Zinc Chloride as a Radical Initiator as Well as a Chelating Agent

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There has been an increase in interest in the problem of stereocontrol in reactions involving acyclic radicals.[1] It has been reported that chirality transfer is accomplished successfully using chiral auxiliaries[2] or stereogenic centers adjacent to the radical center.[3,4] More recently, stereoselectivity enhancement has been observed in radical reactions based on complexation of the radical intermediate with Lewis acids.[5] We report that zinc chloride acts as a *radical initiator* as well as a chelating agent in certain radical reactions of allylstannanes.[6]

Hamon and co-workers reported that 8-phenylmethyl *N*-Boc-2-bromoglycinate reacts with allylic stannanes to give the corresponding allylated products, without assistance of Lewis acids, with high diastereoselectivity.[2e] It occurred to us that the α-bromoglycine derivative having a chiral auxiliary on the nitrogen atom would also produce high diastereoselectivity in the free-radical allylation with allylstannanes. Treatment of **1a**, bearing

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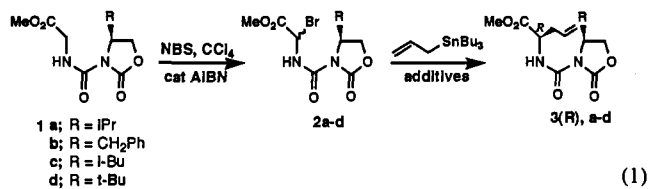
the Evans oxazolidinone chiral auxiliary, with NBS in the presence

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(1) (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.
(2) (a) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791 and references cited therein. (b) Porter, N. A.; Wu, W.-X.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 707 and references cited therein. (c) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (d) Hamon, D. P. G.; Razzino, P.; Massy-Westtropp, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 332. (e) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 722. (f) Stack, J. G.; Curran, D. P.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1991**, *113*, 5918. (g) 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. (h) Porter, N. A.; Bruhnke, J. D.; Wu, W.-X.; Rosenstein, I. J.; Breyer, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7788.
(3) (a) Hart, D. J.; Huang, H.-C. *Tetrahedron Lett.* **1985**, *26*, 3749. (b) Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412. (c) Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507. (d) Crich, D.; Davies, J. W. *Tetrahedron* **1989**, *45*, 5641. (e) Ogura, K.; Yanagissawa, A.; Fujino, T.; Takahashi, K. *Tetrahedron Lett.* **1988**, *29*, 5387. (f) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205. (g) Vassen, R.; Runsink, J.; Schaarf, H.-D. *Chem. Ber.* **1986**, *119*, 3492. (h) Henning, R.; Urbach, H. *Tetrahedron Lett.* **1984**, *24*, 5343. (i) Bullard, M.; Zeitz, H.-G.; Giese, B. *Synlett* **1991**, 423. (j) Giese, B.; Bullard, M.; Zeitz, H.-G. *Synlett* **1991**, 425. (k) Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* **1992**, 441. (l) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Am. Chem. Soc.* **1988**, *110*, 617.
(4) (a) Guindon, Y.; Anderson, P. C.; Yoakim, C.; Girard, Y.; Berthiaume, S.; Morton, H. E. *Pure Appl. Chem.* **1988**, *60*, 1705. (b) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallee, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845. (c) Guindon, Y.; Lavallee, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27.
(5) (a) Renard, P.; Ribezzo, M. *J. Am. Chem. Soc.* **1991**, *113*, 7803. (b) Guindon, Y.; Lavallee, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701. For Lewis acid-mediated cyclization of aminyl radicals, see: Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493.
(6) For ordinary free-radical reactions of allylstannanes, see: Kosugi, M.; Kurino, K.; Takayama, K.; Mogita, T. *J. Organomet. Chem.* **1973**, *56*, c11. Grignon, J.; Pereyre, M. *J. Organomet. Chem.* **1973**, *61*, c33. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.

