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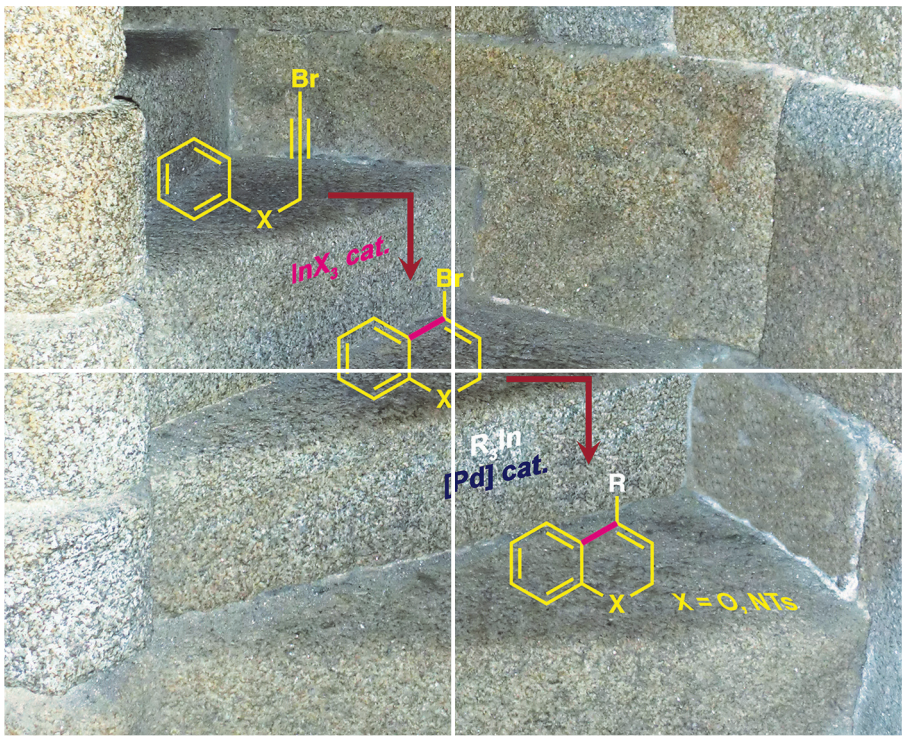

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Sequential In-catalyzed intramolecular hydroarylation and Pd-catalyzed cross-coupling reactions using bromopropargyl aryl ethers and amines†

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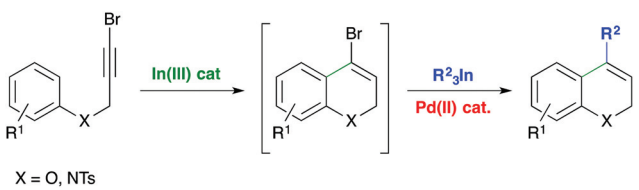
A sequential one-pot indium-catalyzed intramolecular hydroarylation (IMHA) of bromopropargyl aryl ethers and amines, and palladium-catalyzed cross-coupling reaction using triorganoindium reagents (R_3In) has been developed. In this transformation, the IMHA of 3-bromo-2-propynyl aryl ethers under indium(III) catalysis, proceeds regioselectively through a 6-*endo dig* pathway to afford 4-bromo-2*H*-chromenes. Subsequent palladium-catalyzed cross-coupling with R_3In gives 4-substituted-2*H*-chromenes in one-pot. This sequential transformation was extended to 3-bromo-2-propynyl-*N*-tosylanilines to afford 4-substituted-1,2-dihydroquinolines. The dual-catalyzed procedure takes place efficiently with a variety of propargyl aryl ethers and amines and R_3In (R = aryl, heteroaryl, alkyl or alkynyl), showing the efficiency of these organometallics and proving the compatibility of indium and palladium in catalysis.

