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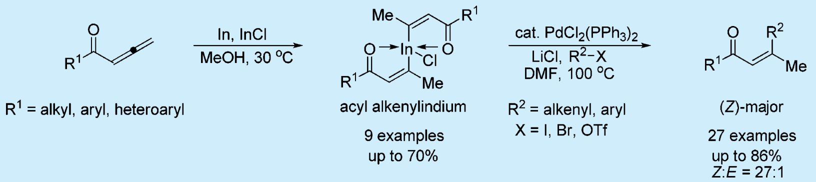
Synthesis of Acyl Alkenylindium Reagents and Their Application in the Synthesis of (*Z*)-*α*,*β*-Unsaturated Ketones *via* Palladium-Catalyzed Cross-Coupling Reaction

Youngchul Park, Jiae Min, Dahan Eom, and Phil Ho Lee*

National Creative Research Initiative Center for Catalytic Organic Reactions, Department of Chemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea

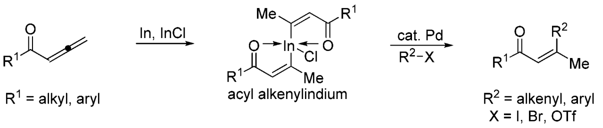
Supporting Information



ABSTRACT: A synthetic method for the preparation of acyl alkenylindium reagents was developed involving the hydroindation reaction of allenyl ketones with indium and indium chloride in methanol under mild conditions. Their synthetic applications were demonstrated from Pd-catalyzed cross-coupling reactions with aryl bromides and iodides and alkenyl and aryl triflates for the synthesis of (*Z*)-*α*,*β*-unsaturated ketones.

Cross-coupling reaction using a variety of organometallic reagents in the presence of a transition metal catalyst has been one of the most significant research subjects for the formation of C−C and C−heteroatom bonds.[1] In particular, the Pd-catalyzed cross-coupling reaction has been widely used as a powerful tool in synthetic chemistry.[2] To date, development of new catalysts, organometallic reagents, and electrophilic coupling partners has been continuously reported to expand the scope of cross-coupling reactions. Among them, because organoindium reagents showed advantageous properties related to their selectivity and reactivity, ease of handling and preparation, thermal stability, and low toxicity,[3] cross-coupling reactions using organoindium reagents have also been of great interest. After Pd-catalyzed cross-coupling reactions using tri(organo)indium reagents were reported by Sarandeses and co-workers,[4] coupling reactions using a large number of organoindium reagents[5] such as allylindiums, allenylindiums, alkenylindiums, 1,3-butadien-2-ylindiums, tri(naphthyl)indiums, tetra(organo)indates, indium tri(organothiolates), acylindiums, *β*-phosphoryl alkylindiums, arylindiums,[6] benzylindiums,[7] and alkylindiums[8] have been demonstrated.[9] Recently, Loh and co-workers reported the synthetic method of indium homoenolates *via* oxidative addition of indium and indium trichloride to *α*,*β*-enones[10] and insertion of indium into a *β*-halo ester.[11] In our continuing efforts to develop Pd-catalyzed cross-coupling reactions using organoindium reagents, we envisioned that if allenyl ketones would be employed in the reaction with In and/or InCl$_n$ (n = 1 and 3), the hydroindation reaction would take place to produce acyl alkenylindium reagents, which can be applicable in Pd-catalyzed cross-coupling reactions, producing *α*,*β*-unsaturated ketones. Herein, we report a novel synthetic method of acyl alkenylindium reagents from allenyl ketones and indium and indium chloride and their synthetic application in Pd-catalyzed cross-coupling reactions for the synthesis of *α*,*β*-unsaturated ketones (Scheme 1).

