Fluoride-triggered indium-mediated synthesis of (hetero)biaryls†‡

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A simple method for the preparation of triorganoindium reagents under mild conditions based in indium-silicon exchange is described.

Coupling of organometallic compounds with organic electrophiles in the presence of a palladium or nickel catalyst is a widespread and useful way for carbon-carbon bond formation.¹ Thus, organoboron, organotin, organosilicon and organozinc compounds, among others, have been extensively studied. A less common strategy is the use of triorganoindium reagents, although they benefit from high reactivity, efficiency, versatility and chemoselectivity, together with a low toxicity of indium derivatives.^{2,3} The preparation of these reagents is mainly achieved by lithiumhalogen exchange, using butyllithium, followed by indium-lithium exchange on the organolithium species,⁴ which limits the functional groups that can be present in the organometallic compound. The direct indium-halogen exchange can also be problematic due to the reducing character of indium metal.⁵ As part of our interest in this field, we were involved in developing an alternative method to prepare triorganoindium reagents mild enough to allow the presence of "sensitive" groups. Here, we wish to report the fluoride promoted indium-silicon exchange as a versatile and simple method to prepare triorganoindium reagents, even in the presence of organolithium-sensitive functional groups (Scheme 1).



Scheme 1 Proposed synthesis of organoindium reagents.

We decided to study the preparation of trisphenylindium starting from triethoxyphenylsilane as a model reaction. Thus, we reacted the trialkoxysilane with indium trichloride and tetrabutylammonium fluoride (TBAF) in THF to prepare the triorganoindium species, which was subsequently reacted in a one pot process with 2-iodothiophene in the presence of

Entry	Ar	TBAF/ mmol	InCl ₃ / mmol	Temp. ^b /time ^b	Ar'	Ar–Ar'	Yield (%) ^c
1	1	0	0.7	rt/l h	a	1a	0
2	1	2.1	0.7	rt/1 h	a	1a	68
3	1	8.4	0.7	rt/1 h	a	1a	31
4	1	2.1	0.0	rt/1 h	a	1a	0
5	1	2.1	0.7	rt/0.5 h	a	1a	46
6	1	2.1	0.7	reflux/2 h	a	1a	68
7	2	2.1	0.7	rt/0.5 h	a	2a	49
8	2	2.1	0.7	rt/1 h	a	2a	89
9	2	2.1	0.7	reflux/2 h	a	2a	87
10	2	2.1	0.0	rt/1 h	a	2a	0
11	3	2.1	0.7	rt/0.5 h	a	3a	90
12	3	2.1	0.7	rt/1 h	a	3a	66
13	3	2.1	0.0	rt/0.5 h	a	3a	25
14	1	2.1	0.7	rt/1 h	\mathbf{b}^{d}	1b	54
15	2	2.1	0.7	rt/1 h	c	2c	82
16	4	2.1	0.7	rt/0.5 h	a	2c	71
17	4	2.1	0.7	rt/1 h	a	2c	45
18	1	2.1	0.0	rt / 1 h		20	0

Table 1 (Hetero) aromatics via triorganoindium reagents formed in situa

^{*a*} Reagents and conditions: ArSi(OEt)₃ 2.1 mmol, TBAF, InCl₃, THF; Ar'-I (2.1 mmol), Pd(PPh₃)₄ (0.06 mmol), reflux, 14 h. ^{*b*} Conditions for the transmetallation step. ^{*c*} Yield of isolated, purified products. ^{*d*} *p*-Bromobenzaldehyde was used instead of the *p*-iodo analogue.

tetrakis(triphenylphosphine)palladium(0) at reflux (Scheme 2, Table 1). The palladium catalyst was selected as result of previous work on heterobiaryl synthesis using triorganoindium reagents.³



Scheme 2 General scheme of the fluoride-triggered organoindium preparation and its palladium-catalyzed coupling.

