

Indium(III) Halide-Catalyzed UV-Irradiated Radical Coupling of Iodomethylphosphorus Compounds with Various Organostannanes

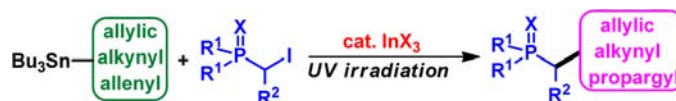
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Received February 25, 2013

ABSTRACT



The first catalytic radical coupling of iodomethylphosphorus compounds was accomplished with allyl-, alkenyl-, and allenylstannanes under UV irradiation in the presence of an indium(III) halide catalyst, for which a transmetalated allylic indium species was confirmed to be an active radical species.

Iodomethylphosphorus compounds are good candidates for the introduction of bioactive phosphorus moieties into organic compounds.¹ Research groups have paid attention to their potential for organic synthesis.² However, few applications to radical coupling have been reported³ because of a radical reactivity that is less than that of iodo-methylcarbonyl compounds, as discussed by Bałczewski et al.⁴

In order to address this problem, active radical partners should be employed for smooth coupling with methyl

phosphonyl radicals. Organostannanes are generally used as good radical precursors.⁵ In addition, the application of organoindiums into radical reactions has recently attracted much attention due to their unique reactivity.⁶

We have previously developed an equimolar radical coupling between iodomethylphosphorus compounds and butenylindium species generated from cyclopropylmethylstannanes and InBr₃.⁷ Herein, we expand the results to the indium(III) halide-catalyzed reaction of allylic stannanes with iodomethylphosphorus, in which allylic indiums were found to be superior radical partners under UV irradiation by comparison with the corresponding allylstannanes. The catalytic protocol was also applicable to the introduction of alkynyl or propargyl moieties into phosphonyl compounds using either an alkynylstannane or an allenylstannane, respectively.

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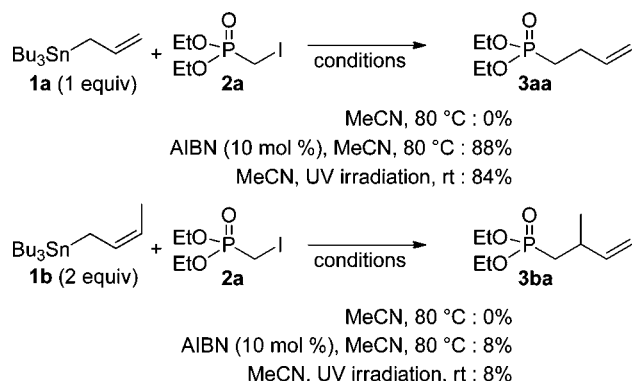
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Scheme 1. Direct Coupling between Diethyl Iodomethylphosphonate **2a** and Allylic Stannanes **1**



First, we investigated the direct coupling reaction between allylic stannanes **1a** or **1b** and diethyl iodomethylphosphonate **2a** (Scheme 1). The reaction using allyl stannane **1a** was effectively promoted under the addition of AIBN or UV irradiation to give the allylated products **3aa** in a high yield. In contrast, crotyl stannane **1b** was barely activated, even by similar radical initiation protocols, to afford the product in a low yield.⁸

Table 1. Optimization of the Reaction Conditions^a

entry	additive	conditions ^d	yield ^b (%)
1	InCl ₃ ^c	THF, UV	66
2	InCl ₃	THF, UV	71 (63) ^e
3	InBr ₃	THF, UV	54
4	InI ₃	THF, UV	64
5	GaCl ₃	THF, UV	24
6	AlCl ₃	THF, UV	5
7	ZnCl ₂	THF, UV	21
8	TiCl ₄	THF, UV	0
9	AIBN, InCl ₃	MeCN, reflux	6
10	Et ₃ B, InCl ₃	MeCN, rt	14
11	none	THF, UV	8
12	InCl ₃ , galvinoxyl	THF, UV	0

^a Reaction conditions: **1b** (1.0 mmol), **2a** (0.5 mmol), catalyst (0.05 mmol), solvent (1 mL). ^b ¹H NMR yield. ^c InCl₃ (1.0 mmol). ^d UV = 300 W high-pressure mercury lamp. ^e Isolated yield.

