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Indium-Catalyzed Intramolecular Hydroarylation of Aryl Propargyl Ethers

Lorena Alonso-Marañón, a M. Montserrat Martinez, a Luis A. Sarandeses a and José Pérez Sestelo* a

Indium(III) halides catalyze efficiently the intramolecular hydroarylation (IMHA) of aryl propargyl ethers. The reaction proceeds regioselectively with terminal and internal alkynes bearing electron-rich and electron-deficient substituents in the benzenes and alkynes alkynes affording only the 6-endo dig cyclization product. Additionally, a sequential indium-catalyzed IMHA and palladium-catalyzed Sonogashira coupling can be performed in one reaction vessel. Experiments with deuterium support a mechanism through electrophilic aromatic substitution.

Introduction

Metal-catalyzed hydroarylation of alkynes is an efficient and atom-economy methodology that enables the insertion of a C–C triple bond into a C–H bond of aromatic compounds. This method offers an attractive alternative to Heck and cross-coupling reactions, and can be performed in an inter- or intramolecular fashion with variable regio- and stereoselectivity depending on the reaction partners, the metal, and the reaction conditions. Intramolecular hydroarylation (IMHA) of alkynes is particularly useful for the synthesis of cyclic frameworks as the reaction can be catalyzed by several transition metals such as palladium, platinum, ruthenium, rhodium, gold, and silver. More recently, non-precious metals such as iron, gallium, and indium have been suggested as promising alternatives in terms of economy and reactivity.

In the context of a research program aimed at developing new metal-catalyzed reactions using indium and gold, we report here the indium-catalyzed intramolecular hydroarylation of aryl propargyl ethers. Although this transformation can be performed with various precious metals, there are still limitations associated with the substrate (i.e., terminal alkynes), regioselectivity (6-endo vs. 5-exo), side reactions such as ether cleavage or alkenne isomerization and the economy of the transformation. Gold(I) catalysis is probably the best choice, although silver cocatalysis or highly active complexes are required. On the other hand, IMHA of aryl propargyl ethers provides a straightforward synthesis of 2H-chromenes, a structural unit that is present in a vast number of naturally occurring and pharmaceutically active compounds. As a result, the development of a general protocol with a non-toxic and affordable catalyst is highly desirable.

In recent decades indium has gained considerable importance in organic synthesis. Indium organometallics have proven to be useful reagents in metal-catalyzed reactions and indium salts are efficient catalysts to promote nucleophilic addition to carbonyl derivatives and unsaturated carbon-carbon bonds. Indium-catalyzed addition to alkynes has been described in inter- and intramolecular reactions involving 1,3-dicarboxyls, in cycloisomerization reactions of alkynyl anilines. Furthermore, indium catalysis has been used in intramolecular hydroarylations during the synthesis of phenanthrenes and derivatives from alkylated biphenyl derivatives. Recently, Corey has also found that indium is an excellent catalyst promoting the cascade polycyclization of enynes, and also has proven effective in the hydroarylation of some aryl propargyl ethers. In addition, indium also offers significant advantages in terms of cost and low toxicity.

Results and discussion

Our research started with the intramolecular hydroarylation of 4-methoxyphenyl 2-propynyl ether (1a) under indium(III) catalysis. Initially, the addition of InCl 3 under different reaction conditions proved to be ineffective (Table 1, entries 1 and 2). However, on using InBr 3 (5 mol%) the reactivity changed dramatically and the hydroarylation product (6-endo dig cyclization product) was obtained in 58% yield after 16 h at room temperature (entry 3). More encouragingly, we found that the use of InI 3 (5 mol%) increased the yield to 85% after only 4 h at rt (entry 4). Interestingly, the reaction proceeded regioselectively to produce only the 6-endo product and cleavage of the ether was not observed. The importance of the halide ion led us to test the reactivity of In(OTf) 3 but, despite some precedents with intermolecular hydroarylation, the use of this reagent led to decomposition of the aryl propargyl ether (entries 5). During our optimization process we found that the reaction can be performed efficiently using other solvents such as CH 2 Cl 2 but not with coordinating solvents such as THF or MeOH (entries 6–9).
As with terminal alkynes, the indium phenyl prepared (Table 3). Hydroarylation of 4 and, with this aim in mind, a variety of internal alkynes were that would allow the synthesis of 4 terminal
Given our success in the intramolecular hydroarylation with
These results support a mechanism based on an electrophilic
indium(III) provides the
interesting to note that, in contrast to gold(I) catalysis,
aryl 2
indium(III) hydroarylation can be performed efficiently with
yields (entries 5 and 6). Overall, it has been demonstrated that
the alkyne reacted efficiently on using InI
the methoxy group on the benzene is not essential, since the
catalyst and toluene as solvent, we found that the presenc
usually sensitive to electronic effects and limitations can arise
ethers (Table 2). The metal
toevaluated the scope of the
part of this study we also assessed the reactivity of
haloalkynes, which are alternative substrates when IMHA does not proceed with terminal alkynes and whose hydroarylation under gold catalysis takes place with 1,2-halide migration.
Interestingly, it was found that reaction of 3-bromo-2-propynyl aryl ether 3i with InI
the corresponding 4-phenyl-2H-chromene 4a was obtained in good yields (65% and 79%, respectively, entry 1). As with terminal alkynes, the indium-catalyzed IMHA afforded only the 6-endo product, as evidenced by 1H NMR spectroscopy. The electronic effects were analyzed with electron-donating and -withdrawing substituents in the benzene and alkyl. Aryl propargyl ethers 3b and 3e bearing a methoxy group in the benzene and p-tolyl or p-acyethylphenyl groups in the alkyl reacted efficiently on using InI (85% and 78%, respectively, entries 2 and 3). Internal alkynes 3d and 3e, both substituted with a methyl carbonyl in the benzene, reacted sluggishly and required longer reaction times and a higher catalyst loading (10 mol%, entries 4 and 5).
To study further the scope of the reaction, methyl alkynes and alkynoates were also assessed. Interestingly, the IMHA reaction of methyl alkynes 3f and 3g, which bear either a methoxy or an ester group in the benzene, proceeded to give 97% and 75% yields, respectively (entries 6 and 7). As observed previously, the nature of the substituent in the benzene determines the reactivity, and the presence of a methyl group in the alkyl did not affect the regioselectivity of the reaction. The IMHA of alkynoate ester 3h afforded the 6-endo-dig cyclization product 4h in 98% yield (Table 3, entry 8).