Entries 1-3 show the effect of the amount of TBAF. Thus, in the absence of fluoride anions the reaction does not proceed, the best ratio being a 1:1 trialkoxysilane: fluoride. The presence

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[‡] General procedure: A solution of TBAF (1 M in THF, 2.1 mmol) was added to a stirring solution of $InCl_3$ (0.7 mmol) and the corresponding trialkoxysilane (2.1 mmol) in THF (20 mL). After 1 h at room temperature, the electrophile (2.1 mmol) and Pd(PPh₃)₄ (0.06 mmol) were added. The resulting mixture was refluxed under argon atmosphere overnight (14 h) and then, the reaction was quenched by addition of water (25 mL). The crude reaction was extracted with diethyl ether (3 × 25 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography.

of indium(III) chloride is necessary for the reaction to proceed as pointed out in entry 4, thus indicating that this is not just an example of Hiyama coupling.⁶ Finally, the effect of time and temperature was studied (entries 2, 5 and 6), where room temperature and 60 min were the best choices. It is noteworthy that the use of indium trifluoride instead of the mixture of TBAF and indium(III) chloride did not afford the coupling product.

After examination of these results, one might be tempted to consider that the Hiyama coupling is a more straightforward synthesis when starting from a trialkoxysilane. However, both trialkoxysilanes and organoindium compounds have their own reactivities and limitations, and thus it could be very useful to have a second choice to select from. In this regard, it is interesting to note that yields for Hiyama couplings can vary from modest to excellent, the latter being frequently obtained with sophisticated palladium complexes.7 Moreover, a typical Hiyama reaction is carried out using 2 equivalents of trialkoxysilane, 2 equivalents of fluoride-releasing agent and up to 10% of palladium catalyst with respect to the aromatic halide,8 while our procedure just employs 1 equivalent of trialkoxysilane, 1 equivalent of TBAF and 3% of Pd(PPh₃)₄ catalyst, thus being a more efficient process. Be this as it may, it is clear that the process here described is not just an example of Hiyama coupling, and can be synthetically useful depending on the complexity of the trialkoxysilane derivative.

For the study of this methodology on an electron-rich heteroaromatic, we selected 2-(triethoxysilyl)thiophene as starting material (Table 1, entries 7–10). Based on the previous set of experiments, we fixed the trialkoxysilane : fluoride : indium ratio to 1:1:0.33, although control experiments without indium salt were performed. Results follow the same trends as in the phenylsilane case. Thus, the better yield is obtained after one hour at room temperature in the presence of indium(III) chloride (entry 8). Once again, in the absence of indium no reaction takes place (entry 10), thus discarding any contribution from an Hiyama coupling. It is noteworthy that yields are better for the thienylsilane derivative, when compared with the phenylsilane one.

Then, we moved to electron-poor heteroaromatics, selecting 3-(triethoxysilyl)pyridine as model compound (Table 1, entries 11–13). Also in this case, we fixed the trialkoxysilane : fluoride : indium ratio to 1 : 1 : 0.33, although control experiments without indium salt were performed. To our surprise, in the pyridine series the best result was obtained with the shorter reaction time, just 30 min (entry 11), and for this condition a certain contribution of Hiyama coupling was observed (entry 13). Longer reaction times gave a lower yield. Perhaps this can be attributed to a lower stability of the tris(pyridyl)indium when compared with the analogous indium compounds bearing phenyl or thienyl rings.

With the previous results in mind, we tried to perform the reaction using an organic electrophile bearing a sensitive functional group, such as the carbonyl of *p*-bromobenzaldehyde (Table 1, entry 14). Thus, reaction of the phenylsilane (2.1 mmol) with TBAF (2.1 mmol) and indium trichloride (0.7 mmol) in THF for 1 h at room temperature, followed by addition of *p*-bromobenzaldehyde and the palladium catalyst (0.06 mmol) and heating at reflux for 14 h yielded the desired compound in 54%.⁹ This relatively low yield is not unexpected, as it has been previously reported that bromoaromatics do not couple with organoindium reagents as well as iodoaromatics do.³ Moreover, as mentioned above, the phenylsilane series leads to poorer results than the thienylsilane one.

We attempted the synthesis of 4-(2-thienyl)acetophenone¹⁰ starting from 2-(triethoxysilyl)thiophene using the standard conditions for the thienyl series (Table 1 entry 15). The desired compound was obtained in 82% yield, thus showing the usefulness of this methodology.