Table 1. Zinc Chloride-Accelerated Radical Allylation of **2a**[a]

entry	Lewis acid (equiv)	other additive (reactn, condn)	*t* (°C)	yield of **3a**[b]
1	none	none	−78	0
2	none	none	−50	11
3	none	AIBN (*hν*)	−50	25
4	none	galvinoxyl	−50	0
5	ZnCl₂·OEt₂ (2)	none	−78	40
6	ZnCl₂·OEt₂ (2)	AIBN (*hν*)	−78	60
7	ZnCl₂·OEt₂ (2)	galvinoxyl	−78	0

[a] To a CH₂Cl₂ solution of **2a** (0.5 mol) were added ZnCl₂·OEt₂ (2.2 M in CH₂Cl₂, 1 mmol) (in the cases of entries 5–7) and allyltin (1 mmol) at −78 °C. The reactions (entries 1, 5–7) were quenched with MeOH–H₂O at −78 °C after 10 min. AIBN (10 mol %) or galvinoxyl (5 mol %) was used. The reaction was conducted at −50 °C and quenched at this temperature after 10 min (entries 2–4). [b] After quenching of the reaction, the methoxy-substituted glycine derivative of **2a** was afforded via substitution of the carbon–bromine bond with methanol, along with **3a**.

of 10 mol % AIBN under reflux of CCl₄ afforded a 1:1 diastereoisomeric mixture of **2a** in essentially quantitative yield.[7] Without further purification, **2a** was treated with allyltributyltin under various conditions (Table 1) (eq 1). At −78 °C, the reaction did not occur (entry 1), whereas it started at −50 °C without additives (entry 2).

The presence of AIBN (10 mol %) accelerated the allylation at −50 °C (entry 3), but the presence of galvinoxyl (5 mol %) halted the reaction completely (entry 4). Accordingly, it is clear that the allylation proceeds through a radical mechanism. The allylation at −78 °C was dramatically accelerated using 2 equiv of ZnCl₂·OEt₂ (cf. entry 5 vs 1). The use of 0.1 equiv of ZnCl₂·OEt₂ also accelerated the reaction very much, but the diastereoselection was enhanced by using 2 equiv of the Lewis acid, as mentioned below. The allylation in the presence of ZnCl₂·OEt₂ was accelerated by AIBN (10 mol %) and was stopped completely by galvinoxy (5 mol %) (entries 6 and 7). Consequently, zinc chloride–diethyl ether acts as a radical initiator in the reaction of **2a** with allylstannanes. To the best of our knowledge, this is the first example of *the radical reaction of allylstannanes* in which the C–C bond formation is initiated by a Lewis acid, such as ZnCl₂·OEt₂.[8] The ethers of ZnBr₂ and ZnI₂ also accelerated the reaction, whereas the acceleration was not observed in the case of BF₃·OEt₂ and SnCl₄.[9]

We next investigated the diastereoselectivities of the allylation in the presence of ZnCl₂·OEt₂ (Table 2). When the reaction was stopped at the early stage (10 min), the highest selectivity was obtained (entry 3), whereas the diastereoselectivity was somewhat diminished at higher conversion (entry 1). Perhaps this decrease is due to intervention of a nonradical bypass to **3a**; the ZnCl₂ mediated allylation of imine **4** (Chart 1), which may be formed in small amounts under the reaction conditions. Actually, treatment of **2a** with triethylamine produced **4** quantitatively at −78 °C, which reacted with allyltin in the presence of 2 equiv ZnCl₂·OEt₂ to give a 60:40 mixture of (*R*)-**3a** and (*S*)-**3a**.[10] It

(7) Simple bromination of **1a** with Br₂ also gave **2a** in essentially quantitative yield. The solvent and HBr generated were removed by water aspirator. The α-bromoglycine **2a**, prepared by the simple bromination, exhibited the same reactivity and selectivity as that prepared from the NBS bromination.
(8) It is well known that triethylborane (a sort of Lewis acid) acts as a radical initiator, but the radical reaction begins by forming ethyl radical upon oxidation of Et₃B with O₂. (a) Suzuki, A.; Nozawa, S.; Itoh, M.; Brown, H. C.; Kabalka, G. W.; Holland, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 3503. (b) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J.-L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 1647. In fact, the allylation of **2a** was initiated also by 0.1 equiv of Et₃B. More recently, Otera and co-workers reported Lewis acid-mediated electron transfer in the Mukaiyama–Michael reaction of ketene silyl acetals. (c) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H.; Fukuzumi, S. *J. Am. Chem. Soc.* **1991**, *113*, 4028. Guindon and co-workers have claimed radical mechanisms in the reduction of α-iodo esters with Bu₃SnH in the presence of MgBr₂ and related Lewis acids (ref 5b).
(9) The yield of **3a** decreased in the presence of such strong Lewis acids.