Introduction

The development of efficient and sustainable chemical methodologies has become one of the most important goals of modern organic chemistry.[1] As an example, sequential one-pot reactions are attractive procedures because the possibility of forming several bonds in one vessel offers important synthetic advantages in terms of economy, sustainability and versatility. Although many sequential or tandem reactions involving classical organic transformations have been reported, orthogonal metal-catalyzed processes, in which more than one catalyst and reagents are combined in a single pot, are particularly challenging because the increased level of complexity enables redox processes or ligand-exchange reactions.[2] Actually, several sequential one-pot systems, which range from isolated catalytic cycles to tandem or orthogonal catalysis, have been designed and this research has become an emerging area.[3]

Recently, we reported the indium-catalyzed intramolecular hydroarylation (IMHA) of propargyl aryl ethers for the synthesis of 2*H*-chromenes.[4] The reaction is highly versatile and takes place regioselectively with terminal and internal alkynes bearing electron-rich and electron-deficient substituents in the arene and alkyne affording the 6-*endo dig* cyclization product. Recent computational studies support a mechanism based on indium(III) activation of the alkyne.[5] In addition, indium catalysis offers significant advantages in terms of cost and low toxicity.[6] Interestingly, the reaction of halopropargyl aryl ethers gives 4-halo-2*H*-chromenes in high yields without 1,2-halogen migration, a side reaction usually observed under gold catalysis.[7] Taking advantage of the halo-substituents, and in combination with our research on metal-catalyzed cross-coupling reactions with triorganoindium reagents (R_3In),[8] we envisioned a sequential one-pot indium-catalyzed IMHA of 3-halopropynyl aryl ethers with a palladium-catalyzed cross-coupling reaction using R_3In (Scheme 1). Additionally, we also propose the extension of this procedure to halopropargyl anilines. The IMHA of *N*-propargyl-*N*-tosylanilines has been reported using precious metals (Au, Pt, Rh) with variable yields based on the



Scheme 1 Sequential one-pot dual catalyzed In/Pd IMHA and cross-coupling.

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alkyne and arene substitution and catalyst loading.[9] The gold-catalyzed IMHA of *N*-(3-iodoprop-2-ynyl)-*N*-tosylanilines takes place with iodide migration affording 3-iodo-1,2-dihydroquinolines.[9g] This methodology should offer a straightforward route to 4-functionalized 2*H*-chromenes and 1,2-dihydroquinolines – structural motifs present in a large number of naturally occurring and biologically active compounds.[10]

During the last few years, the palladium-catalyzed cross-coupling reaction of triorganoindium reagents (R_3In), discovered by this research group,[8a] has gained increasing utility in organic synthesis.[11] R_3In can be easily prepared from the corresponding organolithium using $InCl_3$, or organic halides and the indium metal. Particular features of R_3In are the high efficiency, versatility and selectivity in transferring the three organic groups attached to indium. In comparison with other organometallics, aryl–aryl and aryl–alkenyl couplings using R_3In have become an efficient alternative.[12]

Results and discussion

Our investigation started studying the palladium-catalyzed coupling of R_3In with the 4-bromo-2*H*-chromenes obtained from the indium-catalyzed IMHA of bromopropargyl aryl ethers. In this research, 4-bromo-6-methoxy-2*H*-chromene (**2a**, Table 1) was selected as the starting material since it can be obtained from indium-catalyzed IMHA in high yield.[4] Given that the In-catalyzed IMHA requires a non-coordinating solvent, the coupling reaction was studied in toluene. Under these considerations, we found that the reaction of 0.5 equiv. of triphenylindium with **2a** in toluene under palladium catalysis proceeded after 18 h at 80 °C to give the coupling product **3a** in 87–88% yield (entries 1 and 2). The efficient coupling was also observed using either Pd(II) or Pd(0) complexes, and with a variety of R_3In (heteroaryl-, alkynyl- or alkylindium), thus providing a variety of 4-substituted-2*H*-chromenes (**3b–d**, entries 3–5) in high yields. In order to compare the reactivity of R_3In with other common organometallics in cross-coupling reactions, the coupling was tested using organotin, organozinc and organoboron compounds. Interestingly, the reaction using tributylphenyltin or phenylzinc chloride gave the coupling product **3a** in lower yields, even when a large excess of the organometallic agent was employed (entries 6 and 7). Only the reaction with phenylboronic acid (2.2 equiv.) using Na_2CO_3 as a base afforded **3a** in 87% yield (entry 8). These results illustrate the synthetic utility of R_3In reagents in palladium-catalyzed coupling reactions.

