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

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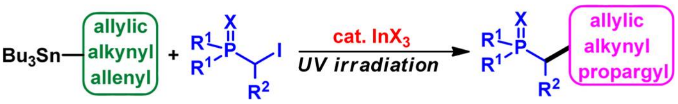
ABSTRACT



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 reported[3] because of a radical reactivity that is less than that of iodomethylcarbonyl 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 precusors.[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 $InBr_3$.[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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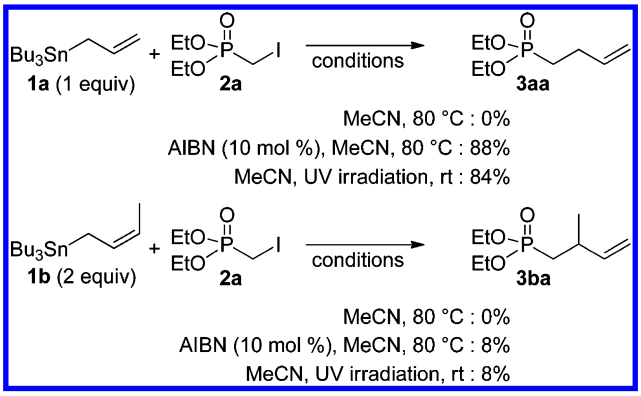
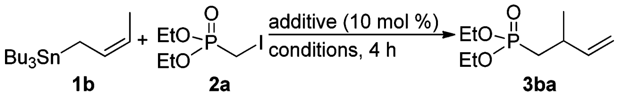
10.1021/ol4005257

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 allystannane **1a** was effectively promoted under the addition of AIBN or UV irradiation to give the allylated products **3aa** in a high yield. In contrast, crotylstannane **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_3B, $InCl_3$	MeCN, rt	14
11	none	THF, UV	8
12	$InCl_3$, galvinoxyl	THF, UV	0

[a] Reaction condtions: **1b** (1.0 mmol), **2a** (0.5 mmol), catalyst (0.05 mmol), solvent (1 mL). [b] ^{1}H NMR yield. [c] $InCl_3$ (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 crotylstannane **1b** with iodomethyl phosphonate **2a** under radical conditions. The addition of equimolar amounts of $InCl_3$ increased the yield to 66%, whereby transmetalated indium species could react effectively (entry 1). Fortunately, a catalytic amount of $InCl_3$ was sufficient to promote allylation in a 71% yield, and no regioisomerically allylated products were detected (entry 2). $InBr_3$ and InI_3 were also effective catalysts (entries 3 and 4). In contrast, $GaCl_3$, $AlCl_3$, $ZnCl_2$, and $TiCl_4$ gave low yields of the product (entries 5−8). Using radical initiators such as either AIBN or Et_3B 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 $InCl_3$ as a catalyst was found to be inherent (entry 11). These results clearly revealed the importance of the combination of $InCl_3$ 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 iodomethylphosphorus 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 $InCl_3$ was investigated by ^{13}C 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 ^{13}C 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 $InCl_3$ 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**$^{\cdot +}$ and **2a**$^{\bullet -}$. Each

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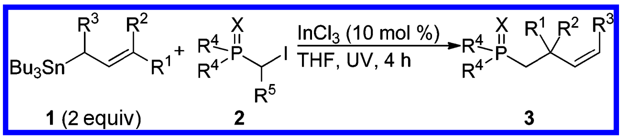
[8] The reaction of allylstannens with α-bromo esters under radical reaction conditions was reported by Migita's group. For details see: Migita, T.; Nagai, K.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2480.

[9] An undefined mixture was detected when phosphonothioate **2e** was used.

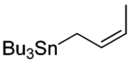
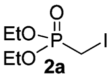
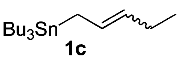
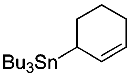
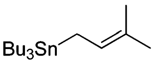
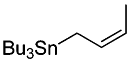
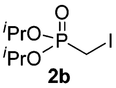
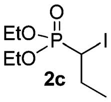
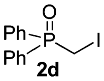
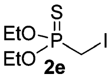
[10] We have already detected transmetalation between other allylic stannanes and $InBr_3$, and identified the structure of allylic indium species by X-ray analysis. For details, see: Yasuda, M.; Haga, M.; Baba, A. *Organometallics* **2009**, *28*, 1998.

