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General Approach to the Coupling of Organoindium Reagents with Imines via Copper Catalysis

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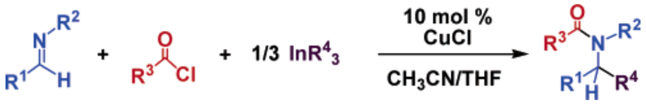
ABSTRACT



A copper-catalyzed three-component coupling of organoindium reagents with imines and acid chlorides is described. This mild carbon–carbon bond forming reaction requires only one-third of an equivalent of indium reagent to proceed in high yield, with the sole byproduct being indium trichloride. The reaction demonstrates broad generality, with aryl-, heteroaryl-, vinyl-, and alkylindiums, as well as functionalized imines and acid chlorides, all providing α-substituted amides or N-protected amines in a single step.

Metal-catalyzed cross-coupling reactions between organic electrophiles and organometallic compounds represent one of the more important current methods to construct carbon−carbon bonds.[1] The performance of these reactions with a diverse variety of substrates, as well as with high conversion, selectivity, and atom economy, remains the focus of intense research efforts.[1a] One class of reagents that has recently been shown to be beneficial in these reactions is tri- and tetraorganoindiums.[2] These compounds have overcome several of the limitations associated with the organometallic reagents commonly employed in cross-coupling (e.g., organostannanes, organoboranes), including the facile coupling with sp^3-hybridized alkylindium groups, the low toxicity indium byproducts, and the important ability to transfer more than one of the organic substituents from the indium reagent.[2]

Although organoindiums have been successfully employed in reactions with a range of traditional cross-coupling partners (e.g., organohalides)[2,3] and a number of other metal-catalyzed processes,[4−8] their application to carbon−carbon bond formation with C═N electrophiles such as imines is much more limited.[9] Barbier and Reformatsky-type reactions have been applied to imines;[10−14] however, these processes are typically

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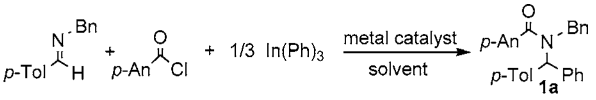
limited to the addition of allylic- or α-ester-indium functionalities. To our knowledge, there is no general method available to couple organoindium reagents with imines, as a mild route to important α-substituted amine building blocks.

We have recently reported that multiply bonded electrophiles such as imines can be activated toward a Stille-like cross-coupling reaction with organostannanes by the simple addition of acid chlorides, to form α-substituted amides.[15] This presumably occurs via the in situ conversion of imine into *N*-acyl iminium salt for reaction with the metal catalyst. Nevertheless, we were unable to transfer many sp^3-hybridized groups from organostannanes, and the reaction leads to the formation of stoichiometric amounts of toxic tin byproducts. We report herein that this approach can be used to generate what is to our knowledge a novel general method to couple organoindium reagents with imines. This reaction occurs with a broad range of organoindium, imine, and acid chloride substrates and provides overall a mild multicomponent method to construct α-substituted amides and N-protected amines.

Our initial studies toward this coupling are outlined in Table 1. The model system involved the coupling of *N*-benzyltolylaldimine, *p*-anisoyl chloride (*p*-An = 4-C_6H_4-OCH_3, *p*-Tol = 4-$C_6H_4CH_3$), and triphenylindium.[16] As can be seen, no coupling is observed when the triorganoindium reagent is used without any catalyst (entry 1) nor does a palladium catalyst lead to a reaction. The latter is in contrast to our results with organostannanes and imines and is potentially the result of a slower transmetalation between indium and the palladium center.[15b] It has previously been reported that unreactive tin reagents can be induced to undergo cross-coupling through the addition of copper salts.[17] Similarly, the addition of 10 mol % of CuCl to this reaction provided the desired α-substituted amide product in 29% yield. Under optimized conditions, this coupling is nearly quantitative (98%, entry 4). Although a number of copper salts proved to be competent catalysts, simple, commercially available CuCl is the most efficient.