Table 2. Diastereoselective Allylation of **2** in the Presence of $ZnCl_2 \cdot OEt_2$

entry	α-bromoglycine **2**	Lewis acid (equiv)	reactn conditions	yield of **3** (%)	isomer ratio (R)-**3**:(S)-**3**
1	**2a**	$ZnCl_2 \cdot OEt_2$ (2)	−78 °C, 1 h	85	87:13
2	**2a**		−78 °C → rt[a]	56	52:48
3	**2a**	$ZnCl_2 \cdot OEt_2$ (2)	−78 °C, 10 min	40	93:7
4	**2a**	$ZnCl_2 \cdot OEt_2$ (0.1)	−78 °C, 1 h	65	67:33
5	**2a**		AIBN (0.1 equiv), benzene, 80 °C, 1 h	66	52:48
6	**2b**	$ZnCl_2 \cdot OEt_2$ (2)	−78 °C → rt	92	74:26
7	**2c**	$ZnCl_2 \cdot OEt_2$ (2)	−78 °C → rt	83	60:40
8	**2d**	$ZnCl_2 \cdot OEt_2$ (2)	−78 °C → rt	∼100	70:30

[a] rt, room temperature.

Chart I
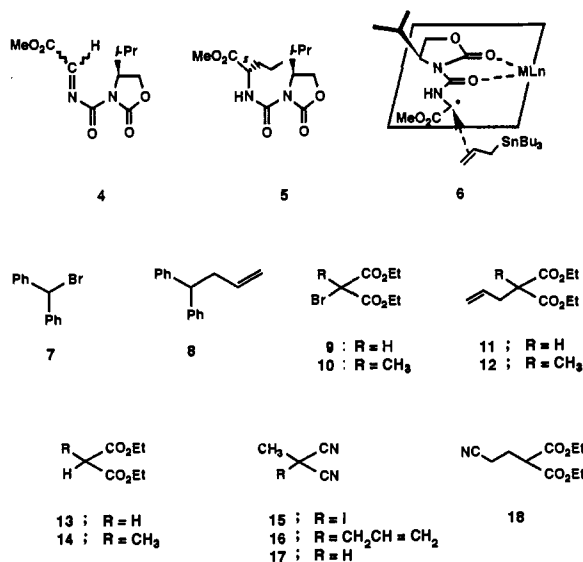
is interesting that the Lewis acid-mediated allylation of the imine **4** produces lower diastereoselectivity than the radical allylation of **2a**. The reactions of **2a** with allyltin without any additives (entry 2), in the presence of 0.1 equiv of $ZnCl_2 \cdot OEt_2$ (entry 4), or in the presence of AIBN (entry 5) afforded lower diastereoselectivities. The reactions of **2b–d** proceeded very smoothly, but the stereoselectivities were lower than those of **2a** (entries 6–8). Metallyltributyltin reacted similarly with **2a** in the presence of 2 equiv of $ZnCl_2 \cdot OEt_2$. Instead of the oxazolidinone auxiliary, we prepared the α-bromoglycine having the Oppolzer's bornane-sultam, but the allylation proceeded with lower diastereoselectivities.

The reaction of (S)-norvaline with SO_2Cl_2 in MeOH gave the hydrogen chloride salt of (S)-norvaline methyl ester, which was converted to **5** (Chart 1) upon treatment with 4(S)-N-(chloroformyl)-4-isopropyl-2-oxazolidinone.[11] Hydrogenation of (S)-**3** in methanol in the presence of $Pd(OH)_2$ catalyst gave **5**, and thus the absolute stereochemistry of **3a** was determined unambiguously by comparing the hydrogenation product with the authentic sample. Since the major product of the allylation of **2a** is (R)-**3a**, the reaction presumably proceeds through the chelated transition state **6** (Chart 1).