Once the reaction conditions for the Pd-catalyzed coupling of R_3In with the 4-bromo-2*H*-chromene **2a** had been established, the sequential one-pot In-catalyzed IMHA and Pd-catalyzed cross-coupling was explored (Table 2). In this scenario, we found that hydroarylation of the 3-bromo-2-propynyl aryl ether **1a** using $InCl_3$ (5 mol%) in toluene at 60 °C for 2 hours, followed by the addition of Ph_3In (THF solution, 0.5 equiv.) and $Pd(PPh_3)_2Cl_2$ (5 mol%) gave the 4-phenyl-2*H*-chromene **3a** in 95% overall yield after 18 h at 80 °C (entry 1). Using $InBr_3$ or InI_3 as catalysts the sequential transformation also afforded the desired product **3a** but in lower yields (57% and 60% respectively, entries 2 and 3). These results can be explained by the higher reactivity of these indium(III) halides, which led to the formation of by-products. Overall, these results demonstrate the compatibility of palladium cross-coupling with the indium IHMA reaction conditions.

Under the previously developed reaction conditions, the one-pot sequence was assessed with a variety of R_3In reagents (Table 2). The procedure using tri(2-thienyl)indium (0.5 equiv.) gave the corresponding 2*H*-chromene **3b** in 85% overall yield (entry 4). The reaction with tri(phenylethynyl)indium also gave the 4-phenylethynyl-2*H*-chromene **3c** on using $Pd(dppf)Cl_2$ as the catalyst (72%, entry 5). The reaction with trialkylindium

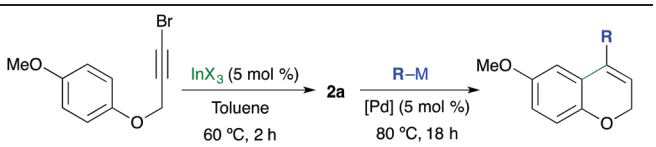
Table 1 Pd-Catalyzed cross-coupling of 4-bromochromene **2a**

2a **3a–d**

Entry	R–M	(Equiv.)	[Pd] cat.	Product	Yield[a] (%)
1	Ph_3In	0.5	$Pd(PPh_3)_2Cl_2$	**3a**	88
2	Ph_3In	0.5	$Pd(PPh_3)_4$	**3a**	87
3	$(2\text{-Thienyl})_3In$	0.5	$Pd(PPh_3)_2Cl_2$	**3b**	89
4	$(PhC{\equiv}C)_3In$	0.5	$Pd(dppf)Cl_2$	**3c**	67
5	Bu_3In	0.5	$Pd(PPh_3)_2Cl_2$	**3d**	60
6	$PhSnBu_3$[b]	4.0	$Pd(PPh_3)_4$	**3a**	30
7	PhZnCl[c]	4.0	$Pd(PPh_3)_4$	**3a**	40
8	$PhB(OH)_2$[d]	2.2	$Pd(PPh_3)_4$	**3a**	87

[a] Isolated yields. [b] Toluene at 100 °C. [c] Toluene/THF 2 : 1. [d] Na_2CO_3 (6.0 equiv.) in toluene/EtOH 2 : 1.

Table 2 Sequential dual-catalyzed In/Pd IMHA-cross-coupling reactions of bromopropargyl aryl ethers

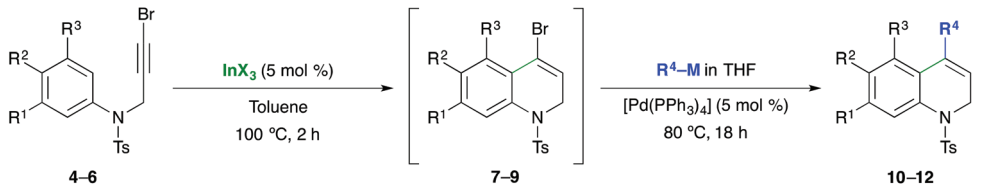


1a **3a–e**

Entry	InX_3	R–M (0.5 equiv.)	[Pd] cat.	Product	Yield[a] (%)
1	$InCl_3$	Ph_3In	$Pd(PPh_3)_2Cl_2$	**3a**	95
2	$InBr_3$	Ph_3In	$Pd(PPh_3)_2Cl_2$	**3a**	57
3	InI_3	Ph_3In	$Pd(PPh_3)_2Cl_2$	**3a**	60
4	$InCl_3$	$(2\text{-Thienyl})_3In$	$Pd(PPh_3)_2Cl_2$	**3b**	85
5	$InCl_3$	$(PhC{\equiv}C)_3In$	$Pd(dppf)Cl_2$	**3c**	72
6	$InCl_3$	Bu_3In	$Pd(PPh_3)_2Cl_2$	**3d**	70
7	$InCl_3$	Me_3In	$Pd(PPh_3)_2Cl_2$	**3e**	89
8	$InCl_3$	PhZnCl[b]	$Pd(PPh_3)_4$	**3a**	40
9	$InCl_3$	$PhSnBu_3$[c]	$Pd(PPh_3)_4$	**3a**	40
10	$InCl_3$	$PhB(OH)_2$[d]	$Pd(PPh_3)_4$	**3a**	87