Table 1. Catalytic Coupling of *N*-Benzyltolylaldimine, *p*-Anisoyl Chloride, and Triphenylindium[a]

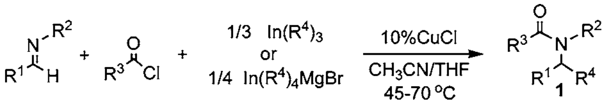


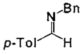
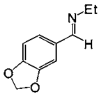
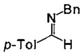
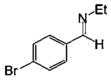
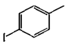
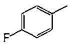
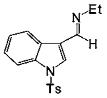
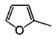
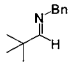
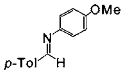
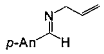
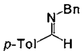
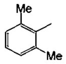
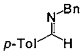
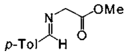
entry	catalyst	solvent	yield **1a** (%)[b]
1	-	CH_3CN	0
2	5% $Pd_2(dba)_3$	CH_3CN	0
3	10% CuCl	CH_3CN	29
4	10% CuCl	CH_3CN/THF	98
5	10% CuCl	THF	45
6	10% CuCl	toluene/THF	69
7	10% $CuCl_2$	CH_3CN/THF	55
8	10% CuI	CH_3CN/THF	95
9	10% Cu(OTf)[c]	CH_3CN/THF	84

[a] 0.50 mmol of imine, 0.60 mmol of acid chloride, 0.167 mmol of triorganoindium, and 0.05 mmol of CuCl in 1:1 CH_3CN/THF (6 mL) for 14 h at 45 °C. [b] NMR yields. [c] Cu(OTf) benzene complex used.

A notable feature of this chemistry is the ability of the organoindium reagent to transfer all of its organic groups to the imine carbon. Thus, the use of only one-third of an equivalent of Ph_3In is required to generate **1a** in near quantitative yield, with the sole byproduct being $InCl_3$. As shown in Table 2, this reaction is not limited to phenyl group transfer, and efficient coupling can also be achieved with vinyl units (**1c**, **1f**, **1k**), functionalized arenes (**1d**, **1j**), and

Table 2. Copper-Catalyzed Three-Component Coupling of Imines, Acid Chlorides, and Organoindium Reagents[a]



#	imine	R^3	R^4	yield (%)[b]
1a		*p*-An	Ph	95 (96)
1b		BnO	Et	92 (94)[c]
1c		BnO		89 (91)
1d				81 (87)
1e			*o*-Tol	79 (84)
1f		CH_3		89 (95)
1g		EtO	*s*-Bu	77 (75)[e]
1h		PhO	Et	84 (84)[d]
1i		*p*-An		84 (94)
1j		*p*-An	*o*-An	86 (90)
1k		*i*-Pr		74

[a] Reactions performed with 0.50 mmol of imine, 0.60 mmol of acid chloride or chloroformate, 0.167 mmol of triorganoindium or 0.133 mmol of tetraorganoindate, and 0.05 mmol of CuCl in 1:1 CH_3CN/THF (6 mL) for 14 h at 45 °C. [b] Yields in parentheses for reactions with tetraorganoindates. [c] 65 °C for 36 h. [d] 55 °C for 24 h. [e] 70 °C for 72 h.

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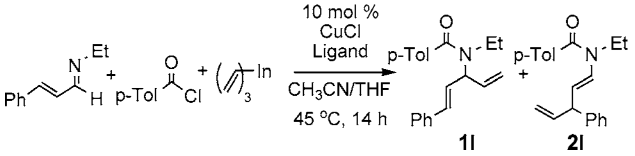
even sterically encumbered aryllindium reagents (**1e**, **1i**). The latter includes a 2,6-dimethylphenyl substrate in 84% yield. Even primary and secondary alkyl groups undergo reaction in good yields at slightly elevated temperatures. This level of diversity far surpasses that which we previously observed in Stille-type couplings with imines. A variety of imines and acid chlorides can also be employed in this coupling, including *N*-aryl and *N*-alkyl substituents, as well as imines derived from aryl, heteroaryl, and nonenolizable alkyl aldehydes. Both alkyl and aryl acid chlorides, as well as a range of chloroformates, provide the α-substituted amides and N-protected α-substituted amines, respectively, in high yield. This chemistry also demonstrates good functional group compatibility, with even acidic substrates (e.g., enolizable acid chlorides, glycine derivatives) being compatible with coupling.