Scheme 1. Synthesis of Acyl Alkenylindium Reagents and Their Synthetic Application in Pd-Catalyzed Cross-Coupling Reaction



At the outset, 1-phenylbuta-2,3-dien-1-one (**1a**) was selected as the substrate to prepare the organoindium reagent. Investigation of a wide range of indium reagents such as In, InCl, InCl$_3$, In/InCl, and In/InCl$_3$ revealed that In and InCl were the reagents of choice for hydroindation (Table 1). Screening of solvents revealed that methanol was an optimal solvent, but other solvents such as CH$_3$CN/H$_2$O, THF/H$_2$O, and MeOH/H$_2$O gave inferior results. The best result was obtained from a reaction of **1a** (0.2 mmol, 1.0 equiv) with In (1.0 equiv) and InCl (0.8 equiv) in MeOH at 30 °C for 30 min, affording benzoyl alkenylindium reagent (**2a**) in 68% isolated yield together with 1-phenylbut-3-en-1-one (**3a**) in 19% yield (entry 8).

X-ray diffraction analysis proved that **2a** is a benzoyl-substituted alkenylindium, having a monomeric structure with chelation of the two carbonyl groups to indium (Figure 1). The coordination conformation of the central indium metal can be

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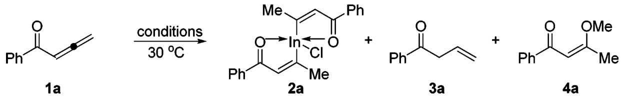
Table 1. Reaction Optimization[a]



entry	conditions (equiv)	solvent	time (h)	yield (%)[b] 2a	3a	4a
1	In (0.8)/$InCl_3$ (0.4)	CH_3CN/H_2O	1			18
2	In (0.8)/$InCl_3$ (0.4)	THF/H_2O	1	50	15	
3	In (0.8)/$InCl_3$ (0.4)	$MeOH/H_2O$	4	34	34	
4	In (1.2)	MeOH	6	18		52
5	$InCl_3$ (1.2)	MeOH	6		64	
6	InCl (1.2)	MeOH	6	15		70
7	In (1.0)/InCl (1.0)	MeOH	0.5	52	15	
8	In (1.0)/InCl (0.8)	MeOH	0.5	68[c]	19	
9	In (1.0)/InCl (0.6)	MeOH	0.5	68	15	
10	In (1.5)/InCl (0.8)	MeOH	0.5	67	18	

[a] Reactions were carried out with **1a** (0.2 mmol, 1 equiv) in solvent (0.8 mL) at 30 °C. [b] NMR yield using CH_2Br_2 as an internal standard. [c] Isolated yield of **2a**.

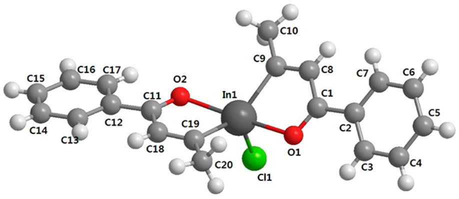
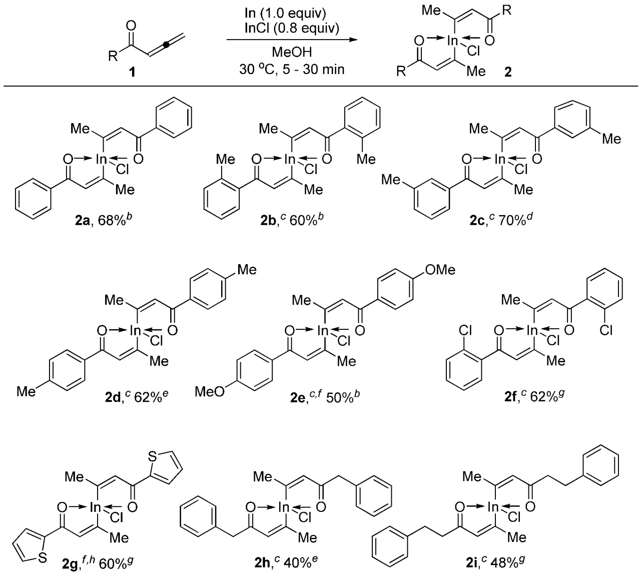


Figure 1. X-ray structure of benzoyl alkenylindium (**2a**).

Scheme 2. Scope of Allenyl Ketones[a]



[a] Reactions were carried out using In (0.2 mmol, 1.0 equiv), InCl (0.8 equiv), and allenyl ketone **1** (1 equiv) in MeOH (0.8 mL) at 30 °C. All yields are isolated yields. [b] For 30 min. [c] In (0.2 mmol, 1.0 equiv) and InCl (1.6 equiv) were used. [d] For 10 min. [e] For 20 min. [f] At 40 °C. [g] For 5 min. [h] In (0.2 mmol, 1.0 equiv) and InCl (1.2 equiv) were used.

