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Unmasked Acyl Anion Equivalent from Acid Chloride with Indium: Reversed-Polarity Synthesis of Unsymmetric Aryl Aryl and Alkenyl Aryl Ketone through Palladium-Catalyzed Cross-Coupling Reaction†

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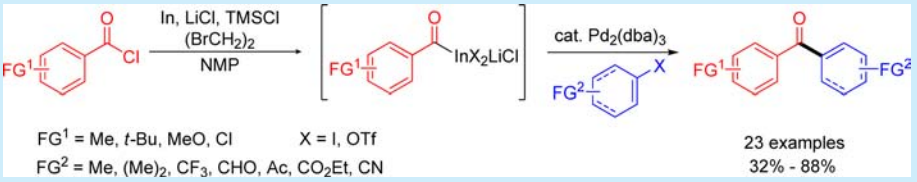
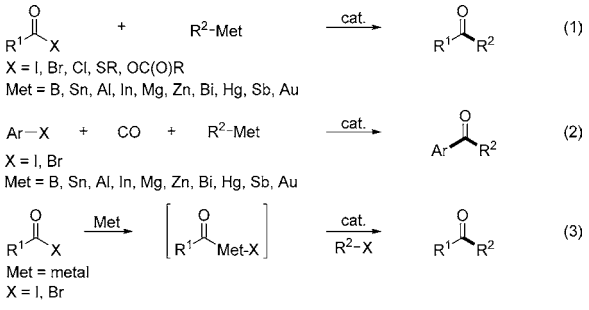
Supporting Information



ABSTRACT: A reversed-polarity synthetic method of a range of unsymmetric aryl aryl and alkenyl aryl ketones has been developed through Pd-catalyzed cross-coupling reaction of acylindium reagents generated in situ from easily available acid chlorides and indium with various electrophiles such as aryl iodide and triflate and alkenyl triflate.

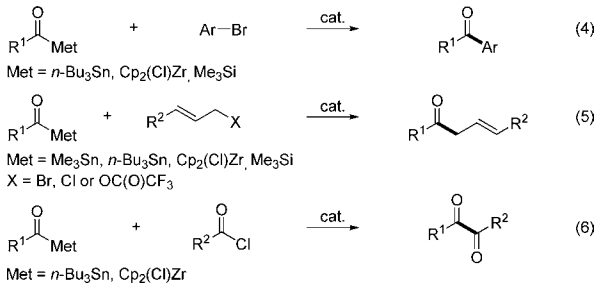
Transition-metal-catalyzed cross-coupling reaction of a number of electrophilic coupling partners with organometallic reagents is one of the most straightforward methods for C−C bond formation.[1] To date, Pd catalysis has been applied widely in the synthesis of a variety of ketones constituting aryl aryl, alkyl aryl, and alkyl alkyl groups. Synthetic strategies of ketones through Pd catalysis could be generally classified into three categories: substitution and cross-coupling reaction of electrophilic acid derivatives with organometallic reagents (eq 1),[2] carbonylative cross-coupling reaction of aryl halides with organometallic reagents under CO atmosphere (eq 2),[3] and cross-coupling reaction of acyl anion equivalents with electrophiles (eq 3) (Scheme 1).

Scheme 1. Synthetic Methods for Ketone Synthesis



The first two methods have been commonly used in the formation of ketones. However, the last one has been limited in application due to difficult preparation of acyl anion equivalents. Although acyl anion equivalents in cross-coupling reaction have been used with some limitations, the use of acyl organometallic reagents provides an effective method for the polarity-reversed synthesis of ketones. Up to now, acylstannanes, -zirconocenes, and -silanes have been generally used as acyl anion equivalents (Scheme 2). Although acylstannanes and -zirconocenes were reacted with aryl halide to afford one example each of ketone in low yield,[4] acylsilanes in reaction with a range of aryl bromides gave diaryl ketones in variable yields (eq 4).[5] These reagents were reacted with allylic halides and esters to afford β,γ-unsaturated ketones (eq 5).[4,6] Acylstannane and -zirconocene reagents produced unsymmetric 1,2-diketones in reaction with acid chlorides (eq 6).[4,7] Aldehydes, imines, or hydrazones were also arylated with aryl iodides and tins or potassium aryl(trifluoro)borates through Pd catalysis.[8] Pd-catalyzed arylation of electron-rich olefins by aryl halides followed by acidic hydrolysis was reported in the formation of diaryl ketones.[9]

Scheme 2. Synthesis of Ketones Using Cross-Coupling Reaction of Acyl Organometallic Reagents



However, these methods require additional and tedious synthetic steps under harsh conditions for the preparation of the unmasked acyl anion equivalents. Also, we are not aware of

