Cross-Coupling

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Copper-Catalyzed Coupling of Triaryl- and Trialkylindium Reagents with Aryl Iodides and Bromides through Consecutive Transmetalations**

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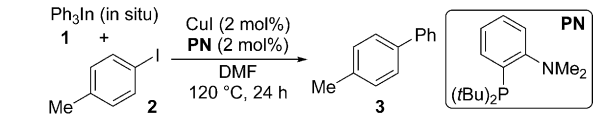
Abstract: *An efficient copper(I)-catalyzed coupling of triaryl and trialkylindium reagents with aryl iodides and bromides is reported. The reaction proceeds at low catalyst loadings (2 mol%) and generally only requires 0.33 equivalents of the triorganoindium reagent with respect to the aryl halide as all three organic nucleophilic moieties of the reagent are transferred to the products through consecutive transmetalations. The reaction tolerates a variety of functional groups and sterically hindered substrates. Furthermore, preliminary mechanistic studies that entailed the synthesis and characterization of potential reaction intermediates offered a glimpse of the elementary steps that constitute the catalytic cycle.*

Cross-coupling reactions remain versatile synthetic methods that are capable of coupling a range of organometallic reagents with organohalides and surrogates to construct carbon–carbon bonds.[1,2] As a result, applications of these coupling processes encompass a wide array of synthetic targets, ranging from the manufacturing of materials and pharmaceuticals to the synthesis of building blocks and natural products.[3] Aside from traditional organometallic reagents (such as RBX_2, $RSiX_3$, RZnX), triorganoindium reagents (R_3In) are increasingly gaining attention as efficient partners for palladium-catalyzed cross-couplings.[4] Furthermore, organoindium reagents have also been shown to undergo transmetalation with copper; this was first demonstrated for allylic substitution reactions.[5] The popularity of R_3In rests on its ability to efficiently transfer all of its three organic nucleophilic moieties (R) onto the products,[6] thereby generating only 0.33 equivalents of indium halide as a byproduct.[7]

Recently, we and others have shown that Cu^I catalysts effect the cross-coupling of organosilicon[8] and organoboron[9] reagents with organohalides.[10] These transformations typically work for the coupling of aryl metal reagents with aryl iodides.[11] However, the reported coupling reactions do not work well with *ortho*-substituted or sterically hindered substrates.[12] Herein, we wish to report a Cu^I-catalyzed coupling of triaryl- and trialkylindium reagents with aryl iodides and bromides that proceeds through three consecutive transmetalations and tolerates sterically hindered substrates. Furthermore, we have conducted preliminary mechanistic studies and propose a catalytic cycle that incorporates the consecutive transmetalations.

We recently reported that a combination of the ligand **PN** (Table 1) and CuI generated active catalysts that enabled the cross-coupling of aryl silicon[8a] and aryl boron[9a] reagents with aryl iodides. As part of our efforts to expand the scope of Cu^I-catalyzed coupling processes for C–C bond formation, we discovered that **PN**/CuI was an efficient catalyst for the coupling of triphenylindium with *para*-iodotoluene and afforded the product in 87% yield without requiring a base (yield determined by GC; Table 1, entry 1). The reaction provided only 10% of **3** in the absence of $InCl_3$ (entry 2).

Table 1: Cross-coupling of triphenylindium with *para*-iodotoluene.[a]



Entry	Modified conditions	Yield [%]
1	–	87
2	PhLi instead of Ph_3In (without $InCl_3$)	10
3	Ph_3In[b]	84
4	Ph_3In (0.33 equiv)	25
5	Ph_3In (0.33 equiv), CsF (1 equiv)	45
6	Ph_3In (0.33 equiv), NaOMe (1 equiv), 100 °C	97 (92)[c]

[a] The reactions were run on a 0.10 mmol scale in DMF (0.5 mL). Ph_3In was generated in situ from the reaction of PhLi with $InCl_3$. Yields determined by GC analysis using 2-nitrobiphenyl as the internal standard. [b] Partially purified to remove excess LiCl. [c] The value in parentheses gives the yield of isolated product for a reaction on a 1.0 mmol scale.

Furthermore, the reaction with Ph_3In that had been partially purified to remove excess LiCl also afforded **3** in comparable yields, suggesting that the halide salt does not play a role in the cross-coupling (entry 3).