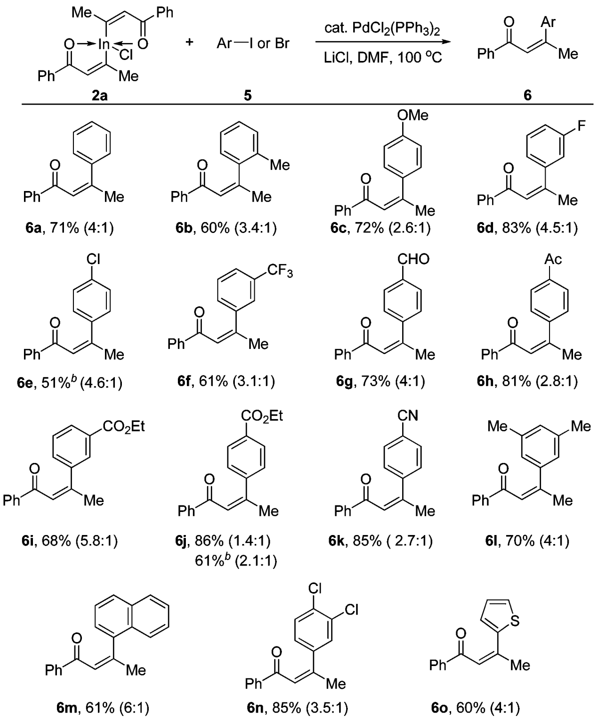
depicted as a distorted trigonal bipyramid, in which C(9), C(19), and Cl(1) occupy the equatorial plane and O(1) and O(2) occupy the apical positions. The average C=O bond length is 1.247 Å, and the average C=C bond [C(8)−C(9) and C(18)−C(19)] lengths, which are adjacent to the In−C bonds, are 1.338 Å.

Next, a wide range of allenyl ketones were studied to demonstrate the scope and limitation of the present method for the synthesis of acyl alkenylindium reagents under optimal reaction conditions (Scheme 2). Electronic variation of substituents on the aryl ring of 1-arylbuta-2,3-dien-1-one (**1**) slightly affected the reaction efficiency. For example, acyl alkenylindium reagents (**2b−d**) with electron-donating 2-, 3-, or 4-methyl substituents on the aryl ring were obtained in moderate to good yields ranging from 60 to 70%. 1-(4-Methoxyphenyl)buta-2,3-dien-1-one (**1e**) bearing a strong electron-donating methoxy group is less reactive, leading to the formation of 4-methoxybenzoyl alkenylindium reagent **2e** in 50% yield. Likewise, 2-chlorobenzoyl alkenylindium reagent **2f** was prepared from the hydroindation reaction of 1-(2-chlorophenyl)buta-2,3-dien-1-one (**1f**) with In and InCl in MeOH. Hydroindation of 1-(thiophen-2-yl)buta-2,3-dien-1-one (**1g**) provided **2g** in 60% yield. When alkyl allenyl ketones were subjected to the hydroindation reaction, the product yields slightly decreased due to the acidic α-proton of the carbonyl group. 1-Phenylpenta-3,4-dien-2-one (**1h**) and 1-phenylhexa-4,5-dien-3-one (**1i**) were converted to the corresponding alkanoyl alkenylindium reagents **2h** and **2i** in 40 and 48% yields, respectively. The corresponding allyl ketones were produced in about 10% yields for all of the allenyl ketones. 1-Phenylpenta-2,3-dien-1-one having a methyl group on the terminal sp^2 carbon did not undergo the hydroindation reaction.

