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Radical Alkenylation of α-Halo Carbonyl Compounds with Alkenylindiums

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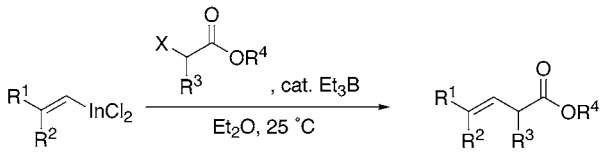
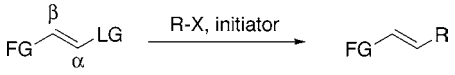
ABSTRACT



Alkenylation reaction of α-halo carbonyl compounds with alkenylindiums proceeded via a radical process in the presence of triethylborane. Unactivated alkene moieties as well as a styryl group could be introduced by this method. The geometry of the carbon–carbon double bonds of the alkenylindiums was retained. Preparation of an alkenylindium via a hydroindation of 1-alkyne followed by radical alkenylation established an efficient one-pot strategy.

Alkenylation reactions of organic halides are among the most important transformations in organic synthesis. Aside from comprehensive studies on transition-metal-mediated alkenylation reactions, alkenylation reactions of organic halides by 1-alkenystannanes[1] or 1-alkenyl sulfones[2] via a free-radical process[3] often offer a unique method for installation of a 1-alkenyl moiety. However, activation of the carbon−carbon double bond with the aid of an electron-withdrawing group or an aryl group at the alkenyl *β*-carbon is indispensable to carry out these reactions (Scheme 1). In addition, vigorous conditions are necessary to perform these reactions successfully. Radical vinylation thus deserves further exploitation. In recent years, we have focused on the chemistry of divalent indium compounds and disclosed their ability as radical mediators in radical chain reactions.[4,5] Now we wish to report a radical alkenylation of α-halo carbonyl compounds under mild conditions by utilizing alkenylindium reagents. The present alkenylation allows us to incorporate unactivated alkene moieties with retention of configuration.

Scheme 1



FG = Ar, Electron Withdrawing Group
LG = Sn^nBu_3, SO_2R

As the starting point of our investigation, we attempted radical alkenylation of ethyl iodoacetate (**3**) with *β*-styrylin-

(1) (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 715−831. (b) Baldwin, J. E.; Kelly, D. R. Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133−134. (c) Baldwin, J. E.; Kelly, D. R. *J. Chem. Soc., Chem. Commun.* **1985**, 682−684. (d) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 2941−2944. (e) Curran, D. P. *Synthesis* **1988**, 417−439. (f) Curran, D. P. *Synthesis* **1988**, 489−513. (g) Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958−2960. (h) Keck, G. E.; Byers, J. H.; Tafesh, A. M. *J. Org. Chem.* **1988**, *53*, 1127−1128. (i) Kraus, G.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741−1744. (j) Gómez. A. M.; López, J. C.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1689−1695. (k) Delouvrié, B.; Fensterbank. L.; Lacôte, E.; Malacria, M. *J. Am. Chem. Soc.* **1999**, *121*, 11395−11401.

(2) (a) Xiang, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 11986−11987. (b) Clark, A. J.; Rooke, S. Sparey, T. J.; Taylor, P. C. *Tetrahedron Lett.* **1996**, *37*, 909−912. (c) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999**, *38*, 1943−1946. (d)Kalaï, C.; Tate, E.; Zard, S. Z. *Chem. Commun.* **2002**, 1430−1431.

(3) Rosenstein, I. J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: New York, 2001; Vol. 1, pp 50−71.

(4) (a) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993−2995. (b) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2003**, *59*, 6627−6635. (c) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627−6631.

(5) Baba also reported radical reactions mediated by dichloroindium radical. (a) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906−907. (b) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2001**, *42*, 4461−4463. (c) Miyai, T.; Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 1929−1932.