[a] Isolated yield. [b] 4.0 equiv. of PhZnCl. [c] 4.0 equiv. of $PhSnBu_3$ at 100 °C. [d] 2.2 equiv. of $PhB(OH)_2$, Na_2CO_3 (6 equiv.) in toluene : EtOH (2 : 1).

Table 3 Sequential In-catalyzed IMHA and Pd-catalyzed cross-coupling using *N*-(3-bromo-2-propynyl)-*N*-tosylanilines



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Entry	Substrate	InX_3	R^1	R^2	R^3	R^4–M (0.7 equiv.)	Product	Yield[a] (%)
1	**4**	$InCl_3$	H	OMe	H	—	**7**	95
2	**4**	$InBr_3$	H	OMe	H	—	**7**	92
3	**4**	InI_3	H	OMe	H	—	**7**	80
4	**4**	$InBr_3$	H	OMe	H	Ph_3In	**10a**	92
5	**4**	InI_3	H	OMe	H	Ph_3In	**10a**	80
6	**4**	$InCl_3$	H	OMe	H	Ph_3In	**10a**	70
7	**4**	$InBr_3$	H	OMe	H	$(2\text{-Thienyl})_3In$	**10b**	86
8	**4**	$InBr_3$	H	OMe	H	$(PhC{\equiv}C)_3In$	**10c**	65[b]
9	**4**	$InBr_3$	H	OMe	H	Bu_3In	**10d**	60
10	**4**	$InBr_3$	H	OMe	H	Me_3In	**10e**	72
11	**4**	$InBr_3$	H	OMe	H	$PhSnBu_3$	**10a**	38[d]
12	**4**	$InBr_3$	H	OMe	H	$PhB(OH)_2$	**10a**	80[c]
13	**5**	$InBr_3$	H	H	H	Ph_3In	**11a**	92
14	**5**	$InBr_3$	H	H	H	$(2\text{-Thienyl})_3In$	**11b**	98
15	**5**	$InBr_3$	H	H	H	$(PhC{\equiv}C)_3In$	**11c**	78
16	**5**	$InBr_3$	H	H	H	Bu_3In	**11d**	74
17	**5**	$InBr_3$	H	H	H	Me_3In	**11e**	85
18	**6**	InI_3	OMe	H	OMe	Ph_3In	**12a**	75
19	**6**	InI_3	OMe	H	OMe	$(2\text{-Thienyl})_3In$	**12b**	55
20	**6**	InI_3	OMe	H	OMe	Me_3In	**12e**	67

[a] Isolated yields. [b] $Pd(dppf)Cl_2$ (5 mol%) as the catalyst. [c] 2.2 equiv. of $PhB(OH)_2$, Na_2CO_3 (6.0 equiv.) in toluene/EtOH 2 : 1 at 80 °C. [d] 4.0 equiv. of $PhSnBu_3$ at 100 °C for 24 h.

reagents such as tributylindium and trimethylindium afforded the 4-substituted-2*H*-chromenes **3d** and **3e** in 70% and 89% yields, respectively (entries 6 and 7). In all of these examples the yields for the two-step one-pot sequence compare favourably with procedures where each step was performed separately and required isolation of the intermediate. The reactivity and compatibility of other organometallic reagents in this sequential process was also evaluated. The use of phenylzinc chloride (4 equiv.) and $Pd(PPh_3)_4$ (5 mol%) provided the coupling product **3a** in a modest 40% isolated yield (entry 8). Analogously, the reaction with tributylphenyltin (4.0 equiv.) at 100 °C gave only 40% yield (entry 9). The use of phenylboronic acid (2.2 equiv.), Na_2CO_3 (6.0 equiv.) and $Pd(PPh_3)_4$ (5 mol%) in a mixture of toluene and ethanol gave the 4-phenyl-2*H*-chromene **3a** in 87% yield (entry 10). These results demonstrate the compatibility of palladium-catalyzed coupling reactions with the indium-catalyzed IMHA in a one-pot protocol and triorganoindium compounds are shown as the reagents of choice.

