Indium(III) Chloride-Catalyzed Coupling Reaction of Acid Chlorides and Allylic Tins

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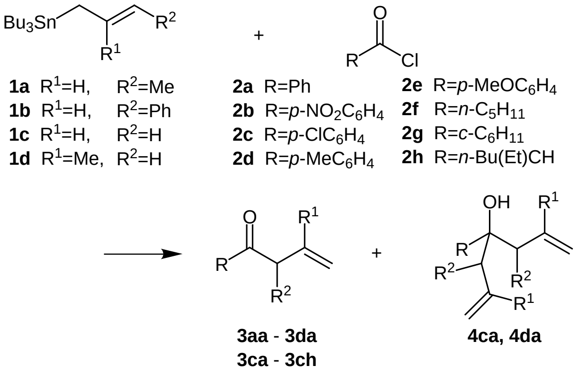
Abstract: Allylic tributyltins and acid chlorides are effectively coupled to yield allylic ketones in indium(III) chloride-catalyzed reactions. In the case of γ-unsubstituted allylic tins, the assistance of a phosphine is essential to prevent further allylation of the produced ketones.

Key words: indium, allylic tin, acid chloride, phosphine, coupling reaction

The synthetic application of indium compounds has attracted much attention in the past decade.[1] The present authors have already reported the characteristic reactivities of organoindium compounds generated by the transmetalation of organotin compounds with indium trichloride ($InCl_3$).[1k-m] In particular, an indium hydride was shown to reduce acid chlorides to the corresponding aldehydes without side reactions, where the addition of a phosphine is essential.[2] In our efforts to expand the scope of the catalytic use of indium compounds, we focused on the coupling reaction of acid chlorides with allyltin compounds. Among reported attempts, Migita and Kosugi achieved selective coupling between benzoyl chloride and allyltri-*n*-butyltin using a rhodium catalyst at 80 °C.[3] Unfortunately, the Pd-catalyzed procedure, called the Migita-Stille reaction, is not ideal due to undesirable side reactions such as isomerization and further allylation of the produced ketones.[4] Here we report the $InCl_3$-catalyzed selective coupling of allylic tributyltins and acid chlorides, for which in certain cases the coordination of phosphines is indispensable for preventing side reactions.[5]

Initially we examined the coupling reaction between benzoyl chloride (**2a**) and crotyltri-*n*-butyltin (**1a**) or cinnamyltri-*n*-butyltin (**1b**). When 10 mol% of $InCl_3$ was added under the conditions detailed in Table 1, the desired adducts **3aa** and **3ba** were obtained exclusively, at ambient temperature without side reactions (entries 1 and 2). No reaction occurred in the absence of $InCl_3$. The perfect γ-selectivity, giving α-substituted allyl ketones **3aa** and **3ba**, is in sharp contrast to the low regioselectivity in the Rh(III)-catalyzed reaction.[4,6]



Scheme 1

The use of allyltri-*n*-butyltin (**1c**) resulted in the further allylation of the produced allylketone, yielding the diallylated product **4ca** (entry 3) exclusively in only 29% yield based on the acid chloride. None of desired allylketone **3ca** was obtained under any of the conditions examined. However, the catalytic effect of $InCl_3$ in the coupling is characteristic, because other group-13 elements such as $AlCl_3$ and BCl_3 exhibit no catalytic effect despite their stronger Lewis acidity (entries 4 and 5). In a similar way to **1c**, methallyltri-*n*-butyltin (**1d**) predominantly gave the diallylated product **4da** in 44% yield along with a minor amount of **3da** (entry 6). The lack of further allylation of **3aa** and **3ab** is thought to depend on the sluggish route to steric demanding tertiary alcohols **4** ($R^2 \neq H$) from **3** ($R^2 \neq H$).

A variety of coordinative compounds were tested in the reaction of **1c** and benzoyl chloride (**2a**) as a means of preventing diallylation, which occurs in the coupling of γ-unsubstituted allylic tins. Amines such as triethylamine, tetramethyl ethylenediamine and pyridine, however, had only a negative effect, and no reaction took place. The addition of HMPA also resulted in merely the recovery of the starting substrates. It is expected that these additives coordinate to indium species too strongly to direct any subtler reactivity. Fortunately, phosphines were found to have a remarkable effect, as shown in Table 1. While 10 mol% of Ph_3P was sufficient to achieve coupling (91%), the use of 20 mol% increased the yield up to 99% (entries 7 and 8).[7] The moderate coordination ability of phosphines is thought to promote selective coupling, giving monoallylated ketones in 73%–99% yield (entries 8-11). A large difference between tri-*n*-butylphosphine and tricyclohexylphosphine was observed, affording the adduct