We next examined Pd-catalyzed cross-coupling of benzoyl alkenylindium reagent **2a** with ethyl 4-iodobenzoate (**5j**) (see Supporting Information). A wide range of solvents such as DMA, THF, toluene, DMSO, and DMF in the presence of $PdCl_2(PPh_3)_2$ (5.0 mol %) were examined in the cross-coupling reaction, and it was found that DMF was the solvent that provided optimal yields. It is noteworthy that the *E*-product was selectively produced in DMA, while the *Z*-product was selectively produced in DMSO. A large number of Pd catalysts, such as $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $Pd(PhCN)_2Cl_2$, $[Pd(\pi\text{-allyl})Cl]_2$, and $PdCl_2(PPh_3)_2$, were screened in DMF. The optimal reaction conditions were obtained from reactions of **2a** (0.7 equiv) with **5j** (0.15 mmol, 1 equiv) in the presence of $PdCl_2(PPh_3)_2$ (5.0 mol %) and LiCl (2.0 equiv) in DMF (1.0 mL) at 100 °C for 2 h, leading to the formation of α,β-unsaturated ketone **6j** in 86% yield ($Z/E = 1.4{:}1$). When LiCl was not used, the product yield slightly decreased 72% and *Z*-selectivity significantly increased ($Z/E = 13{:}1$).

To demonstrate the scope and limitation of this cross-coupling reaction, we investigated the reaction of **2a** with a large number of aryl iodides and bromides under the optimal reaction conditions (Scheme 3). Electronic modification of substituents on the aryl ring of **2a** did not largely influence the reaction efficiency. 1-Iodobenzenes with electron-donating 2-methyl and 4-methoxy substituents underwent the cross-coupling reaction, furnishing the corresponding α,β-unsaturated ketones **6b** (60%) and **6c** (72%). The cross-coupling reaction was compatible with a fluoro group. 3-Trifluoromethylphenyl iodide **5f** was coupled with indium reagent to the desired product **6f**. Iodobenzene having electron-withdrawing groups such as formyl, acetyl, ethoxycarbonyl, and nitrile are suitable for the cross-coupling reactions, providing the desired α,β-unsaturated ketones (**6g−k**) in good yields, ranging from 68 to 86%. There are no products arising from the addition of the nucleophilic acyl alkenylindium

Scheme 3. Scope of Aryl Iodides and Bromides[a]

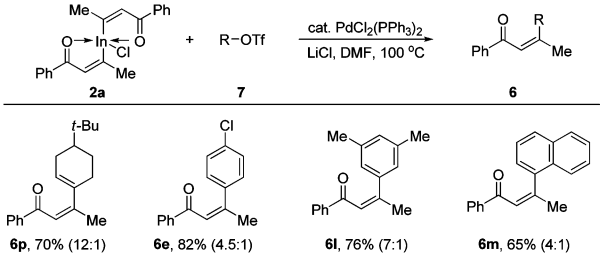


[a] Reactions were carried out with **2a** (0.7 equiv), **5** (0.2 mmol, 1 equiv), and LiCl (2.0 equiv) in DMF (1.3 mL) at 100 °C for 2 h. Isolated yield. Numbers in parentheses indicate *Z*/*E* ratio. [b] Aryl bromides were used.

reagents to the carbonyls. 1-Iodo-3,5-dimethylbenzene (**5l**) was subjected to the cross-coupling reaction to deliver **6l** in 70% yield. When 1-naphthyl iodide was treated with indium reagent **2a**, the cross-coupling reaction took place to produce **6m** in 61% yield. Treatment of 3,4-dichloro-1-iodobenzene with **2a** afforded the *α*,*β*-unsaturated ketone **6n** in 85% yield. 2-Iodothiophene was applied to the present Pd-catalyzed coupling reaction, affording **6o** in 60% yield. Aryl bromides are less reactive than the corresponding iodides. For instance, 1-bromo-4-chlorobenzene gave the desired product **6e** in 51% yield. Ethyl 4-bromobenzoate was also reacted with indium reagent **2a**, producing **6j** in 61% yield. (*Z*)-*α*,*β*-Unsaturated ketones were produced as the major isomer in all of the cross-coupling reactions.