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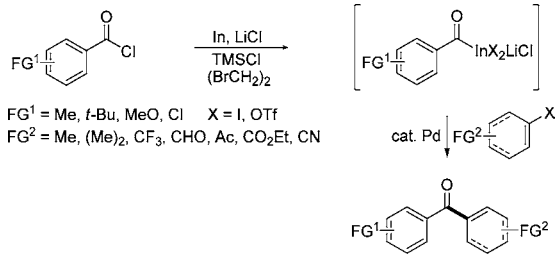
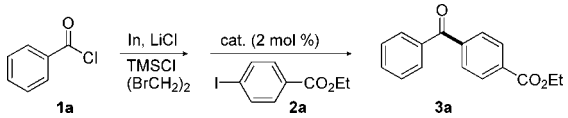
any reported synthetic examples of acyl anion equivalent generated in situ from easily available acid chloride. In our continuing efforts to develop Pd-catalyzed cross-coupling reactions using organoindium reagents,[10] we have been interested in development of a novel synthetic route to acyl anion equivalents using indium and then envisioned a cross-coupling reaction of electrophilic coupling partners with acyl anion equivalents generated in situ from indium and acid halides. Herein, we report the challenging reversed-polarity synthetic method of a diversity of ketones via Pd-catalyzed cross-coupling reaction of acylindium reagents generated in situ from easily accessible acid chlorides and indium at room temperature (Scheme 3).

Scheme 3. Reversed-Polarity Synthesis of Ketones via Cross-Coupling Reaction with Acylindium Reagents



To access unmasked acyl anion equivalents from acid chlorides, we studied the reactions of ethyl 4-iodobenzoate (**2a**) with organoindium reagents generated in situ from benzoyl chloride (**1a**) and indium in the presence of palladium catalyst and additive (Table 1). After **1a** was treated with indium in the presence of LiCl, TMSCl, and 1,2-dibromoethane in DMF (50 °C, 3 h), the reaction mixture was subjected to **2a** in the presence of $Pd_2(dba)_3$, producing ethyl 4-benzoyl benzoate **3a** in 31% yield together with 4,4′-diethoxycarbonyl-1,1′-biphenyl (27%, **4**) (entry 1). However, the reaction did not proceed in DMSO (entry 2). Surprisingly, NMP as a solvent increased yield of **3a** to 77% (entry 3). Therefore, the formation of acyl anion equivalent was assumed.

Table 1. Reaction Optimization of Reversed-Polarity Ketone Synthesis[a]



entry	cat.	solvent	temp (°C)	time (h)	yield[b] (%)
1	$Pd_2(dba)_3$	DMF	90	2	31 (27)
2	$Pd_2(dba)_3$	DMSO	90	12	0
3	$Pd_2(dba)_3$	NMP	60	5	77 (11)
4	**$Pd_2(dba)_3$**	**NMP**	**25**	**3**	**86**
5	$Pd(OAc)_2$	NMP	60	12	0
6	$Pd(Ph_3P)_2Cl_2$	NMP	60	12	0
7	$Pd_2(dba)_3CHCl_3$	NMP	60	12	48 (15)
8	$Pd(Ph_3P)_4$	NMP	60	12	0

[a] **1a** (1.5 equiv) and **2a** (1 equiv) were used in the presence of In (3 equiv), LiCl (3 equiv), TMSCl (6 mol %), and $(BrCH_2)_2$ (15 mol %) in NMP. Indium reagent was prepared at 50 °C (entries 1−3) and 40 °C (entries 4−8) for 3 h. In the case of $Pd(OAc)_2$ and $Pd(Ph_3P)_4$, 4 mol % of catalyst was used. [b] Numbers in parentheses is isolated yield of 4,4′-diethoxycarbonyl-1,1′-biphenyl (**4**).

Among the solvents (THF, DMF, DMSO, NMP, THF−NMP, TH−DMF, and TH−DMSO) tested, NMP gave the best result (see the Supporting Information). The best result was obtained from the reaction of **2a** with acylindium reagent, which was generated in situ from **1a** (1.5 equiv) and indium (3 equiv) with lithium chloride (3 equiv), TMSCl (6 mol %), and 1,2-dibromoethane (15 mol %) at 40 °C for 3 h, in the presence of $Pd_2(dba)_3$ (2 mol %) in NMP at room temperature after 3 h, producing **3a** in 86% yield (entry 4). The use of a wide array of ligands [Xantphos, DPEphos, Ph_3P, Cy_3P, Cy_2(Biphenyl)P, $(furyl)_3P$, and $(o\text{-tolyl})_3P$] did not increase the yield (see the Supporting Information). Other palladium catalysts such as $Pd(OAc)_2$, $Pd(Ph_3P)_2Cl_2$, and $Pd(Ph_3P)_4$ were totally ineffective (entries 5, 6, and 8). A number of additives such as LiBr, LiI, KBr, and KI failed to give the coupling product in good yield (see the Supporting Information). Control experiments in the reaction of 4-iodoacetophenone with benzoyl chloride and indium suggest that use of TMSCl as well as dibromoethane is essential for giving successful results (see the Supporting Information). Commercially available indium does not react with benzoyl chloride. However, when LiCl was added to indium powder that had been activated with 1,2-dibromoethane and TMSCl, an efficient insertion occurred.[10−12] Ethyl 4-iodobenzoate pretreated with indium, lithium chloride, TMSCl, and dibromoethane in NMP was reacted with benzoyl chloride in the presence of $Pd_2(dba)_3$ to produce **3a** (12%) and **4** (52%), indicating that 4-ethoxycarbonylphenylindium was not involved in this reaction.[11] Because benzoyltrimethylsilane was not detected in the treatment of **1a** with In, LiCl, and TMSCl, the coupling reaction via the formation of benzoyltrimethylsilane ruled out.[5]