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Table 1 Coupling Reaction of **2a** with Allylic Tins **1**, and Effect of Additives[a]

Entry	Allylic Tin	Additive	Yield (%)[b]				
			3		**4**		
1	**1a**	none	**3aa**	70	**4aa**	0	
2	**1b**	none	**3ba**	89	**4ba**	0	
3	**1c**	none	**3ca**	0	**4ca**	58	(29)[f]
4[c]	**1c**	none	**3ca**	0	**4ca**	0	
5[d]	**1c**	none	**3ca**	0	**4ca**	0	
6	**1d**	none	**3da**	8	**4da**	44	(22)[f]
7[e]	**1c**	Ph_3P	**3ca**	91	**4ca**	0	
8	**1c**	Ph_3P	**3ca**	99	**4ca**	0	
9	**1c**	n-Bu_3P	**3ca**	88	**4ca**	0	
10[e]	**1c**	dppb	**3ca**	81	**4ca**	0	
11[e]	**1c**	dppe	**3ca**	73	**4ca**	0	
12	**1c**	$(c$-$C_6H_{11})_3P$	**3ca**	0	**4ca**	0	
13	**1d**	Ph_3P	**3da**	99	**4da**	0	
14	**1a**	Ph_3P	**3aa**	0	**4aa**	0	
15	**1b**	Ph_3P	**3ba**	0	**4ba**	0	

[a] $InCl_3$ 0.1 mmol, additive 0.2 mmol, **1** 1 mmol, **2a** 1 mmol, MeCN 1 mL, r.t., 2.5 h.

[b] Yields based on tin compounds.

[c] $AlCl_3$ was used instead of $InCl_3$.

[d] BCl_3 was used instead of $InCl_3$.

[e] 0.1 mmol of additive was used.

[f] Yields based on **2a**.

3ca in 88% and 0% yields, respectively (entries 9 and 12). This result indicates that increasing the steric demand of phosphines primarily disturbs the interaction between indium species and acid chloride or allylic tin,[8] because both phosphines have similar basicities. The choice of solvent is also essential for efficient reaction; acetonitrile (99%) is superior to CH_2Cl_2 (90%), THF (67%) and toluene (37%). Among them, THF suppresses the coordination of triphenylphosphine, giving the diallylated product **4ca** in 30% yield along with the desired adduct **3ca**. Methallyltri-*n*-butyltin (**1d**) also effected the selective monoallylation with the aid of triphenylphosphine, giving the corresponding monomethallylated ketone **3da** in 99% yield (entry 13). In contrast, a surprising result was that the coupling reaction using crotyltri-*n*-butyltin (**1a**) or cinnamyltri-*n*-butyltin (**1b**) was completely inhibited by the addition of triphenylphosphine (entries 14 and 15). Apparently, the phosphine suppressed the allylation in contrast to the reported reduction of acid chlorides.[2]

Table 2 Phosphine-Controlled Monoallylation of Acid Chlorides **2** by **1c**[a]

Entry	R (**2**)		Conditions	Yield of **3** (%)	
1	Ph	(**2a**)	r.t., 2.5 h	**3ca**	99
2[b]	Ph	(**2a**)	r.t., 2.5 h	**3ca**	98
3	p-$NO_2C_6H_4$	(**2b**)	r.t., 0.5 h	**3cb**	99
4	p-ClC_6H_4	(**2c**)	r.t., 0.5 h	**3cc**	99
5	p-MeC_6H_4	(**2d**)	r.t., 1.0 h	**3cd**	91
6	p-$MeOC_6H_4$	(**2e**)	r.t., 7.0 h	**3ce**	86
7[c]	n-C_5H_{11}	(**2f**)	r.t., 17.5 h	**3cf**	64
8	c-C_6H_{11}	(**2g**)	r.t., 22.0 h	**3cg**	60
9	c-C_6H_{11}	(**2g**)	60 °C, 1.0 h	**3cg**	77
10	*n*-Bu(Et)CH	(**2h**)	r.t., 22.0 h	**3ch**	17
11	*n*-Bu(Et)CH	(**2h**)	60 °C, 2.5 h	**3ch**	83

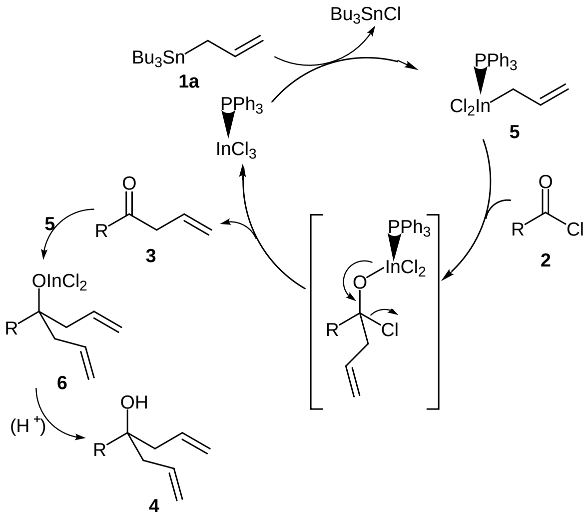
[a] $InCl_3$ 0.1 mmol, Ph_3P 0.2 mmol, **1c** 1 mmol, **2** 1 mmol, MeCN 1 mL.