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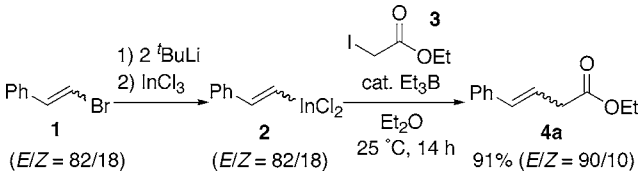
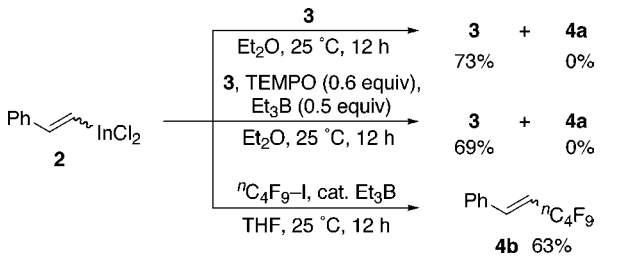
Scheme 2



dium dichloride (**2**) (Scheme 2). The indium reagent was prepared in situ via transmetalation of indium trichloride with β-styryllithium[6] in ether. Treatment of **3** with a small excess of **2** and 50 mol % of triethylborane as a radical initiator at ambient temperature afforded an alkenylation product **4a** in high yield.[7]

β-Styrylindium prepared from β-styryl Grignard reagent and indium trichloride in THF resulted in a lower yield of **4a**.[8] Both indium tribromide and indium triiodide could replace indium trichloride, but the reactions were inferior to that with indium trichloride. We also attempted to apply distyrylindium chloride and tristyrylindium to this radical alkenylation reaction. However, both of the reactions were unsuccessful. This alkenylation reaction did not proceed in the absence of triethylborane as depicted in Scheme 3. Addition of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) thoroughly prevented the reaction. Furthermore, nonafluorobutyl iodide, wherein nucleophilic substitution is difficult, was also alkenylated by this method.[9]

Scheme 3



These results strongly suggest that this reaction proceeds via a radical chain mechanism as illustrated in Scheme 4. Ethoxycarbonylmethyl radical **5** generated from **3** adds to the carbon atom that is attached to the indium atom. The elimination of dichloroindium radical **7** from **6** affords alkenylated product **4**, and the released indium radical abstracts iodine from substrate **3** to regenerate the radical **5**.

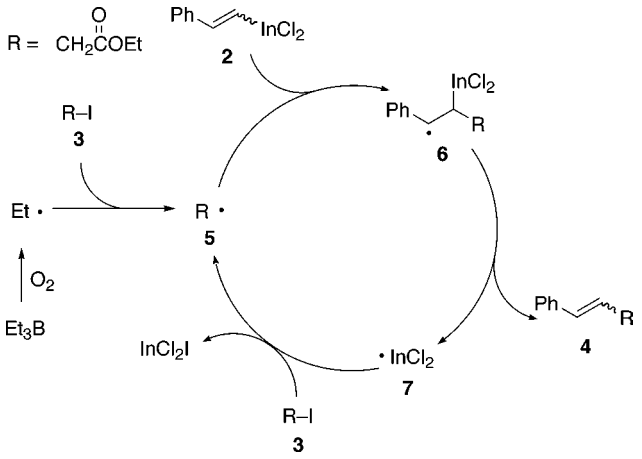
(6) β-Styryllithium was prepared from β-bromostyrylene (**1**, E/Z = 82/18) and 2 equiv of *tert*-butyllithium. The stereochemistry of alkenylindium **2** was determined by iodolysis.

(7) When a higher yield was requested, an increasing amount of **2** and injection of air into the reaction flask were particularly effective. All particulars of the reaction are shown in the Supporting Information.

(8) This result is attributed mainly to the choice of THF as solvent. The influence of magnesium salt is not a serious problem. In fact, addition of an equimolar amount of $MgBr_2$ in the reaction of Scheme 2 did not show a significant effect.