Finally, we also carried out the synthesis of 4-(2thienyl)acetophenone by preparing the triorganoindium derivative of the acetophenone (Table 1, entries 16–18). The results resembled those of the pyridine series. Thus, the best conditions are achieved by using shorter periods of time (entry 16). No product was detected in the absence of indium trichloride (entry 18). These results indicated that this methodology can be applied to the preparation of organoindium reagents bearing groups which are sensitive to organolithium species.

To develop a better understanding of the role of the indium salt, *i.e.* whether it forms the triorganoindium reagent or just acts as a Lewis acid inducing the cross-coupling,11 we performed some experiments to record the NMR of the intermediate species. Thus, 2-(triethoxysilyl)thiophene was treated with TBAF and indium(III) chloride in THF at room temperature for one hour, the solvent was distilled off and the residue was dissolved in CDCl₃. To our satisfaction, comparison of the ¹H-NMR spectrum of the starting trialkoxysilane (A) with that of the residue (B) showed the disappearance of the former (Fig. 1 and ESI[†]). Thus, in (B) there are not even traces of signals from the starting compound at 7.21 ppm, and the signals at 3.89 and 1.25 ppm corresponding to the ethoxy groups of the starting trialkoxysilane have completely disappeared. The only clear signals in (B) are those of the thienyl group, tetrabutylammonium chloride (formed as byproduct) and some traces of THF (ESI). Moreover, we prepared tris(thienyl)indium by an accepted standard procedure, namely treatment of thienyllithium with indium(III) chloride in THF; after distillation of the solvent, the ¹H-NMR in CDCl₃ was recorded (Fig. 1C and ESI), showing a reasonable match, within 0.01 ppm, with the aromatic signals of Fig. 1B (spectrum 1B contains the intermediate compound and tetrabutylammonium chloride, while spectrum 1C contains only the intermediate species).

We were not able to record a ¹³C-NMR spectrum in CDCl₃, because the compound decomposed generating thiophene. Then, we performed the same experiments but dissolving the residue in THF-d₈. In this way we could obtain a ¹³C-NMR spectrum of the intermediate obtained from the In-Si exchange (ESI), which showed the complete disappearance of the starting material. Thus, the signals at 137.5, 132.6, 130.6 and 128.7 corresponding to 2-(triethoxysilyl)thiophene have vanished, new ones emerging at 135.9, 130.0 and 127.6. We could not find the quaternary carbon atom, because prolonged acquisition times resulted in decomposition of the intermediate in this complex mixture, with many new signals appearing, while the intensity of the three signals of the tris(thienyl)indium decreased. At higher field we could only observe signals corresponding to tetrabutylammonium chloride and some traces of THF and triethoxyfluorosilane (ESI). As in the ¹H-NMR experiments, we recorded the ¹³C-NMR of tris(thienyl)indium prepared via In-Li exchange (ESI), obtaining once again a reasonable match of the aromatic signals. Taking into account that (a) the aromatic signals in both ¹H- and ¹³C-NMR are the same, no matter whether the intermediate is



Fig. 1 Expanded aromatic region of the ¹H-NMR of commercially available 2-(triethoxysilyl)thiophene (A), tris(thienyl)indium prepared by indium–silicon exchange (B) and tris(thienyl)indium prepared by indium–lithium exchange (C).

prepared by indium–silicon exchange or by the well-precedented indium–lithium exchange, (b) the NMR signals seem to correspond to just one compound, not a mixture, and (c) our previous work³ and the amount of InCl₃ used, we propose that the active species is the tris(thienyl)indium.

In conclusion, we have devised a new strategy for the preparation of triorganoindium reagents, which is mild enough to allow the presence of organolithium-sensitive functional groups. Moreover, yields ranging from good to excellent have been obtained although equimolar amounts of trialkoxysilane, TBAF and aromatic halide were used, as opposed to Hiyama couplings were 100% excess of trialkoxysilane and TBAF is usually employed. Further work to extend the variety of organosilanes used as precursors, the functional group tolerance and the type of organometallics available with this methodology is currently underway.

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