Table 1 shows the results of the promotion of the coupling of crotyl stannane **1b** with diethyl iodomethyl phosphonate **2a** under radical conditions. The addition of equimolar amounts of InCl₃ increased the yield to 66%, whereby transmetalated indium species could react effectively

(8) The reaction of allyl stannanes with α -bromo esters under radical reaction conditions was reported by Migita's group. For details see: Migita, T.; Nagai, K.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2480.

(entry 1). Fortunately, a catalytic amount of InCl₃ was sufficient to promote allylation in a 71% yield, and no regioisomerically allylated products were detected (entry 2). InBr₃ and InI₃ were also effective catalysts (entries 3 and 4). In contrast, GaCl₃, AlCl₃, ZnCl₂, and TiCl₄ gave low yields of the product (entries 5–8). Using radical initiators such as either AIBN or Et₃B in the presence of an indium catalyst resulted in low yields (entries 9 and 10). Because UV irradiation without an additive gave only 8% of the product, the role of InCl₃ as a catalyst was found to be inherent (entry 11). These results clearly revealed the importance of the combination of InCl₃ as a catalyst with UV irradiation for the coupling. The addition of galvinoxyl to the optimized reaction conditions completely disturbed the formation of the adduct, which indicated that this reaction included a radical step (entry 12).

The scope and limitations of allylic stannanes and iodo-methylphosphorus compounds are summarized in Table 2. We found that 2-pentenylstannane **1c** and cyclohexenylstannane **1d** were both applicable to give **3ca** and **3da** effectively, while no coupling of prenylstannane **1e** was observed (entries 2–4). Diisopropyl iodomethylphosphonate **2b** gave the desired product **3bb** in a similar yield to the diethoxy derivative **2a**. 3-Iodopropylphosphonate **2c** also afforded the coupling product **3bc** with no effect of steric hindrance. Other types of α -iodo phosphorus compounds, phosphine oxide **2d** and phosphonothioate **2e**, gave the desired coupling products **3bd** and **3be**, respectively.⁹

The transmetalation between (*Z*)-crotylstannane **1b** and InCl₃ was investigated by ¹³C NMR to confirm the formation of crotylindium **5** as a mixture of *E/Z* regioisomers in 2 h at room temperature, which was isolated by evaporation of the volatiles and successive washing with hexane (Figure 1). These results indicated that the transmetalation into methallylindium **4** was followed by isomerization to give crotylindium **5** as an *E/Z* mixture (Scheme 2).¹⁰ The isomerization from **4** to **5** would be considerably faster because the formation of **4** was not detected by ¹³C NMR. When the isolated crotylindium **5** in THF-*d*₈ was added to **2a**, the corresponding coupling product **3ba** was obtained (see the Supporting Information). In addition, because InCl₃ was essential for the coupling, we speculated that transmetalated indium species **5** is an active species in the coupling with iodophosphorus compounds.

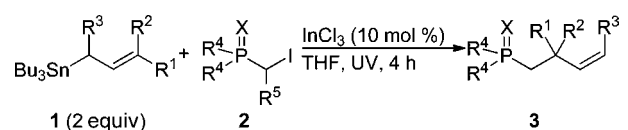
A plausible reaction mechanism is shown in Scheme 3. Fast decomposition of each crotylindium **5** and diethyl iodomethylphosphonate **2a** under UV irradiation was observed (see the Supporting Information), so a SET reaction route would be plausible.¹¹ Crotylindium **5** derived from crotylstannane **1b** is excited by UV irradiation and reacts with **2a** giving a radical ions **5**^{•+} and **2a**^{•−}. Each

(9) An undefined mixture was detected when phosphonothioate **2e** was used.

(10) We have already detected transmetalation between other allylic stannanes and InBr₃, and identified the structure of allylic indium species by X-ray analysis. For details, see: Yasuda, M.; Haga, M.; Baba, A. *Organometallics* **2009**, *28*, 1998.

(11) This mechanism was inspired by Tanner's report about ET process of allylation of α -halo ketones by allyltributylstannane. See: Li, X.; Chen, J. J.; Tanner, D. D. *J. Org. Chem.* **1996**, *61*, 4314.