(9) In this case, the reaction was performed in THF with β-styryl Grignard reagent in place of β-styryllithium.

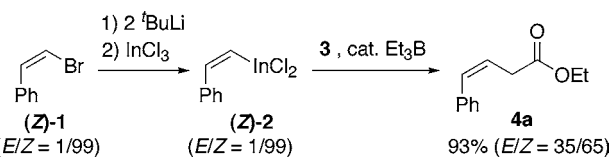
Scheme 4



To broaden the scope of the present method, we applied this system to a variety of α-halo carbonyl compounds (Table 1). Styrylation of α-alkylated α-iodo esters also took place smoothly (entries 1 and 2). In contrast, α,α-dialkylated α-iodo ester did not undergo the alkenylation at all. This reaction can be applied not only to α-iodo esters but also to α-iodo amide without any difficulty (entries 3 and 4). α-Iodo ketone can also be employed although the β,γ-unsaturated ketone generated at the initial stage of the reaction isomerized to α,β-unsaturated ketone **8** during the reaction (entry 5). Unfortunately, alkenylation of α-bromo ester was unsatisfactory under the same reaction conditions (entry 6). Employing a catalytic amount of V-70 (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)) as a radical initiator instead of triethylborane also yielded **4a** in moderate yield (entry 7). This result eliminates the possibility of an S_N2 alkenylation of α-halo carbonyl compound with an alkenylmetal reagent and supports the radical-chain mechanism which we propose in Scheme 4. Use of a 2-fold excess of the styrylindium reagent provided sufficient improvement in yield (entry 8). Under these modified conditions, various α-bromo carbonyl compounds can be styrylated in good to high yields (entries 9−11). On the other hand, styrylation of α-chloro carbonyl compounds was very sluggish (entries 12 and 13).

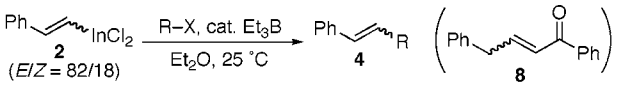
When the reaction was performed with (*Z*)-enriched styrylindium dichloride **(*Z*)-2**, the thermodynamically disfavored (*Z*)-alkenylated product was mainly obtained (Scheme 5). The stereochemistry of styrylindium **(*Z*)-2** generated in

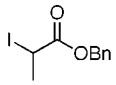
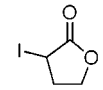
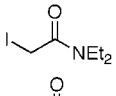
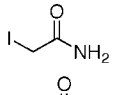
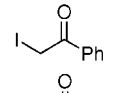
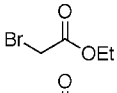
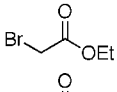
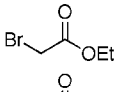
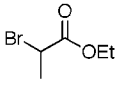
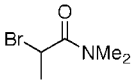
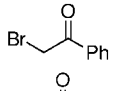
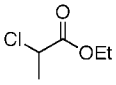
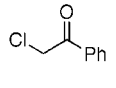
Scheme 5



situ was determined by deuteration and iodination. To explain this moderate stereospecificity, we propose a plausible

Table 1. Radical Styrylation of Various α-Halo Carbonyl Compounds[a]



entry	**2**/mmol	R–X	**4**	yield/%	*E*/*Z*
1	1.1		**4c**	93	90/10
2	1.1		**4d**	99	86/14
3	1.1		**4e**	85	94/6
4	1.1		**4f**	91	88/12
5	1.1		**8**[c]	71	93/7
6	1.1		**4a**	50	95/5
7[b]	1.1		**4a**	62	95/5
8	2.0		**4a**	88	97/3
9	2.0		**4g**	86	95/5
10	2.0		**4h**	57	95/5
11	2.0		**8**[c]	71	93/7
12	2.0		**4g**	4	nd
13	2.0		**8**[c]	28	95/5