However, despite the potential to transfer all three phenyl groups onto the products, the reaction of 0.33 equivalents of Ph_3In afforded the product only in 25% yield (entry 4). Addition of CsF improved the yield only marginally (45%). Investigations with in situ generated potential intermediates that were likely to be formed after the first (Ph_2InCl and

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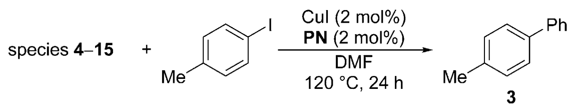
Ph_2InF) and the second ($PhInCl_2$ and $PhInF_2$) transmetalations in the absence and presence of CsF indicated that these latter species were inactive for further reactions (Scheme 1).[7c,e,h] Gratifyingly, studies with other anion sources (NaOMe, MeLi, and Me_2NLi) revealed that the phenylindium species $Ph_2In(OMe)$ and $PhIn(OMe)_2$, which were generated in situ from the reaction of two or one equivalents of PhLi with $InCl_3$ in the presence of one or two equivalents of NaOMe, were reactive and provided the cross-coupled product in 75 % and 63 % yield, respectively (Scheme 1). After identifying MeO^- as an effective anion, we conducted the reaction with only 0.33 equivalents (33.3 mol %) of Ph_3In with *para*-iodotoluene in the presence of one equivalent of NaOMe and 2 mol % of **PN**/CuI. The reaction proceeded at 100 °C and afforded the product in 97 % yield in 24 hours (entry 6).

After optimizing the reaction conditions, we examined the substrate scope of the current reaction. The transformation displays a broad substrate scope, and the coupling of electron-rich or electron-poor aryl iodides with electron-neutral or electron-rich organoindium reagents proceeded well (Table 2 A). The coupling of aryl iodides that contain highly sensitive functional groups, such as esters or nitriles, gave the desired products in good yields (**27**–**30**). With heteroaryl iodides, the reaction proceeded in the absence of **PN** to provide the corresponding products in excellent yields, and a variety of functional groups, such as alkoxy and chloride moieties, were tolerated (Table 2 B). This method is also

$$Ph_3In \xrightarrow[\text{(CuX)}]{\text{1st TM}} Ph_2InX \xrightarrow[\text{(CuX)}]{\text{2nd TM}} PhInX_2 \xrightarrow[\text{(CuX)}]{\text{3rd TM}} InX_3$$