Table 2. Scope of Applicable Stannanes **1** and Iodomethylphosphorus Compounds **2**^a



entry	allylic stannane	iodomethylphosphorus compounds	product	yield/ % ^{b,c}
1			3ba	71(62)
2			3ca	65(59)
3			3da	69(55)
4			-	0
5			3bb	72(63)
6			3bc	55(33) (dr = 58:42)
7			3bd	55(30)
8			3be	21(8)

^a Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), catalyst (0.05 mmol), solvent (1 mL). ^b ¹H NMR yield. ^c Isolated yield in parentheses.

radical ion decomposes into a crotyl radical **6/6'**, phosphonylmethyl radical **2a'**, and an indium halide. The afforded radical **2a'** adds to crotylindium **5** to give radical intermediate **7**, which forms the desired product **3ba** and indium radical (left cycle) or abstracts iodine atom from **2a** giving radical **2a'** and alkyl iodide **8** followed by β -elimination to afford **3ba** (right cycle).^{6a-c,12}

In general, allylic indium species are prepared by transmetalation between the corresponding Grignard reagents and indium halides or by a reductive method using allylic halide and In(0).¹³ We applied these protocols to radical coupling with iodomethyl phosphonate **2a** (Scheme 4). Neither reaction, however, proceeded effectively. In the case of Grignard reagent **9**, MgCl₂ given after transmetalation

(12) Alternative reaction mechanism might be proposed. The formed radicals **6/6'** and **2a'** are coupled into the product **3ba**.

(13) Araki, S.; Hirashita, T. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M. P., Crabtree, R. H., Eds.; Elsevier: Oxford, UK, 2007; Vol. 9. pp 649–751.

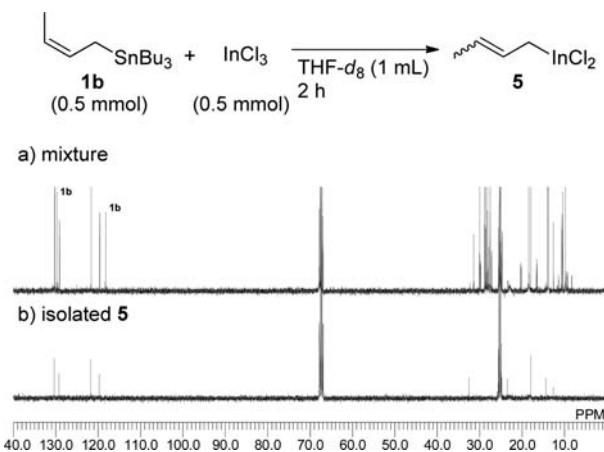
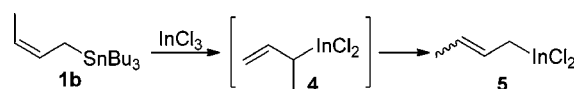
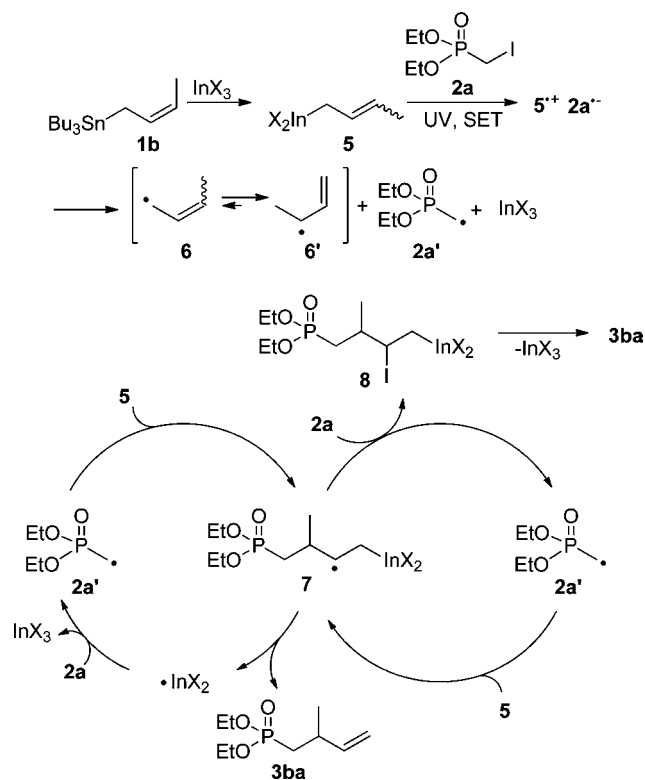


