

Multifold and sequential cross-coupling reactions with indium organometallics†

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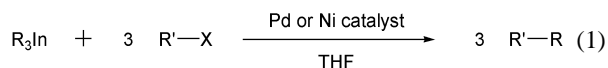
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Multifold and sequential palladium-catalyzed cross-coupling reactions can be performed between triorganoindium compounds and oligohaloarenes using only a small excess of the organometallic reagent, low catalyst charge loading and short reaction times.

The chemistry of compounds containing highly unsaturated, conjugated π -systems has received a great deal of attention in recent years due the potential uses of these compounds in materials science.^{1,2} Among the wide variety of conjugated architectures, polyphenylene and polyphenylacetylene structures, as well as derivatives bearing a heterocyclic unit in their structure, are of particular interest. Their utility as liquid crystals,³ core structures for dendrimers,⁴ building blocks for two-dimensional carbon networks,⁵ electronic and optoelectronic devices,⁶ and molecular wires,² has been studied extensively.

Although several synthetic approaches to these highly unsaturated and conjugated π -systems have been developed, palladium-catalyzed cross-coupling reactions remain the most useful and straightforward strategies.^{1,7} Usually, the cross-coupling reactions are performed between oligohaloarenes and the appropriate acetylenic or organometallic partners to afford the desired multifold cross-coupling products in one step. Unfortunately, the reactions usually require a large excess of the organometallic reagent, harsh reaction conditions (high temperatures and pressure, long reaction times) and the yields obtained are sometimes low.⁸

We recently developed an atom-efficient palladium-catalyzed cross-coupling reaction between triorganoindium compounds (R_3In) and electrophiles, where the indium organometallics transfer all three organic groups to the electrophile (eqn. (1)).⁹ The high efficiency of this procedure, which is carried out with only a small excess of organometallic reagent and a low catalyst loading, has stimulated our interest in its application to multifold cross-coupling reactions. The first successful examples of the use of triorganoindium compounds in multiple and sequential palladium-catalyzed cross-coupling reactions are described herein.



As the starting oligohaloarenes we chose a benzene derivative, 1,3,5-tribromobenzene (**1**), an electron-deficient heteroaromatic compound, 2,6-dibromopyridine (**2**), and an electron-rich heteroaromatic compound, 2,5-dibromothiophene (**3**). As R_3In we were mainly interested in the introduction of acetylenic and aromatic units.‡ In our first attempt the cross-coupling of 1,3,5-tribromobenzene (**1**) and Ph_3In (130 mol%) in the presence of $Pd(dppf)Cl_2$ (4 mol%) afforded, after 6 h under reflux in THF, 1,3,5-triphenylbenzene (**4a**) in 97% yield, a result that demonstrates the efficient transfer of all three organic groups attached to the indium(III). Following the same experimental procedure, the reaction of **1** with tri(phenylethynyl)indium afforded the threefold cross-coupling product **4b** in

quantitative yield. 1,3,5-Triphenylbenzene (**4a**) and its acetylenic derivative **4b** (Fig. 1) have interesting physical properties as liquid crystals¹⁰ or non-linear optical materials.¹¹ Other triphenyl- and triethynylbenzene derivatives can be prepared using the same experimental procedure (Table 1, entries 3 and 4). Remarkable features in this process are the small excess of R_3In used, the short reaction times and the high yields obtained.

Encouraged by these results, we explored the reactivity of other types of aromatic ring. Aryl-substituted pyridines have received significant attention as fluorescent chemosensors¹² and as chelating agents in coordination chemistry,¹³ but the preparation of these compounds by cross-coupling reactions have involved certain synthetic difficulties.¹⁴ The reaction of 2,6-dibromopyridine (**2**) with triphenylindium (80 mol%) or tri(phenylethynyl)indium (100 mol%) in the presence of a catalytic amount of $Pd(dppf)Cl_2$ (4 mol%) afforded the twofold cross-coupling products **5a** and **5b**, respectively, in excellent yields (Table 1, entries 5 and 6). Other organic residues such as the vinyl group or acetylenic derivatives could also be efficiently coupled, although in these cases larger amounts of

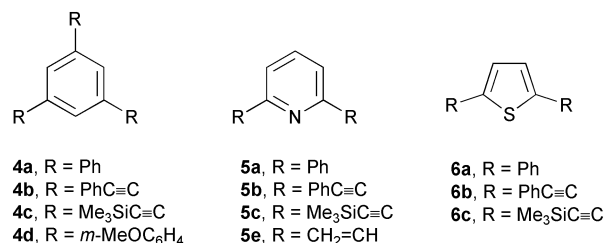


Fig. 1 Multifold cross-coupling products.