TM = transmetalation; X = I, Cl, F, Me, NMe_2, OMe

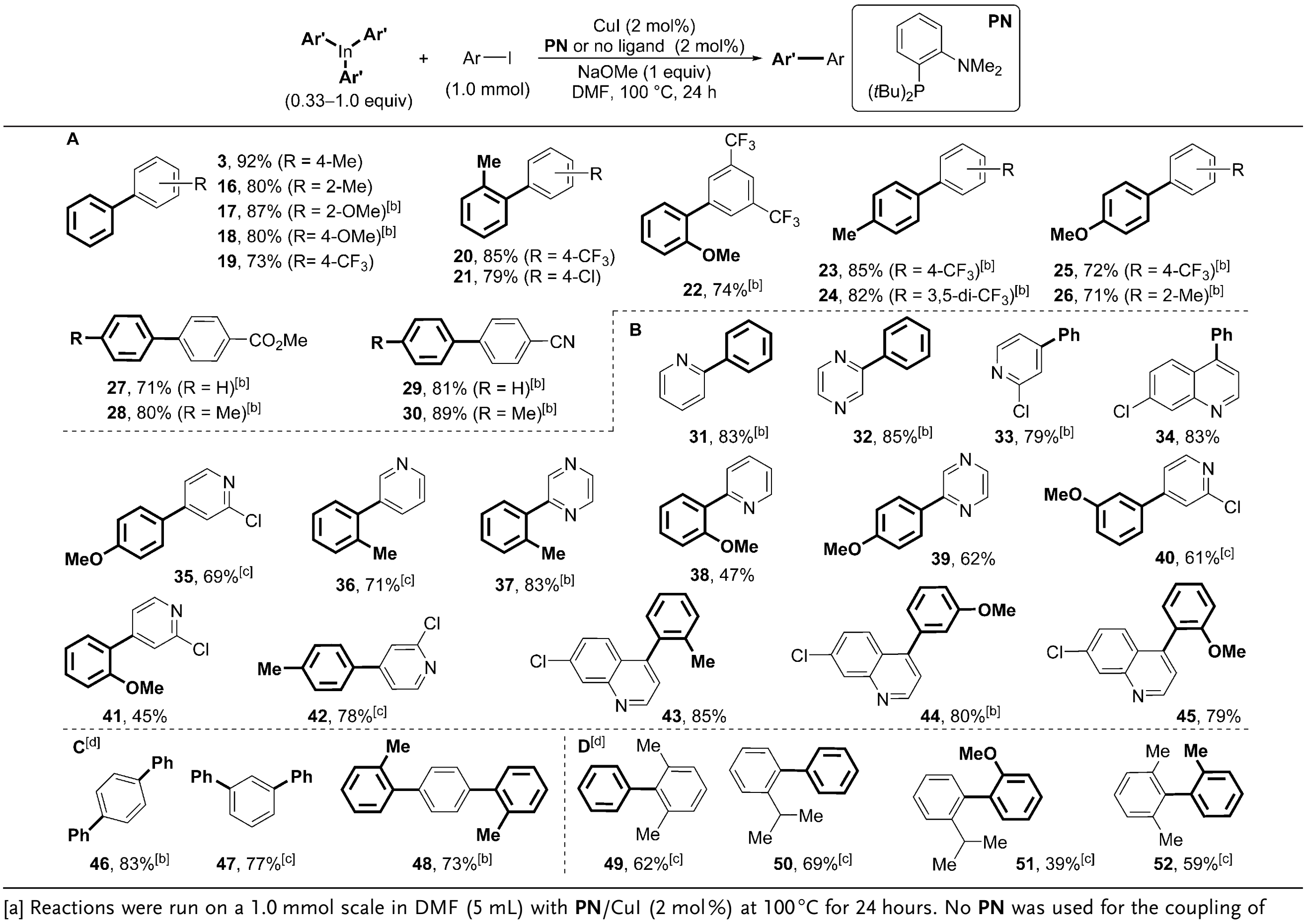


GC yields of product **3** for the reaction of **4**–**15** with *para*-iodotoluene:

Ph_3In **4**, 87%	Ph_2InCl **5**, trace	$PhInCl_2$ **6**, 0%	Ph_2InF **7**, 12%
$PhInF_2$ **8**, 0%	Ph_2InOMe **9**, 75%	$PhIn(OMe)_2$ **10**, 63%	$PhIn(OMe)Cl$ **11**, trace
$PhInMe_2$ **12**, 35%	Ph_2InMe **13**, 40%	$PhIn(NMe_2)_2$ **14**, 0%	Ph_2InNMe_2 **15**, 0%

Scheme 1. Reactions of various phenylindium species that can be formed by consecutive transmetalations with *para*-iodotoluene. Reaction conditions: 0.10 mmol scale, **PN**/CuI (2 mol %), 120 °C, 24 h in DMF (0.5 mL). The phenylindium reagents were prepared from the reaction of $InCl_3$ with the required amount of the corresponding base (MeLi, $LiNMe_2$, or NaOMe) and PhLi in THF at room temperature. Yields were determined by GC analysis using 2-nitrobiphenyl as the internal standard.

Table 2: Coupling of triarylindium reagents with aryl and heteroaryl iodides.[a]

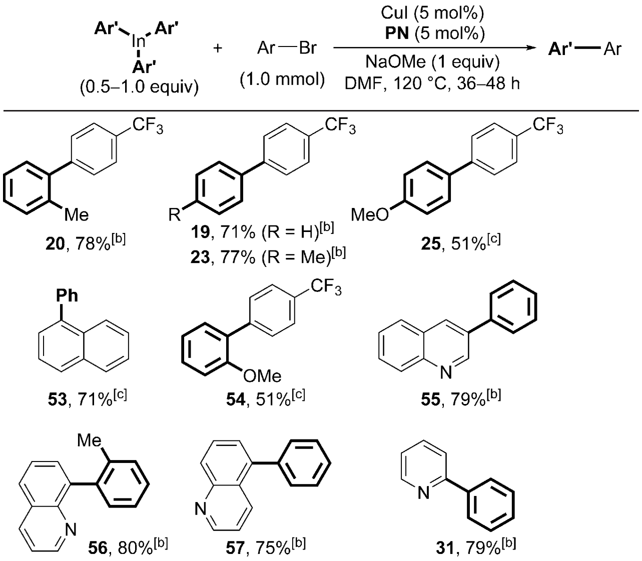


[a] Reactions were run on a 1.0 mmol scale in DMF (5 mL) with **PN**/CuI (2 mol %) at 100 °C for 24 hours. No **PN** was used for the coupling of heterocyclic substrates. Ar'_3In reagents (0.33 equiv) were prepared in situ from the reaction of $InCl_3$ with the corresponding ArLi reagent in THF at room temperature. Yields of isolated products are given. [b] Ar_3In (0.5 equiv). [c] Ar_3In (1.0 equiv). [d] 120 °C.