Figure 1. ¹³C NMR for transmetalation between crotylstannane **1b** and InCl₃ in THF-*d*₈: (a) reaction mixture of **1b** and InCl₃ after 3 h, (b) isolated **5** from the reaction mixture by washing with hexane.

Scheme 2. Formation of Crotylindium **5** from (Z)-Crotylstannane **1b**

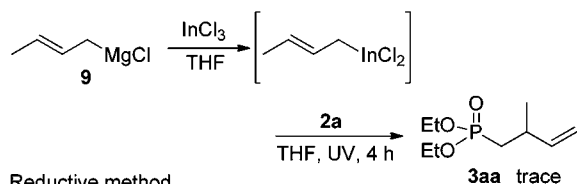


Scheme 3. Plausible Reaction Mechanism

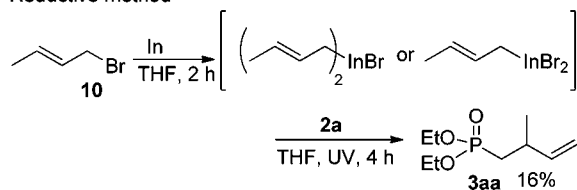


Scheme 4. Influence on the Preparation Methods of Crotylindium

Grignard method



Reductive method



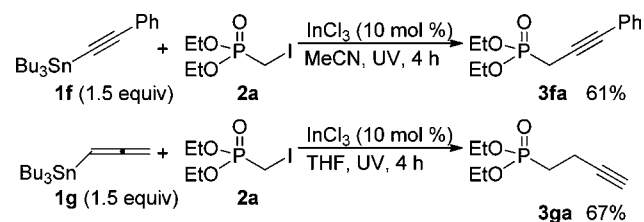
as a byproduct negatively affected the coupling due to its high Lewis acidity, which agreed with the results in our previous work.⁷ In fact, the reaction was disturbed by the addition of MgCl_2 to our Sn/In transmetalation system (see the Supporting Information). In the case of a reductive method using crotyl bromide **10**, the indium species are considered to be a mixture of mono- and dicrotylindium.¹⁴ We did not fully elucidate why the coupling was ineffective. One plausible explanation could be that the residue of $\text{In}(0)$ reacted with iodomethylphosphonate **2a**. These results showed that our Sn/In transmetalation system has considerable advantages for the radical reaction.

This indium halide catalyzed reaction system was found to be applicable to the alkynylation and propargylation of iodomethylphosphorus compounds using alkynylstannane **1f** and allenylstannane **1g**, respectively (Scheme 5). Other metal halides such as AlCl_3 , GaCl_3 , and ZnCl_2 , along with

(14) Yasuda, M.; Haga, M.; Nagaoka, Y.; Baba, A. *Eur. J. Org. Chem.* **2010**, 5359.

the addition of AIBN, barely promoted the coupling reactions (see the Supporting Information). These results strongly indicated that the combination of an indium halide catalyst with UV irradiation has great potential for the functionalization of iodomethylphosphorus compounds by a variety of organostannanes.

Scheme 5. Reaction of Diethyl Iodomethylphosphonate **2a** with Alkynylstannane **1f** and Allenylstannane **1g**



In conclusion, the first catalytic radical coupling of iodomethylphosphorus compounds with organostannanes was achieved by the combination of a catalytic amount of indium halides and UV irradiation. Crotyl-, alkynyl-, and allenylstannanes were applicable to the functionalization of iodomethylphosphorus compounds.

Acknowledgment. This work was supported by the Ministry of Education, Culture, Sports, Science and Technology (Japan). Thanks are due to Mr. Moriguchi, Faculty of Engineering, Osaka University, for assistance in obtaining the MS spectra.

Supporting Information Available. Experimental procedures, characterization, and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.