In an effort to increase the chemical diversity of this sequential dual-catalyzed In/Pd protocol, the methodology was then studied with 3-bromopropargyl anilines. This sequential transformation should allow the synthesis of 4-substituted-1,2-dihydroquinolines, a structural unit present in naturally occurring products, pharmaceuticals and also used as building blocks in organic synthesis.[10] In our initial experiments we found that the IMHA of *N*-(3-bromoprop-2-ynyl)-*N*-tosylaniline **4** using $InCl_3$ (5 mol%) takes place at 100 °C to give the 4-bromo-1,2-dihydroquinoline **7** in 95% yield (Table 3, entry 1). In comparison with the IMHA of propargyl aryl ethers, the amines are less reactive, probably due to electronic effects. The use of $InBr_3$ or InI_3 (5 mol%) as catalysts at 100 °C also gave **7** in shorter reaction times and high yields (92% and 80% respectively, entries 2 and 3). With these results in mind, the sequential IMHA-coupling using the different indium(III) halides in toluene at 100 °C and reaction with Ph_3In (THF solution, 0.5 equiv.) and $Pd(PPh_3)_4$ (5 mol%) at 80 °C was tested. Under these conditions, the cross-coupling step was not complete after 18 h and the desired 4-phenyl-1,2-dihydroquinoline **10a** was obtained in moderate yield. Optimal results were obtained using 0.7 equiv. of Ph_3In and $InBr_3$ as the catalyst (92%), although the use of $InCl_3$ or InI_3 also gave satisfactory yields (Table 3, entries 4–6).

Under the previously developed conditions, the sequential procedure was tested using different triorganoindium reagents. The reaction using heteroarylindium reagents such as tri(2-thienyl)indium (0.7 equiv.) gave the 4-thienyldihydroquinoline **10b** in 86% yield (entry 7). The use of trialkynylindium reagents such as tri(phenylethynyl)indium also afforded the dihydroquinoline **10c** in 65% yield with $Pd(dppf)_2Cl_2$ as the catalyst (entry 8). The reaction with tributylindium and trimethylindium also gave the corresponding 4-substituted dihydroquinolines **10d** and **10e** in 60% and 72% yields respectively (entries 9 and 10), thus showing the utility of indium organometallics in the cross-coupling with alkyl nucleophiles. This sequential transformation was also assessed employing

other organometallic reagents. Interestingly, the reaction using tributylphenyltin gave a low isolated yield (38%) (entry 11), and only the reaction of phenylboronic acid worked efficiently using Na_2CO_3 as the base (80%, entry 12).

With the purpose to expand the synthetic utility of the methodology, we tested the procedure with other bromopropargyl anilines. The indium-catalyzed IMHA of *N*-(3-bromoprop-2-ynyl)-*N*-tosylaniline **5** using $InBr_3$ (5 mol%) in toluene at 100 °C for 2 h, followed by the addition of triphenylindium (THF solution, 0.7 equiv.) and $Pd(PPh_3)_4$ (5 mol%) overnight at 80 °C, afforded *N*-tosyl-4-phenyl-1,2-dihydroquinoline (**11a**) in an excellent 92% yield (entry 13).[13] Analogously, the use of tri(2-thienyl) indium gave the corresponding dihydroquinoline **11b** in 98% yield (entry 14). The dual-catalyzed process with the tri(phenylethynyl)indium reagent also gave 4-phenylethynyldihydroquinoline **11c** in 78% yield (entry 15). Furthermore, butyl- and methyldihydroquinolines **11d** and **11e** were successfully prepared by using tributylindium and trimethylindium reagents in 74% and 85% yields (entries 16 and 17), respectively.

Additionally, the one-pot sequence with *N*-(3-bromo-2-propynyl)-3,5-dimethoxy-*N*-tosylaniline **6** also proceeded efficiently to give the desired dihydroquinolines. In this case, the best yields were obtained using InI_3 as the catalyst and the 4-phenyl-1,2-dihydroquinoline **12a** was obtained in 75% overall yield (entry 18).[13] Under the established conditions, the reaction with tri(2-thienyl)indium and trimethylindium provided **12b** and **12e** in 55% and 67% overall yields (entries 19 and 20), respectively. These results show the versatility of this novel sequential one-pot In/Pd catalyzed IMHA-cross-coupling reaction using indium organometallics and demonstrate its application to the synthesis of 4-substituted-1,2-dihydroquinolines.