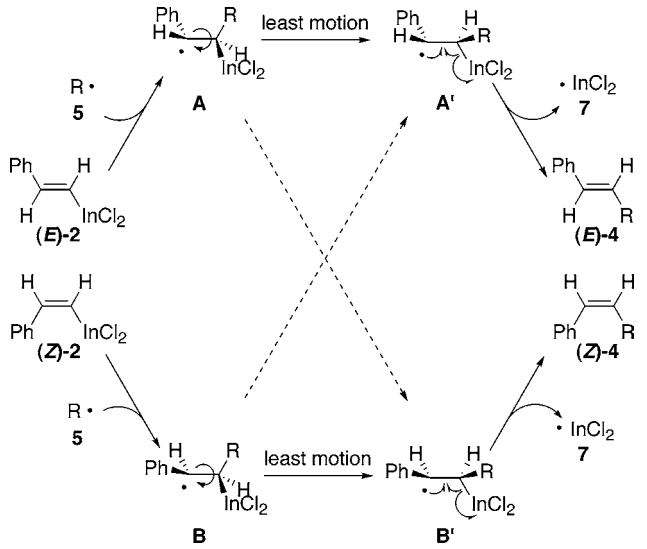
[a] All reactions were performed with R−X (1.0 mmol) and triethylborane (0.50 mmol). [b] The reaction was performed with 10 mol % of V-70 in place of triethylborane at 45 °C. [c] The expected product **4** was not observed at all.

mechanism (Scheme 6). The intermediates **A** and **B**, which are generated at the first step, liberate dichloroindium radical **7** to generate alkenylation products **4**. We are tempted to assume that this indium radical elimination is fast enough to proceed via a least motion process[10] because of the great elimination ability of dichloroindium radical **7**.

Next, we tried to employ unactivated alkenylindiums to this reaction system (Scheme 7). Unfortunately, it was difficult to achieve vinylation with unsubstituted vinylindium dichloride **9**. On the contrary, 2,2-dimethyl substitution

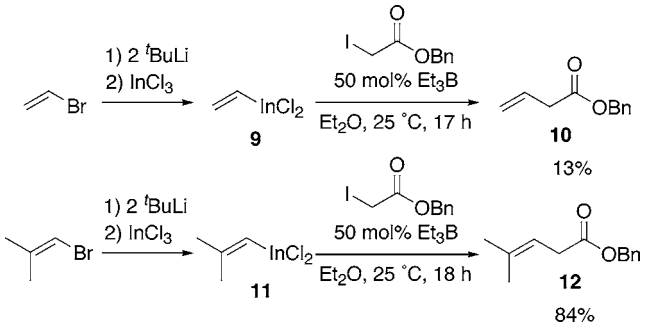
(10) The same least motion mechanism has been proposed for the styryl sulfone-mediated reaction. See ref 2a.

Scheme 6

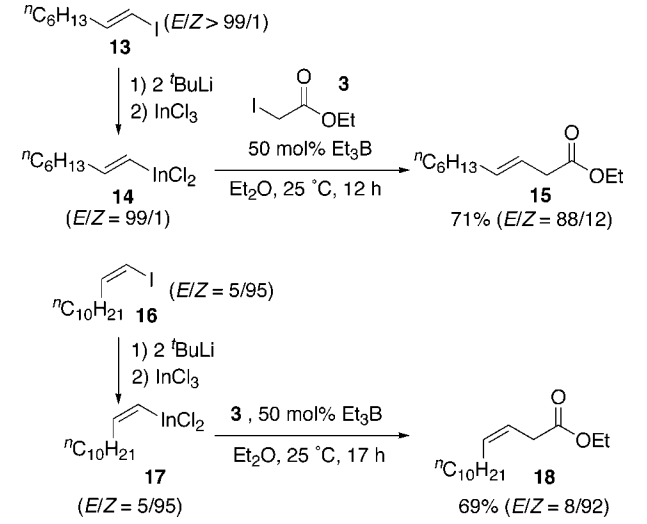


dramatically improved the reactivity of the alkenylindium dichloride.