Next, a large number of alkenyl and aryl triflates were employed in the Pd-catalyzed cross-coupling reactions with **2a** (Scheme 4). 4-*tert*-Butyl cyclohexen-1-yl triflate was applied to the present coupling reaction, affording the corresponding dienyl ketone (**6p**) in 70% yield (*Z*/*E* = 12:1). When phenyl trifluoromethanesulfonates with 4-chloro and 3,5-dimethyl groups were employed, the desired *α*,*β*-unsaturated ketones **6e** and **6l** were obtained in 82 and 76% yields, respectively. 1-Naphthyl triflate (**7m**) was compatible with the coupling reaction conditions.

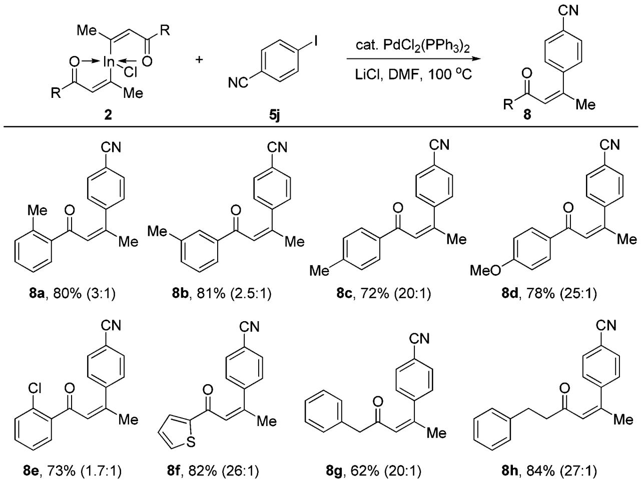
Scheme 4. Scope of Alkenyl and Triflates[a]



[a] Reactions were carried out with **2a** (0.7 equiv), **7** (0.2 mmol, 1 equiv), and LiCl (2.0 equiv) in DMF (1.3 mL) at 100 °C for 2 h. Isolated yield. Numbers in parentheses indicate *Z*/*E* ratio.

With these results in hand, we scrutinized the cross-coupling reaction of a wide range of acyl alkenylindium reagents **2** with **5j** (Scheme 5). Acyl dialkenylindium reagents (**2b–d**) bearing electron-donating 2-, 3-, or 4-methyl substituents on the aryl ring were reacted with **5j** to produce the corresponding *α*,*β*-unsaturated ketones **8a**, **8b**, and **8c** in good yields ranging from 72 to 81%. Indium reagent **2e** obtained from 1-(4-methoxyphenyl)buta-2,3-dien-1-one having a strong electron-donating methoxy group also worked, leading to the *α*,*β*-unsaturated ketone **8d** in 78% yield (*Z*/*E* = 25:1). 2-Chlorobenzoyl alkenylindium reagent **2f** prepared from 1-(2-chlorophenyl)buta-2,3-dien-1-one underwent the cross-coupling reaction with **5j**, resulting in the formation of **8e** in 73% yield. When acyl alkenylindium **2g** with a thiophen-2-yl moiety was employed, the desired *α*,*β*-unsaturated ketone **8f** was obtained in 82% yield (*Z*/*E* = 26:1). The cross-coupling reaction was amenable to reactions with indium reagents generated from 1-phenylpenta-3,4-dien-2-one and 1-phenylhexa-4,5-dien-3-one to afford **8g** (62%) and **8h** (84%), keeping the high *Z*-selectivity.

Scheme 5. Scope of Acyl Alkenylindium Reagents in the Coupling Reaction[a]



[a] Reactions were carried out with **2** (0.7 equiv), **5j** (0.2 mmol, 1 equiv), and LiCl (2.0 equiv) in DMF (1.3 mL) at 100 °C for 2 h. Isolated yield. Numbers in parentheses indicate *Z*/*E* ratio.

In conclusion, we have developed a synthetic method for the preparation of acyl alkenylindium reagents from the hydroindation reaction of allenyl ketones with indium and indium chloride in methanol under mild conditions. Their synthetic applications were demonstrated from Pd-catalyzed cross-coupling reactions with aryl bromides and iodides and alkenyl and aryl triflates for the synthesis of (*Z*)-*α*,*β*-unsaturated ketones.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02043.

Experimental procedures, characterization data, X-ray crystallography data (**2a**), and copies of NMR spectra for all products (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: phlee@kangwon.ac.kr.

Notes

The authors declare no competing financial interest.

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