Next, we applied this catalytic system to various electrophiles to demonstrate the efficiency and scope of the present method (Scheme 4). Phenyl iodide was reacted with acylindium to produce benzophenone **3b** in 78% yield. The presence of an electron-donating group on the phenyl ring lowered the product yield. 3- and 4-Iodotoluene were converted to the corresponding ketones **3c** and **3d** in 58% and 47% yields, respectively, under modified conditions [4 mol % of $(Ph_3P)_4Pd$, 60 °C]. However, 3- and 4-iodobenzotrifluoride having an electron-withdrawing trifluoromethyl group gave the corresponding 3- and 4-trifluoromethylphenyl phenyl ketones **3e** (71%) and **3f** (63%). When 3-iodobenzaldehyde having an electrophilic labile formyl group was subjected to the standard conditions, the desired product **3g** was obtained in 77% yield. Treatment of 3- and 4-iodoacetophenone with acylindium reagent also provided the desired ketones **3h** and **3i** in 71% and 78% yields, respectively. Aryl iodide having an ethoxycarbonyl group furnished the desired ketone **3j** in 88% yield. 4-Iodobenzonitrile was reacted with acylindium, affording 4-cyanophenyl phenyl ketone **3k** in 67% yield. The tolerance of the formyl, ketone, ester, and nitrile group is especially significant, as successive functional group transformations are hopeful. As an extension of this work, we applied this catalytic system in aryl and alkenyl triflate. The reactivity of aryl triflate derived from ethyl 4-hydroxybenzoate is similar to that of ethyl 4-iodobenzoate, providing **3a** in 81% yield in the presence of 4 mol % of $Pd_2(dba)_3$. Subjecting alkenyl triflate to generated in situ acylindium produced the corresponding alkenyl aryl ketone **3l** in 67% yield.

Encouraged by these results, we investigated the coupling reaction of acyl anion equivalents having useful functional groups with a variety of aryl iodides **2** (Scheme 5). Acylindium

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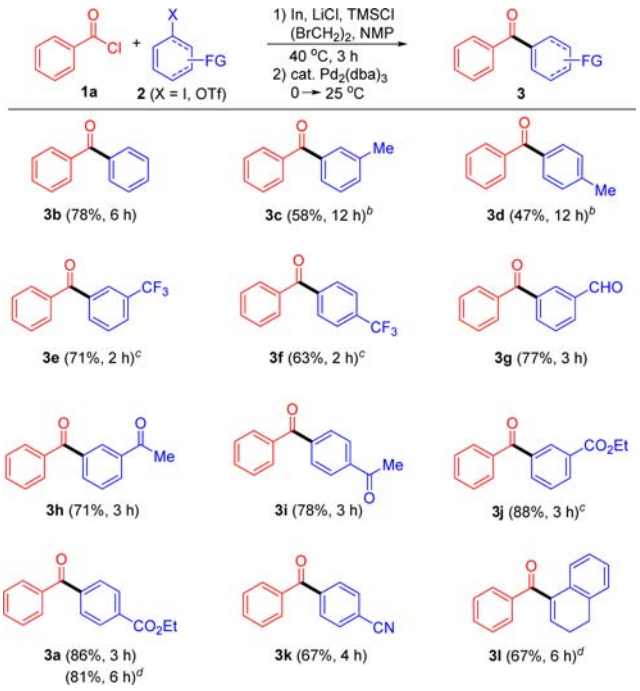
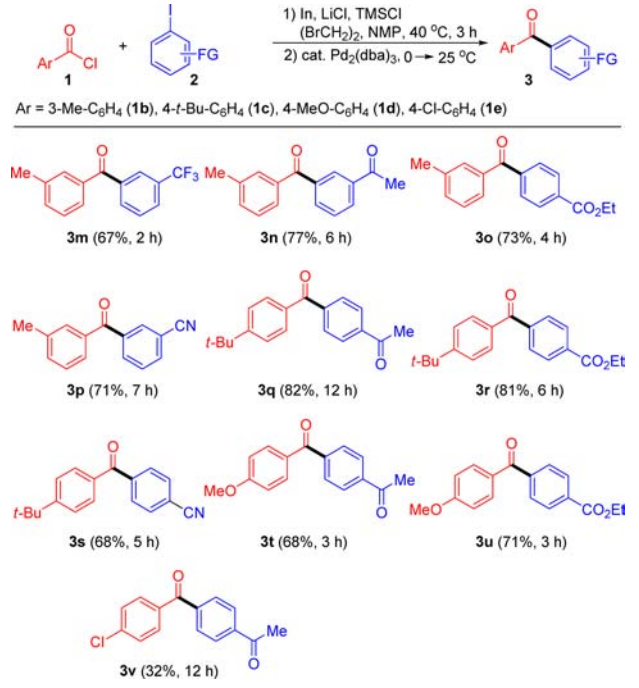
Scheme 4. Preparation of Ketones from Coupling of Acylindium with Electrophiles[a]