applicable to the arylation of diiodoarenes; both iodo groups were arylated with ease (Table 2C). Unlike previously reported Cu^I-catalyzed cross-couplings with organoboron and organosilicon reagents,[8,9] the current reaction works very well for *ortho*-substituted and sterically hindered substrates, even for tris(2-methoxyphenyl)indium and tris(2-methylphenyl)indium reagents with 2-isopropyl- and 2,6-dimethyliodobenzene, respectively (Table 2D). However, these reactions required stoichiometric amounts of Ar_3In and a higher temperature (120 °C).

The current reaction conditions also allow for the efficient cross-coupling of triarylindium reagents with aryl bromides (Table 3). Typically, the reaction proceeded well with neutral and electron-poor aryl bromides, affording the corresponding products in good yields. A variety of heteroaryl bromides could also be coupled with different triarylindium reagents to generate the desired products in excellent yields. Furthermore, the reaction can be extended to the coupling of trialkylindium reagents with aryl iodides to afford the cross-coupled products in good to excellent yields (Table 4). However, these reactions required stoichiometric amounts of the organoindium reagents. The reaction proceeded with both primary and secondary alkylindium reagents. Unlike with trialkylindium species that had been prepared from alkyllithium reagents (**63**), the reactions of alkylindium reagents that had been generated from Grignard reagents and $InCl_3$ proceeded in the absence of NaOMe (**58–62**, **64**, and **65**).

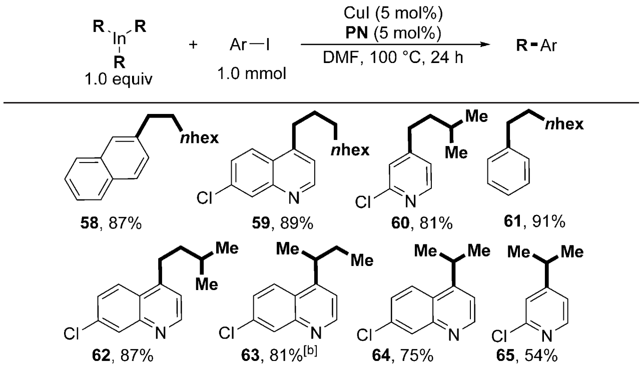
Table 3: Coupling of triarylindium reagents with aryl and heteroaryl bromides.



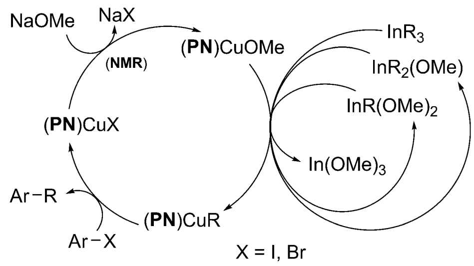
[a] Reactions were run on a 1.0 mmol scale in DMF (5 mL). Ar'_3In reagents were prepared in situ from the reaction of $InCl_3$ with the corresponding ArLi reagent (3 equiv) in THF at room temperature. Yields of isolated products are given. [b] Ar_3In (0.5 equiv). [c] Ar_3In (1.0 equiv).

We further conducted preliminary mechanistic studies, and a possible catalytic cycle is presented in Scheme 2. We showed by ^1H and ^{31}P NMR studies in [D7]DMF that

Table 4: Coupling of trialkylindium reagents with aryl and heteroaryl iodides.[a]

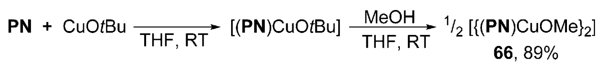


[a] Reactions were run on a 1.0 mmol scale in DMF (5 mL). R_3In reagents were prepared in situ from the reaction of $InCl_3$ with RLi or RMgX (3 equiv) in THF at room temperature. Yields of isolated products are given. [b] The reaction of PhI with $(iPr)_3In$ provided the cross-coupled product in only 30% yield based on ^1H NMR spectroscopy. R_3In reagents for the synthesis of products **58–62**, **64**, and **65** were generated from the reactions of the corresponding RMgX reagents with $InCl_3$.



Scheme 2. Proposed catalytic cycle incorporating consecutive transmetalations.

