction. The non-selective process is more important for reactions proceeding from the bromide (route ii.) than it is for the addition-trapping sequence (route i.). This is presumably due to a favorable **1-L.A.*** equilibrium and the fact that the radical addition is more subject to Lewis acid catalysis than is the bromine atom transfer. Substantial conversion of **2** to **4** does occur in the presence of initiator but in the absence of Lewis acid.

Radicals substituted α to esters or amides have preferred confomations that minimize allylic strain as shown in Figure 2.[1,12] Thus, radicals such as **3** normally prefer the "*Z*" C(O)-Cα conformer while the Cα–Cβ bond minimizes allylic strain by adopting the two confomations shown in Figure 2b. Complexation of the radical with the chiral Lewis acid may alter the conformational equilibria shown in Figure 2 and makes the two conformations shown in Figure 2b diastereomeric, favoring a transition state derived from one of the diastereomers. Wrong-face attack on the chiral Lewis acid-radical complex is more likely for smaller R groups such as methyl and ethyl and stereoselectivity is therefore

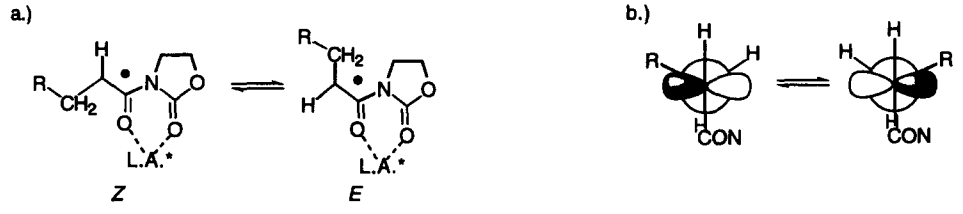


Figure 2. a.) C(O)-Cα confomations of radical **3.** b.) Cα–Cβ confomations of radical **3.**

attenuated according the the Taft steric parameter for addition reactions involving these radicals.

A model for the Lewis acid promoted allyl transfer reaction must take into account the effect of complex geometry,[2] C(O)-Cα conformation,[2] and Cα-Cβ conformation, in determining product configuration and optical purity. Nevertheless, the data for the reaction promoted by zinc triflate Lewis acid and bisoxazoline **5a** suggest that the transformation is dependent on substituent steric effects of the *achiral* radical component of the complex and indicate that exploration of these effects is appropriate in investigations of other enantioselective radical processes. In support of the proposal that the steric size of the β R group is important in determining stereoselectivity in this system (see Figure 2b), reaction of the bromide **2e** in which R=H under the standard reaction conditions gives product **4e** that is racemic.[13]

Acknowledgments: NSF support and the receipt of an NIH MERIT Award is gratefully acknowledged. We thank Dr. Mukund Sibi for extensive and infomative discussions.

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13. Experiments to suppress the non-selective background reaction and to investigate analogous transformations involving other chiral Lewis acids are ongoing and will be reported in due course.

(*Received in USA* 3 *January* 1997; *revised* 7 *February* 1997; *accepted* 9 *February* 1997)