[b] Galvinoxyl (0.01 mmol) was added.

[c] Toluene was used instead of MeCN.

Table 2 lists the results for the selective monoallylation of various acid chlorides with **1c**. The possibility of free radical processes can be discounted by the observation that the inclusion of a radical scavenger, galvinoxyl, did not affect the coupling at all (entry 2). Electron-withdrawing substituents on the aromatic ring were found to accelerate the allylation, giving **3cb** and **3cc** in quantitative yields within 30 min (entries 3 and 4). Of worth noting is the high selectivity with the use of *p*-nitrobenzoyl chloride (**2b**), because Pd-catalyzed allylation has been reported to result in the low selective formation of **3cb**.[4a] The introduction of an electron-releasing substituent lengthened the reaction time yet afforded **3ce** in high yield (entry 6). Aliphatic acid chlorides, **2f** and **2g**, gave only moderate yields at ambient temperature even after long periods (entries 7 and 8). The reaction of secondary aliphatic acid chloride **2h** resulted in only 17% yield ever after 22 h (entry 10), however heating to 60 °C increased the yield of **3ch** to 83% without side products (entry 11).

Scheme 2 illustrates the proposed catalytic cycle, consisting of three steps; (1) the generation of allyl indium by transmetalation, (2) the nucleophilic addition to an acid chloride, and (3) the formation of a β,γ-unsaturated ketone and regeneration of $InCl_3$.[9] This cycle is quite similar to that previously proposed for the reduction of acid chlorides to aldehydes, where allyltri-*n*-butyltin has been only replaced by tri-*n*-butyltin hydride.[2] However, there is a sharp contrast in the role of phosphine. The coupling reaction is somewhat depressed by the coordination of phosphine as observed in the treatment of crotyl-*n*-tributyltin, whereas indium hydride affected the reduction only in the presence of phosphine. Although the origin of this difference has yet to be clarified explicitly, it appears that the coordination reduces the Lewis acidity of allylindium and



Scheme 2

indium hydride, inhibiting extended reactions. If further allylation did take place, the catalytic cycle would be interrupted because indium becomes trapped as alkoxide **6**, which exhibits virtually no regeneration of active species as reported previously.[11]

Therefore, the coordination of phosphine is essential for the completion of the catalytic cycle. Although a mechanistic study is now under investigation, our indium-catalyzed coupling of allylic tins with acid chlorides has some synthetic advantages; (1) no expensive transition metal catalyst is necessary, and (2) side reactions such as isomerization of the double bond and further allylation are not problems.

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(7) **A typical experimental procedure:** A 10 mL flask charged with InCl$_3$ (0.1 mmol) was heated at 150 °C in vacuo for 1 h. After nitrogen gas was filled, MeCN (1 mL), triphenylphosphine (0.2 mmol), allyltri-*n*-butyltin (**1c**) (1.0 mmol) and benzoyl chloride (**2a**) (1.0 mmol) were successively added at ambient temperature and the resulting mixture was stirred for 2.5 h. After quenching with 10 mL of aqueous NH$_4$F, the mixture was extracted with Et$_2$O (30 mL × 2), dried over anhyd MgSO$_4$, filtered and concentrated in vacuo. NMR analysis revealed the formation of **3ca** in 99% yield. Purification was performed by column chromatography (silica gel) and then Kügelrohr distillation.

(8) (a) The corn angles of Ph$_3$P, *n*-Bu$_3$P and (c-C$_6$H$_{11}$)$_3$P are 145°, 136° and 179°, respectively: Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313. (b) The basicities (pKa values of the corresponding conjugate acids) are 2.73, 8.43 and 9.70 respectively: Golovin, M. N.; Rahman, M. M.; Belmonte, J. E.; Giering, W. P. *Organometallics* **1985**, *4*, 1981.

(9) Allylindium species generated by the transmetallation between tributylallyltin and indium trichloride in THF-d_8 solvent were characterized by ^{1}H NMR: δ 1.97 (d, 2 H, J = 8.3 Hz), 4.6-4.95 (m, 2 H), 5.9-6.1 (m, 1 H). However, no spectral proof of coordination of Ph$_3$P was available because of the poor solubility of the indium-phosphine complex.