Lewis Acid-Enhanced Reactivity of α,β-Unsaturated Ester and Amide toward Radical Addition

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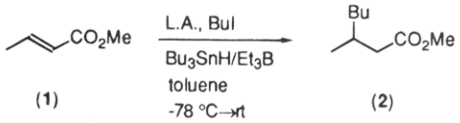
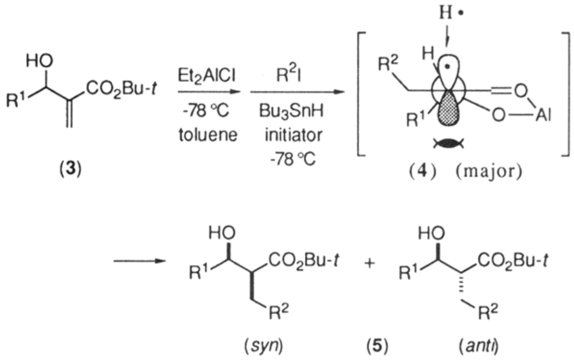
Since alkyl radicals which are most frequently utilized in organic synthesis are generally of a nucleophilic character,[1] their addition to olefinic substrates is enhanced by electron-withdrawing substituent(s) on the olefinic linkage.[2,3] Thus, a synthetic design to improve reactivity of the substrates (hence, to increase the product yields) is usually made by placing an effective electron-withdrawing group in the substrate or by increasing the number of such substituents. Among olefinic compounds having an electron-withdrawing group, α,β-unsaturated esters and amides belong to a group of relatively unreactive substrates in radical reactions. In fact, we encountered a low product yield in performing alkyl radical addition to certain α,β-unsaturated esters (*vide infra*). We conceived that prior complexation of a Lewis acid (LA) to the carbonyl group of an unsaturated ester would decrease the electron density of its olefinic moiety and thus function to increase the electron-withdrawing properties of this substituent. Although this methodology for activation of α,β-unsaturated carbonyl compounds is well established in Diels−Alder reactions[4] and in ionic reactions such as 1,4-addition of nucleophiles,[5] to our knowledge, radical acceptor activation by LA has not been investigated in organic synthesis.[6,7] Herein we would like to disclose our findings on the use of LA for the above purpose.

The effect of LA was surveyed in butyl radical addition to methyl crotonate (**1**), which afforded the product **2** in only a trace amount (<1%) under the conditions in eq 1 [BuI (3 equiv), Bu_3SnH (3 equiv), Et_3B (0.3 equiv)][8] without LA. However, the product yield was increased with LA (1.5 equiv) under the same reaction conditions in the following order: $TiCl_4$, <2%; $BF_3{\cdot}OEt_2$, 5%; Bu_2BOTf, 7%; Et_2AlCl, 18%; $EtAlCl_2$, 33%. These results show that aluminum chlorides are the reagent of choice for this purpose.



(1)

This finding is readily extended to synthetic applications. When a mixture of α-methylene ester **3**[9a] and BuI (3 equiv) was treated with Bu_3SnH (3 equiv) under standard reaction conditions (eq 2 and entries 1 and 2 in Table 1), the product yields were around 30% after virtually all of the added Bu_3SnH had been consumed by simple reduction of BuI. However, prior addition of 1 equiv of Et_2AlCl improved the (isolated) yield to 76% (entry 3 in Table 1).[10] This phenomenon is reasonably general for a variety of starting materials, giving consistent yields in the range of 51−73% (entries 3−6). One of the advantages of radical reactions is compatibility with functional groups, and this is preserved also in the LA-promoted radical reaction. Thus, the 2-siloxyethyl group could be transferred to **3** as well (entry 4), which confirmed that the alkyl transfer is actually a radical-mediated one rather than an anionic transfer likely via organoaluminum species. The diastereoselectivity was also improved in the case where a LA was added (entries 1−3). This may come from a tighter chelation between the substrate and the aluminum atom (see structure **4**) than the corresponding hydrogen bonding in the absence of the LA. The preference for *syn* selectivity was explained by the delivery of hydrogen radical from the less hindered side of the intermediate radical **4** as shown in eq 2.[11] That the decrease in the steric bulk of R^1 (Et → Me, entries 1 and 6) as well as the increase in the size of R^2 (Bu → $TBSO(CH_2)_2$ → $c\text{-}C_6H_{11}$, entries 3−5) decreased the *syn* selectivity is in accord with the proposed intermediate **4**.