[(**PN**)CuOMe] (**66**) is readily generated from the reaction of [(**PN**)CuI] with NaOMe at room temperature. The formation of [(**PN**)CuOMe] was confirmed by comparison of the ^1H and ^{31}P NMR signals of the reaction mixture with those of NaOMe and independently synthesized and fully characterized samples of [(**PN**)CuI][9a] and [(**PN**)CuOMe]. [(**PN**)CuOMe] was synthesized by stirring [(**PN**)CuO*t*Bu], which had been generated in situ by mixing a 1:1 ratio of **PN** and CuO*t*Bu, with MeOH in THF at room temperature (Scheme 3) and characterized by NMR spectroscopy, elemental analysis, and single-crystal X-ray diffraction. Based on



Scheme 3. Synthesis of [{(PN)CuOMe}$_2$] (**66**).

its X-ray structure, [(**PN**)CuOMe] exists as a methoxy-bridged dimer in the solid state (Figure 1). Complex **66** is also catalytically active and afforded the cross-coupled product **3** in 92% yield (determined by GC) from the reaction of Ph_3In (0.33 equiv) with *para*-iodotoluene under the standard reaction conditions. Therefore, we anticipate that R_3In and the intermediate species $R_2In(OMe)$ and

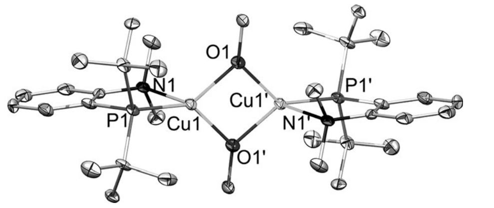
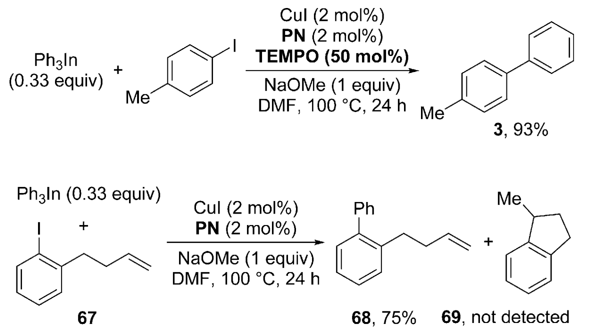


Figure 1. X-ray crystal structure of **66**. Selected bond lengths [Å] and angles [°]: Cu(1)–O(1) 1.995(5), Cu(1)–P(1) 2.1234(19), Cu(1)–N(1) 2.421(6); O(1)-Cu(1)-P(1) 140.78(14), O(1)-Cu(1)-N(1) 100.1(2), P(1)-Cu(1)-N(1) 84.02(14).

$RIn(OMe)_2$ undergo consecutive transmetalations with [(**PN**)CuOMe] in reactions conducted with **PN**/CuI in the presence of NaOMe.

Moreover, we conducted experiments with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical scavenger and the radical probe **67** to provide evidence for the presence or absence of free aryl radical intermediates during the reaction (Scheme 4). The reaction of Ph_3In (0.33 equiv) with *para*-iodotoluene remained unaffected by the addition of 50 mol% of TEMPO (93% yield as determined by GC). Furthermore, the radical probe **67** reacted with Ph_3In (0.33 equiv) under the standard reaction conditions to afford the arylated product **68** in 75% yield. However, the cyclized product **69**, which was expected to arise from the presence of the corresponding *ortho*-(3-butenyl)phenyl free radical, was not detected. These experiments suggest that the transformation is unlikely to proceed via free aryl radical intermediates,[13] implying that the reaction likely proceeds by an oxidative addition/reductive elimination pathway.[14]



Scheme 4. Mechanistic studies to probe the presence of aryl radical intermediates.

In summary, we have developed an efficient copper(I)-catalyzed coupling of triorganoindium reagents with aryl iodides and bromides. All of the three organic nucleophilic moieties of the reagent were transferred to the products through three consecutive transmetalations. Aside from triarylindium reagents, the reaction also proceeded well with trialkylindium compounds for alkyl–aryl cross-couplings. The transformation tolerates sterically hindered aryl halides and *ortho*-substituted triarylindium reagents. Preliminary mechanistic studies were conducted by independently synthesizing possible reaction intermediates and by following the stoichiometric reactions by NMR spectroscopy to elucidate the sequence of elementary steps in the catalytic cycle.

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