[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]



1 (2 equiv) **2** **3**

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

[a] Reaction condtions: **1** (1.0 mmol), **2** (0.5 mmol), catalyst (0.05 mmol), solvent (1 mL). [b] ^{1}H 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**, $MgCl_2$ given after transmetalation

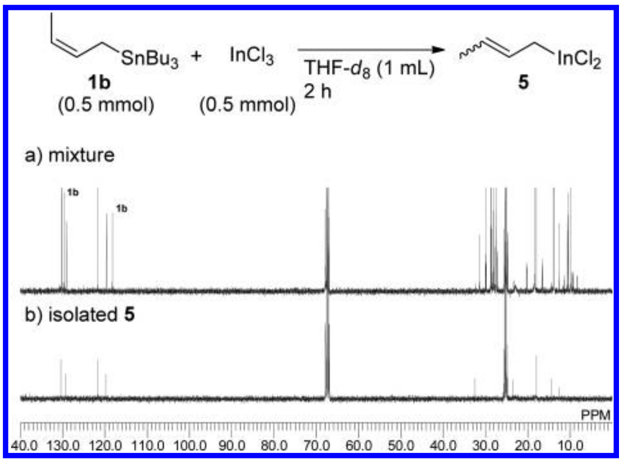
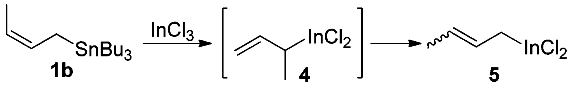
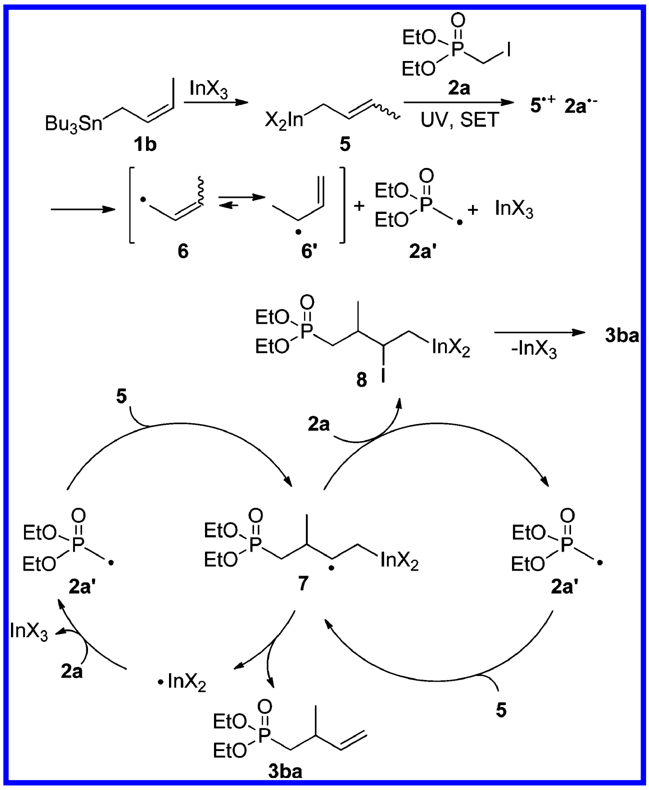


Figure 1. ^{13}C NMR for transmetalation between crotylstannane **1b** and $InCl_3$ in THF-d_8: (a) reaction mixture of **1b** and $InCl_3$ after 3 h, (b) isolated **5** from the reaction mixture by washing with hexane.

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



Scheme 3. Plausible Reaction Mechanism



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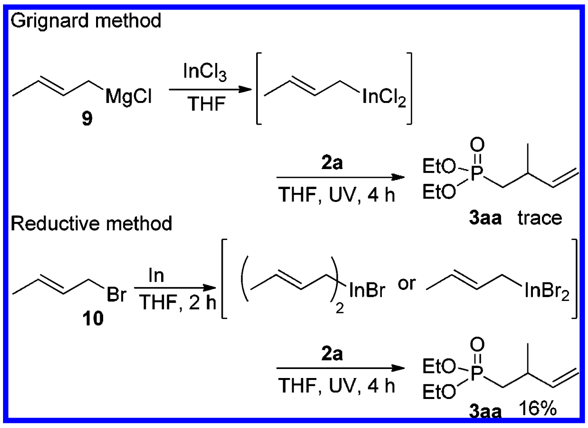
(12) Alternative reaction mechanism might be proposed. The formed radicals **6**/**6**′ and **2a**′ are coupled into the product **3ba**.

(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.

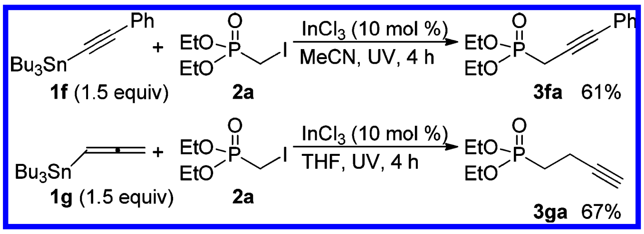
Scheme 4. Influence on the Preparation Methods of Crotylindium



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 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 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 iodomethyphosphorus 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.

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

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The authors declare no competing financial interest.