(2)

The change in chemoselectivity resulting from complexation of a LA to the substrate demonstrates another

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(1) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 715.

(2) Reviews: Smadja, W. *Synlett* **1994**, 1 and other review articles cited therein.

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(6) LA's have been utilized in radical reactions to direct a stereochemical outcome, see: (a) Urabe, H.; Kobayashi, K. Sato, F. *J. Chem. Soc., Chem. Commun.*, in press. (b) Renaud, P.; Bourquard, T.; Gerster, M.; Moufid, N. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1601. (c) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtaka, Y.; Yamamura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455. (d) Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. *J. Org. Chem.* **1994**, *59*, 3547. (e) Nagano, H.; Kuno, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 987. (f) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421. (g) Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464. (h) Clive, D. J.; Postema, M. H. D. *J. Chem. Soc., Chem. Commun.* **1993**, 429. (i) Rück, K.; Kunz, H. *Synthesis* **1993**, 1018. (j) Renaud, P.; Björup, P.; Carrupt, P.-A.; Schenk, K.; Schubert. S. *Synlett* **1992**, 211. (k) Guindon, Y.; Lavallée, 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) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300.

(7) For a relevant observation, see ref 6m. For study on activation of radical acceptors with LA in the field of polymer science, see: Afchar-Momtaz, J.; Polton, A.; Tardi, M.; Sigwalt, P. *Eur. Polym. J.* **1985**, *21*, 1067. For activation of radicals (rather than acceptor) by complexation with LA, see: Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493. Ref 6d.

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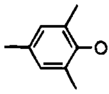
Table 1. Lewis Acid-Enhanced and -Stereocontrolled Addition of Bu•/H• to α,β-Unsaturated Esters[a]

entry	3/R^1	R^2	Et$_2$AlCl[b]	5		
					yield (%)[c]	*syn/anti*[d]
1	Et (**a**)	Bu	−	**a**	(34)	65:35
2		Bu	−	**a**	31	70:30
3		Bu	+	**a**	76 (82)	87:13
4		TBSO(CH$_2$)$_2$	+	**b**	60	75:25[e]
5		*c*-C$_6$H$_{11}$	+	**c**	73	60:40[e]
6	Me (**b**)	Bu	+	**d**	51 (61)	75:25

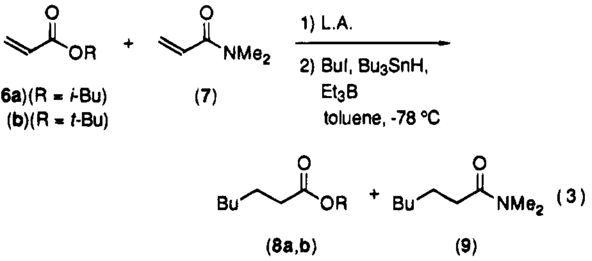
[a] See eq 2. Reactant ratio of $3/Et_2AlCl/R^2I/Bu_3SnH/Et_3B$ = 1:1:3:3:0:3. Concentration of **3**: *ca.* 0.1 M. The reactions, which were terminated after the consumption of Bu_3SnH, were performed in C_6H_6 at reflux with AIBN as initiator (entry 1) or in toluene at −78 °C with Et_3B (others). [b] Sign +: added, −: not added. [c] Isolated yields. Yields determined by ^{1}H NMR analysis are in parentheses. [d] Determined by ^{1}H or ^{13}C NMR analysis of a crude or a roughly purified product. For structural assignment, see ref 10. [e] The structures were assigned by analogy.