It has been previously demonstrated that tetraorganoindium reagents can also behave as cross-coupling partners in a fashion similar to triorganoindium and provide an atom-economical method to transfer all four organic groups on the indium.[2d,3c] These reagents can also be employed in this reaction with imines (Table 2) and require only one-fourth of an equivalent of indium for the reaction to proceed in generally even higher yields than those observed with triorganoindium compounds.

The use of an α,*β*-unsaturated imine in this coupling leads to the clean formation of the 1,4-addition product **2l** (Table 3). Interestingly, this Michael addition product contrasts with the previously reported mixture of 1,2- and 1,4-addition products in reactions with vinylstannanes under identical conditions.[15a] Although the mechanism of this process is still under investigation, these data suggest a distinct carbon−carbon bond forming step with organoindium reagents, potentially with an interaction between the indium compound and copper catalyst **4** (Figure 1) or coordination of the Lewis acidic indium with an in situ generated *N*-acyl iminium salt (**3**) prior to nucleophilic attack.[18] At present, these possibilities cannot be distinguished, although it is notable that the addition of ligands to catalysis, which could presumably coordinate to copper and displace any indium association, leads to the favored formation of the 1,2-addition product **1l**. This selectivity is similar to that observed with organostannanes.[19] Importantly, this also provides a useful catalyst-based method to influence 1,2-addition (CuI) vs 1,4-addition (CuCl), by simply modifying the copper salt employed.

Table 3. 1,2- vs 1,4-Addition with α,*β*-Unsaturated Imines[a]



ligand	% **1l**	% **2l**	ratio **1l**/**2l**
-		81	1:>20
bipy	41	16	2.5:1
dppe	21	25	1:1.2
phen	24	12	2:1
3,4,9,10-tetramethylphenanthroline	49	20	2.4:1
CuBr[b]	61	16	3.8:1
CuI[b]	73	11	7:1
Bu_4NBr[c]	31	23	1.3:1
Bu_4NI[c]	13	32	1:2.5

[a] 0.13 mmol of imine, 0.16 mmol of acid chloride, 0.042 mmol of triorganoindium, and 0.013 mmol of CuCl in 1:1 CH_3CN/THF (6 mL) for 14 h at 45 °C. [b] Used as catalyst instead of CuCl. [c] 1 equiv.

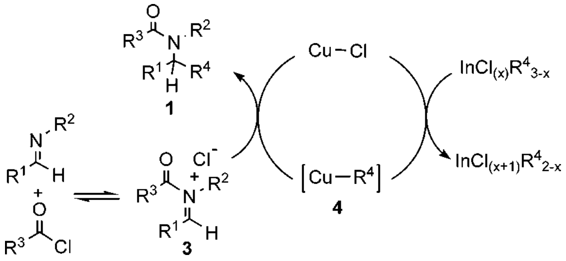


Figure 1. Proposed mechanism of the copper-catalyzed multicomponent coupling.

In conclusion, we have developed a general, copper-catalyzed method for coupling organoindium reagents with imines and acid chlorides. This provides an efficient method to construct α-substituted amides and N-protected α-substituted amines, as well as one that can be readily diversified. The method is highly regiospecific and is atom efficient. Studies directed toward control of enantioselectivity in this process, as well as the use of other transmetalating agents, are currently underway.

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Supporting Information Available: Synthesis and spectral data for α-substituted amide products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Although a radical pathway is also possible, the addition of radical traps 9,10-dihydroanthracene and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) to the reaction does not perturb the reaction rate or product yield.

(19) The selectivity observed with ligands present is similar to that noted with vinylstannanes (e.g., phenanthroline/CuI with vinyl(Bu)$_3$Sn: 3:1 ratio favoring the 1,2-addition product **1l**).[15a]