Conclusions

In summary, starting from easily available bromopropargyl aryl ethers and amines, we have developed a sequential one-pot indium-catalyzed IMHA and palladium-catalyzed cross-coupling process that allows the regioselective synthesis of 4-substituted 2*H*-chromenes and dihydroquinolines. This sequence demonstrates the possibility of combining dual-catalyzed In/Pd transformations and highlights the efficiency of triorganoindium reagents in this one-pot sequential procedure transferring a variety of organic groups (aryl, heteroaryl, alkyl and alkynyl) with high efficiency and good yields. Moreover, these results support the possibility to develop the orthogonal tandem catalytic processes combining indium and palladium.

Experimental

General procedure for palladium-catalyzed cross-coupling reactions of 4-bromo-6-methoxy-2*H*-chromene (2a) with triorganoindium reagents (Table 1, entries 1–5)

In a Schlenk tube filled with argon, a THF solution of the corresponding triorganoindium reagent (0.5 equiv., 0.207 mmol) was added to a toluene solution of **2a**[4] (0.415 mmol) and the palladium catalyst (0.021 mmol). The reaction mixture was heated at 80 °C until the starting material was consumed. The mixture was allowed to cool down to room temperature and was quenched by the addition of a few drops of MeOH. The solvent was concentrated *in vacuo* and the residue was diluted with EtOAc (10 mL) and poured into a separating funnel with H_2O (10 mL). The product was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (15 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford, after concentration and high vacuum drying, the corresponding cross-coupling product (**3a–d**).

General procedure for sequential IMHA-cross coupling reactions of 4-methoxyphenyl-(3-bromoprop-2-ynyl)ether (1a) with triorganoindium reagents (Table 2, entries 1–7)

In a Schlenk tube filled with argon, a solution of **1a** (0.415 mmol) and $InCl_3$ (0.021 mmol) in toluene (5 mL) was heated at 60 °C for 2 h. The reaction was cooled down to rt and the palladium catalyst (0.021 mmol) and a solution of R_3In (50 mol%, 0.207 mmol, ~0.1 M in THF) were added. The resulting mixture was heated at 80 °C for 16 h and then quenched by the addition of a few drops of MeOH. The solvent was removed *in vacuo* and the residue was diluted with EtOAc (10 mL) and poured into a separatory funnel with H_2O (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried, filtered and concentrated *in vacuo* to afford the corresponding cross-coupling product (**3a–e**) after purification by column chromatography.

General procedure for the preparation of *N*-(3-bromoprop-2-ynyl)-*N*-tosylanilines 4–6

$AgNO_3$ (0.217 g, 1.27 mmol) and NBS (0.790 g, 4.44 mmol) were added to a rt solution of the corresponding *N*-(3-bromoprop-2-ynyl)-*N*-tosylaniline (3.17 mmol) in dry acetone (40 mL). The reaction mixture was stirred overnight, the solvent was evaporated and the residue was diluted with EtOAc (50 mL). The organic phase was washed with brine (25 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford, after concentration and high vacuum drying, the corresponding *N*-(3-bromoprop-2-ynyl)-*N*-tosylaniline.

General procedure for sequential IMHA-cross coupling reactions of *N*-(3-bromo-2-propynyl)-*N*-tosylanilines with triorganoindium reagents (Table 3, entries 4–10 and 13–20)

In a Schlenk tube filled with argon a solution of $InBr_3$ or InI_3 (0.021 mmol) and the corresponding *N*-(3-bromo-2-propynyl)-*N*-tosylaniline (0.415 mmol) in toluene (5 mL) was heated at 100 °C until the starting material had been consumed (TLC). Then, the palladium catalyst (0.021 mmol) and the solution of

R_3In (70 mol%, 0.291 mmol, ~0.1 M in dry THF) were added and the mixture was heated at 80 °C until the starting material had been consumed. The reaction was quenched by the addition of a few drops of MeOH and the mixture was concentrated *in vacuo.* EtOAc (10 mL) and H_2O (10 mL) were added. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to afford, after concentration and high vacuum drying, the corresponding IMHA-cross-coupling product.

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13 The indium-catalyzed IMHA of compounds **5** and **6** afforded the 4-bromo-1,2-dihydroquinolines **8** and **9** in 88% and 75% isolated yields, respectively.