Table 2. Change in Chemoselectivity of the Radical Addition in the Presence of a Lewis Acid[a]

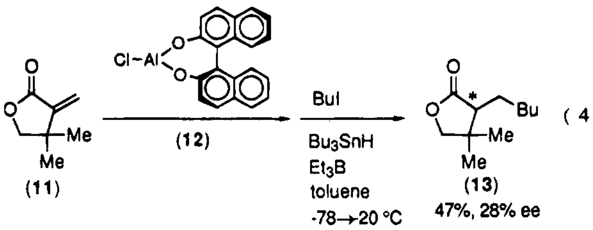
Entry	Starting mixture	L.A.	Yield (%)[b,c]	8/9[c]	8a/b[c]
1	**6a+7**	None	57	80:20	
2	"	 $-O)_2AlCl$ (**10**)[d]	83	42:58	
3	**6b+7**	None	41	68:32	
4	"	**10**	78	24:76	
5	**6a+b**	None	66		58:42
6	"	**10**	98		79:21

[a] See eq 3. Reactant ratio, see text. Concentration of each substrate: *ca.* 0.1 M. [b] Combined yield of **8+9** or **8a+b**. [c] Determined by ^{1}H NMR and/or GC analysis. [d] Prepared *in situ* from Et_2AlCl and the phenol.

use of LA-enhanced radical reaction. The α,β-unsaturated ester is a more reactive acceptor than the corresponding amide, because the former has a more electron-deficient enone moiety. In fact, the relative reactivity between methyl acrylate and *N*-acryloylpiperidine toward cyclohexyl radical has been kinetically determined to be 3:1.[12] In accord with this, addition of butyl radical to a mixture of α,β-unsaturated ester **6a** and amide **7** under standard conditions [BuI (1.1 equiv), Bu_3SnH (1 equiv), Et_3B (0.1equiv)] without LA afforded **8a** and **9** in a ratio of 80:20 (eq 3 and entry 1 in Table 2). However, the same reaction of **6a** and **7** in the presence of a LA such as **10**[13] (1 equiv) increased the proportion of **9** (**8a/9** = 42:58, entry 2).[10] This should arise from the fact that the amide substrate which was preferentially complexed by the LA due to its electron-rich character relative to the ester now becomes a less eletron-rich double bond. This tendency was more evident in the reaction of **6b** and **7** where a combination of sterically hindered *tert*-butyl ester **6b** and LA **10** forced the more selective complexation of **10** to **7**, eventually reversing the ratio of **8b/9** (entries 3 and 4). This rationale was reinforced by the fact that the less hindered isobutyl ester **6a** became more reactive than *tert*-butyl ester **6b** in the presence of **10** (entries 5 and 6). It should be noted that the total product yield of **8+9** or **8a+b** also increased in the presence of the LA (entries 2, 4, and 6).



Coordination of optically active LA **12**[13−15] to an α-methylenebutyrolactone **11**[9bc,16] promoted the butyl radical addition (by TLC analysis). Furthermore, it effected an asymmetric hydrogen radical transfer from Bu_3SnH to the resultant radical α to the lactone carbonyl to give optically active **13** as shown in eq 4.[10] A low yet measurable asymmetric induction was observed in **13**, which is the first example of asymmetric radical reaction controlled by a chiral LA. The dual role of the LA will be useful in the synthetic point of view.



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Supplementary Material Available: Typical procedures for the preparation of **5a**, **8b+9**, and **13**, structural determination and physical properties of **5a−d** and **13** (8 pages).

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(10) Experimental details are described in the supplementary material.

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(16) This substrate was chosen due to the ease of determination of ee in product **13** by ^{1}H NMR chiral shift study.