Scheme 7



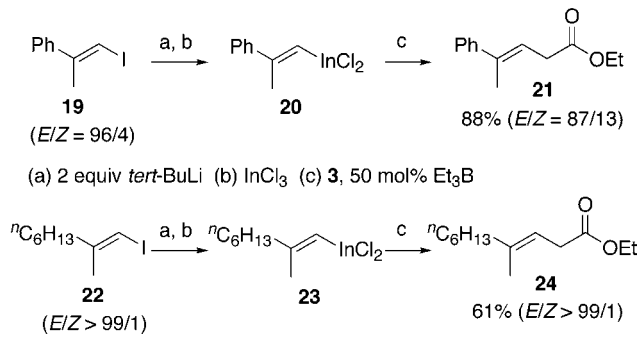
Scheme 8



As observed in the case of the styrylation, the reaction starting with (*E*)-iodo alkene **13** was high yielding and retained the geometry of the alkene moiety (Scheme 8).[11] The reaction with (*Z*)-alkenylindium **17** yielded the thermodynamically less stable (*Z*)-alkenylation product **18** predominantly.

Alkenylindium **20**, prepared from corresponding iodide **19**, effected alkenylation of **3** to provide **21**, predominantly as the *E* form (Scheme 9). The reaction with **23** also afforded the expected product **24** with complete retention of configuration.

Scheme 9



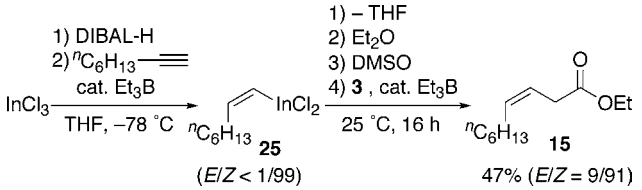
In our previous report, we disclosed a stereoselective preparation of alkenylindiums via a hydroindation reaction.[4a,c] Accordingly, we attempted to construct a one-pot hydroindation−alkenylation sequence. When we performed the alkenylation reaction with alkenylindium reagent prepared via the hydroindation reaction,[12] only unsatisfactory results were obtained. After extensive modifications, we could successfully combine these two reactions by the use of DMSO as a cosolvent (Scheme 10). The stereospecificity of the alkenylation reaction was largely retained in this one-pot system.

In summary, we disclose a radical alkenylation of α-halo carbonyl compounds with alkenylindiums. This reaction

(11) The stereochemistry of alkenylindiums **14** and **17** was determined by iodolysis and deuteriolysis.

(12) The stereochemistry of alkenylindium **25** was determined by iodolysis.

Scheme 10



realizes a facile introduction of unactivated alkene moieties to α-halo carbonyl compounds via a radical process, which is hard to carry out by previous radical alkenylation methods. During this reaction, the stereochemistry of alkenylindiums is considerably retained. A combination of the alkenylation reaction with hydroindation of alkynes gives the significance of this alkenylation reaction. Further investigations are currently underway.

A Typical Procedure for Radical Alkenylation. *tert*-Butyllithium (1.5 M in pentane, 1.5 mL, 2.2 mmol) was added to **1** (211 mg, 1.15 mmol) in 6 mL of ether at −78 °C under argon. The solution was immediately warmed to 25 °C and was stirred for 30 min. The solution was added to a stirred white suspension of indium trichloride (243 mg, 1.1 mmol) in ether (4 mL) that was prepared in another reaction flask beforehand. After 30 min, **3** (214 mg, 1.0 mmol) and triethylborane (1.0 M in hexane, 0.50 mL, 0.50 mmol) were added, and the whole mixture was vigorously stirred for 14 h. Extractive workup followed by chromatographic purification afforded **4a** (*E*/*Z* = 90/10, 173 mg, 0.91 mmol).

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Supporting Information Available: Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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