Table 1 Results of the multifold cross-coupling reaction of triorganoindium compounds (R_3In) with oligohaloarenes (1–3)

Ar—X _n		R ₃ In		Pd(II) catalyst		Ar—R _n	
1–3		THF				4–6	
Entry	Ar—X _n ^a	R	R ₃ In (mol%) ^c	Product	Yield (%) ^b		
1	1	Ph	130	4a	97		
2		PhC≡C	130	4b	99		
3		Me ₃ SiC≡C	150	4c	80		
4		<i>m</i> MeOC ₆ H ₄	130	4d	70		
5	2	Ph	80	5a	91		
6		PhC≡C	100	5b	99		
7		Me ₃ SiC≡C	200	5c	88		
8		CH ₂ =CH	150	5e	70		
9	3	Ph	200	6a	84		
10		PhC≡C	150	6b	91		
11		Me ₃ SiC≡C	150	6c	77		

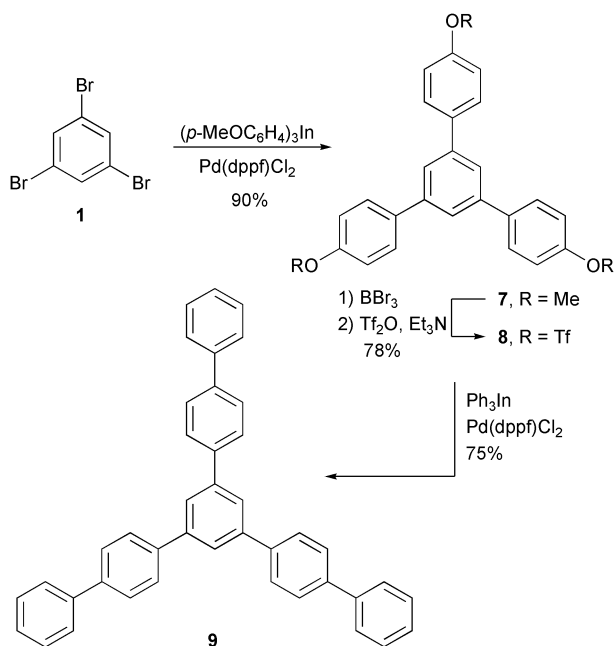
^a **1**: 1,3,5-Tribromobenzene; **2**: 2,6-dibromopyridine; **3**: 2,5-dibromothiophene. ^b Isolated yield. ^c Reactions were carried out in THF at reflux in 1–7 h using 4 mol% of $Pd(dppf)Cl_2$ as catalyst.

† Electronic supplementary information (ESI) available: ¹H and ¹³C NMR data for compounds. See <http://www.rsc.org/suppdata/cc/b2/b206346h/>

indium organometallic reagent were necessary (Table 1, entries 7 and 8).

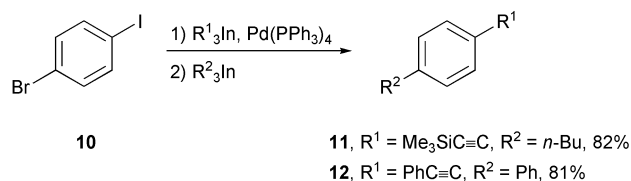
The multiple cross-coupling with an electron-rich aromatic ring, *i.e.* thiophene **3**, was also tested. The phenyl or ethynyl groups were efficiently incorporated, although up to 200 mol% of the indium organometallic was necessary to optimize the yield (Table 1, entries 9–11). The twofold cross-coupling products obtained (**6a–c**, Fig. 1) have been proposed as molecular wires.²

At this stage we envisioned the use of R_3In in the synthesis of dendritic-type molecules by successive multifold cross-coupling reactions.¹⁵ The reaction of 1,3,5-tribromobenzene (**1**) with tris(*p*-methoxyphenyl)indium, in the presence of Pd(dppf)Cl₂ as catalyst, afforded the threefold coupling product **7** in 90% yield (Scheme 1). In order to obtain the next generation dendrimer, trimethoxyphenylene **7** was converted into the tris(triflate) **8** by treatment with BBr₃ and subsequent reaction with triflic anhydride (78% yield, two steps). The cross-coupling reaction of **8** with Ph₃In afforded the polyphenylene dendritic-type compound **9** in 75% yield. The synthesis of **9** demonstrates the scope of indium organometallics in multifold cross-coupling reactions towards polyphenylene dendrimers.



Scheme 1 Synthesis of polyphenylene **9**.

Additionally, we also explored the use of indium organometallics in sequential one-pot metal-catalyzed cross-coupling reactions. The successive addition of different indium organometallics to an oligohaloarene such as 1-bromo-4-iodobenzene (**10**) could provide information about the chemoselectivity of these reagents. On the other hand, the construction of a variety of different carbon–carbon bonds in a one-pot reaction is a relevant methodology from an economic and environmental point of view. With these aims in mind, a refluxing solution of **10** and Pd(PPh₃)₄ (2 mol%) was treated successively with two different organoindium compounds (40 mol% each), affording the corresponding twice-cross-coupled products (**11** and **12**) in good yields (81 and 82% respectively, Scheme 2). These results illustrate the chemoselectivity of the reaction and the utility of indium organometallics in the one-pot preparation of unsymmetrically substituted aromatic compounds.



Scheme 2 Sequential cross-coupling reactions with triorganoindium compounds (R_3In).

In conclusion, we have demonstrated that indium organometallics can be efficiently employed in multifold palladium-catalyzed cross-coupling reactions using polyhalogenated aromatic compounds. Comparing with other organometallics, the reactions are performed under relatively milder conditions and short reaction times. In addition, a novel sequential cross-coupling reaction using indium organometallics is reported. The study of further applications of this methodology is now underway.

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Notes and references

‡ Triorganoindium compounds were prepared by treatment of the corresponding organolithium or Grignard reagents (3 equiv.) with InCl₃ (1.1 equiv.) in dry THF at –78 °C and warming up to room temperature. For further experimental details, see ref. 9.

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