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Multifold and sequential cross-coupling reactions with indium organometallics†

Miguel A. Pena, Ignacio Pérez, José Pérez Sestelo* and Luis A. Sarandeses*
Departamento de Química Fundamental, Universidade da Coruña, E-15071 A Coruña, Spain.
E-mail: qfsarand@udc.es; Fax: +34 981 167 065; Tel: +34 981 167 000

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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.

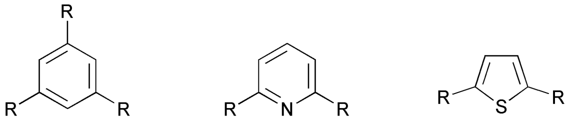
Although several synthetic approaches to these highly unsaturated and conjugated π-systems have been developed, palladium-catalyzed cross-coupling reactions remain the most useful and straightforward strategies.[1,7] Usually, the cross-coupling reactions are performed between oligohaloarenes and the 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.

$$R_3In + 3\ R'{-}X \xrightarrow[\text{THF}]{\text{Pd or Ni catalyst}} 3\ R'{-}R \quad (1)$$

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 crystals[10] 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 chemosensors[12] 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



4a, R = Ph
4b, R = PhC≡C
4c, R = $Me_3SiC{\equiv}C$
4d, R = *m*-$MeOC_6H_4$

5a, R = Ph
5b, R = PhC≡C
5c, R = $Me_3SiC{\equiv}C$
5e, R = $CH_2{=}CH$

6a, R = Ph
6b, R = PhC≡C
6c, R = $Me_3SiC{\equiv}C$

Fig. 1 Multifold cross-coupling products.

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

$$\underset{\textbf{1–3}}{Ar{-}X_n} + R_3In \xrightarrow[\text{THF}]{\text{Pd(II) catalyst}} \underset{\textbf{4–6}}{Ar{-}R_n}$$

Entry	Ar–X_n[a]	R	R_3In (mol%)[c]	Product	Yield (%)[b]
1	**1**	Ph	130	**4a**	97
2		PhC≡C	130	**4b**	99
3		$Me_3SiC{\equiv}C$	150	**4c**	80
4		*m*$MeOC_6H_4$	130	**4d**	70
5	**2**	Ph	80	**5a**	91
6		PhC≡C	100	**5b**	99
7		$Me_3SiC{\equiv}C$	200	**5c**	88
8		$CH_2{=}CH$	150	**5e**	70
9	**3**	Ph	200	**6a**	84
10		PhC≡C	150	**6b**	91
11		$Me_3SiC{\equiv}C$	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.

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

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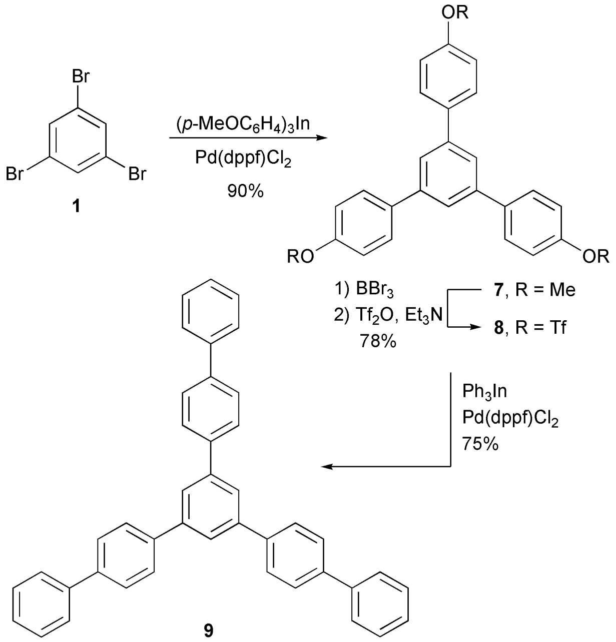
indium organometallic reagent were necessary (Table 1, entries 7 and 8).

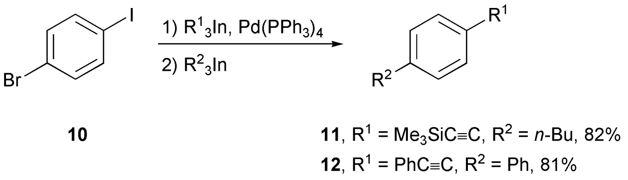
The multiple cross-coupling with an electron-rich aromatic ring, *i.e.* thiophene **3**, was also tested. The phenyl or ethynyl groups were efficiently incorporated, although up to 200 mol% of the indium organometallic was necessary to optimize the yield (Table 1, entries 9–11). The twofold cross-coupling 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 $Pd(dppf)Cl_2$ 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 tristriflate **8** by treatment with BBr_3 and subsequent reaction with triflic anhydride (78% yield, two steps). The cross-coupling reaction of **8** with Ph_3In 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 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 $Pd(PPh_3)_4$ (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 $InCl_3$ (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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