It is now clear that ZnX_2 act as a radical initiator as well as a chelating agent in the reaction of **2** with allyltributyltin. The radical generated from **2a** is stabilized by the capto-dative substituents.[12] To clarify whether $ZnCl_2$ works as a radical initiator even in the case of rather simple substrates, we investigated the allylation of reactive halides with allyltributyltin in the presence of $ZnCl_2 \cdot OEt_2$. The allylation proceeded in high

yields in cases of tertiary, allylic, α-alkoxy, and sec-benzyl halides, whereas the reaction did not occur with primary and secondary halides. For example, the reaction of **7** with allyltin in the presence of 0.1 (or 1.0) equiv of $ZnCl_2 \cdot OEt_2$ (at −78 °C to room temperature) gave **8** in 91% yield (Chart 1). Without $ZnCl_2 \cdot OEt_2$, no reaction took place. Treatment of **7** with 1.0 equiv of $ZnCl_2 \cdot OEt_2$ afforded diphenylmethane (49%) along with benzhydryl chloride (9%), whereas no reaction occurred by the use of $BF_3 \cdot OEt_2$ instead of $ZnCl_2 \cdot OEt_2$. The above results suggest that a radical process may be involved in the $ZnCl_2$-mediated allylation reaction of reactive halides.

However, it is well known that $TiCl_4$-mediated reaction of reactive halides with allyltrimethylsilane proceeds through carbocation intermediates to give the corresponding allylated derivatives.[13] One can still be suspicious that a similar cationic mechanism could be involved in the allyltin reactions.[14] The radicals, derived from bromomalonate and bromomalononitrile, are known to react well in radical processes, but a cationic pathway would be precluded. The reaction of **9** with allyltributyltin (1.5 equiv) in the presence of $ZnCl_2 \cdot OEt_2$ (1 equiv) in CH_2Cl_2 at room temperature gave **11** (30%) and **13** (25%) (Chart 1). No reactions took place between allyltributyltin and **9** in the absence of $ZnCl_2 \cdot OEt_2$ nor between allyltributyltin and $ZnCl_2 \cdot OEt_2$ without **9**. The zinc chloride-mediated allylation of **10** under similar conditions afforded **12** in higher yield: **12** (59%) and **14** (0%) (Chart 1). This is reasonable since the radical generated from **10** is stabilized, in comparison with the radical from **9**, by the capto-dative substituents. The reaction of **15** with allyltributyltin (1.5 equiv) in the presence of $ZnCl_2 \cdot OEt_2$ (1.0 equiv) in CH_2Cl_2 at −78 °C produced **16** (36%) and **17** (44%) (Chart 1). Further, we examined the radical trap reaction using acrylonitrile and bromomalonate. The radical pathway should allow for the formation of **18** (Chart 1), while it should not be formed via any sort of cationic pathway. The reaction of **9**, allyltin, and acrylonitrile (10 equiv) in the presence of $ZnCl_2 \cdot OEt_2$ at 0 °C afforded a mixture of **13** (13%), **18** (16%), and **9** (4%) without forming **11**. On the other hand, the treatment of **9** with acrylonitrile in the presence of $ZnCl_2 \cdot OEt_2$ under similar observations resulted in recovery of **9**, indicating that the presence of allyltin is essential to formation of **18**.[15] Consequently, it is clear that the radical pathway is involved in the $ZnCl_2$-mediated reaction of allyltributyltin with certain reactive halides.

Supplementary Material Available: Synthesis of the α-bromoglycine derivatives, experimental datails of the allylation reactions, and analytical data for all products (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) For the reaction of α-imino esters with organometallics, see: Yamamoto, T.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.

(11) See supplementary material.

(12) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917.

(13) Fleming, I.; Paterson, I. *Synthesis* **1979**, 446. Hosomi, A.; Imai, T.; Endo, M.; Sakurai, H. *J. Organomet. Chem.* **1985**, *285*, 95. Yamamoto, Y.; Sasaki, N. In *Stereochemistry of Organometallic and Inorganlic Compounds*; Bernal, I., Ed.; Elsevier: Amsterdam, 1989; Vol. 3, p 365.

(14) For previous ZnX_2-mediated reactions of allyltin with allyl bromides, see: Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599.

(15) It is presumed that an electron transfer from allyltin to the $ZnCl_2$-**9** complex triggers the radical pathway (see also ref 5b). Detailed investigation on the Lewis acid-mediated radical reaction is in progress.