[a]**1a** (1.5 equiv) and **2** (1 equiv) were used in the presence of In (3 equiv), LiCl (3 equiv), TMSCl (6 mol %), $(BrCH_2)_2$ (15 mol %), and $Pd_2(dba)_3$ (2 mol %) in NMP unless otherwise noted. [b]4 mol % of $(Ph_3P)_4Pd$ was used. Coupling was carried out at 60 °C. [c]Coupling was carried out at 10 °C. [d]Triflate was used. 4 mol % of $Pd_2(dba)_3$ was used.

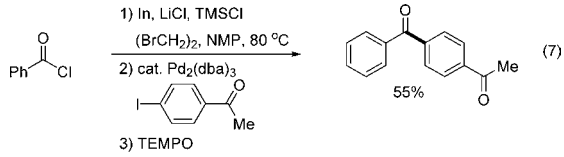
Scheme 5. Preparation of Unsymmetric Aryl Aryl Ketones from Coupling of Acylindium[a]



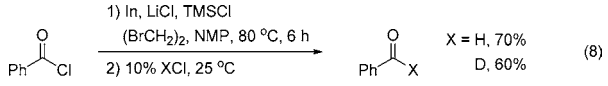
[a]**1** (1.5 equiv) and **2** (1 equiv) were used in the presence of In (3 equiv), LiCl (3 equiv), TMSCl (6 mol %), $(BrCH_2)_2$ (15 mol %), and $Pd_2(dba)_3$ (2 mol %) in NMP unless otherwise noted.

reagent generated in situ from 3-methylbenzoyl chloride **1b** and indium under the standard conditions was reacted with 3-iodobenzotrifluororide, 3-iodoacetophenone, ethyl 4-iodobenzoate, and 3-iodobenzonitrile to produce the corresponding unsymmetric aryl aryl ketones **3m**, **3n**, **3o**, and **3p** in good yields. Reaction of 4-*tert*-butylbenzoyl chloride **1c** with indium delivered also an acyl anion equivalent that coupled with aryl iodides having labile acetyl, ethoxycarbonyl, and nitrile group to provide the desired unsymmetric ketones **3q**, **3r**, and **3s**. Acylindium reagent derived from 4-methoxybenzoyl chloride **1d** worked equally well with electron-deficient aryl iodide. However, preparation of acylindium reagent from 4-chlorobenzoyl chloride **1e** and indium is not effective.

To prove the mechanism of the present reaction, we conducted the reaction of acylindium reagent generated in situ from benzoyl chloride with 4-iodoacetophenone under the standard conditions in the presence of radical inhibitor. As expected, adding 2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) did not retard or suppress the reaction (eq 7). These results indicate that the present reaction does not seem to proceed through a radical process promoted by indium.[13]



To prove the anion character of acylindium reagent generated in situ from benzoyl chloride and indium, the prepared reagent was quenched with 10% HCl and 10% DCl to afford benzaldehyde (70%) and benzaldehyde-d_1 (60%), respectively (eq 8). These results indicate that a variety of



organoindium reagents obtained from the present reactions have anion character, and the possibility of a radical intermediate rules out the mechanism. The elucidation of the detailed reaction mechanism must wait further study.

In conclusion, we have developed a reversed-polarity synthetic method for a diversity of unsymmetric aryl aryl and aryl alkenyl ketones via Pd-catalyzed cross-coupling reaction of acylindium reagents generated in situ from acid chlorides and indium. Because the direct synthetic method of unmasked acyl anion equivalents from easily available acid chlorides with indium has been developed for the first time under mild conditions, the present reaction is highly useful and promising. The tolerance of formyl, ketone, ester, and nitrile groups is especially practical, providing an opportunity for further functionalization.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

†This paper is dedicated to Professor T. Livinghouse (Montana State University) on the occasion of his 60th birthday.

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