<table>
<thead>
<tr>
<th>Table 1. Indium-catalyzed hydroarylation of aryl propargyl ether 1a.</th>
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<tr>
<td>Entry</td>
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<tr>
<td>1</td>
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<td>2</td>
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<sup>a</sup> Isolated yield. <sup>b</sup> Recovered starting material in parentheses. <sup>c</sup> Conversion determined by 1H NMR.

As part of this study we also assessed the reactivity of haloalkynes, which are alternative substrates when IMHA does not proceed with terminal alkynes and whose hydroarylation under gold catalysis takes place with 1,2-halide migration. Interestingly, it was found that reaction of 3-bromo-2-propynyl aryl ether 3i with InI (5 mol%) proceeded at rt in 6 h to give the 4-bromo-2H-chromene (4i) in 95% yield as a single product. On the other hand, the reaction with InCl<sub>3</sub> took place at 60 °C in 4 h (entry 9). As observed previously, when the reaction was performed with 3j, which contains an ester group, the reactivity decreased but the IMHA product 4j was obtained in 95% yield after 24 h at 100 °C (entry 10). Moreover, the indium-catalyzed IMHA was extended to iodoalkyne 3k and, in this case, the best results were obtained on using InCl<sub>3</sub> (entry 11). In general, it has been shown that 4-halo-2H-chromenes can be efficiently prepared from the corresponding haloalkynes 3l–k and that these compounds are more reactive than aryl alkynyl ethers 3a–e.
Table 3. Indium-catalyzed hydroarylation with internal alkynes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl propargyl ether</th>
<th>conditions</th>
<th>2H-Chromene</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>rl, 16h</td>
<td>3a</td>
<td>65b 79</td>
</tr>
<tr>
<td>b</td>
<td>p-Tol</td>
<td>rl, 16h</td>
<td>3b</td>
<td>85</td>
</tr>
<tr>
<td>c</td>
<td>p-AdPh</td>
<td>100 ºC, 36h</td>
<td>3c</td>
<td>78</td>
</tr>
<tr>
<td>d</td>
<td>p-Tol</td>
<td>100 ºC, 72h</td>
<td>3d</td>
<td>45(38)</td>
</tr>
<tr>
<td>e</td>
<td>p-AdPh</td>
<td>100 ºC, 72h</td>
<td>3e</td>
<td>38(45)</td>
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<tr>
<td>f</td>
<td>rt, 16h</td>
<td></td>
<td>3f</td>
<td>97</td>
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<td>g</td>
<td>100 ºC, 24h</td>
<td></td>
<td>3g</td>
<td>75</td>
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<tr>
<td>h</td>
<td>100 ºC, 4h</td>
<td></td>
<td>3h</td>
<td>98</td>
</tr>
<tr>
<td>i</td>
<td>rt, 6h</td>
<td>60 ºC, 4h</td>
<td>3i</td>
<td>95 95b</td>
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<tr>
<td>j</td>
<td>100 ºC, 24h</td>
<td>3j</td>
<td>95 85d</td>
<td></td>
</tr>
<tr>
<td>k</td>
<td>rt, 16h</td>
<td>60 ºC, 1h</td>
<td>3k</td>
<td>30</td>
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</table>

The synthesis of 4-halo-2H-chromenes (4i-k) prompted us to study the possibility of combining the indium-catalyzed hydroarylation with palladium-catalyzed cross-coupling reactions. The development of sequential metal-catalyzed reactions is an appealing trend in organic synthesis, although the combination of two metals in one-pot may lead to significant interference through either redox processes, ligand exchange or incompatible reaction conditions. Nevertheless, we attempted to combine the indium-catalyzed IMHA with a palladium-catalyzed Sonogashira coupling in one vessel. It was found that the hydroarylation reaction of bromoalkyne 3i with InCl3 (5 mol%) in toluene at 60 ºC, followed by addition of phenylethyne (2 equiv) and Pd(PPh3)2Cl2 (5 mol%) gave, after 12 h, the 4-phenylethynyl-2H-chromene 5a in 85% overall yield (two steps). Interestingly, and despite their higher reactivity in the IMHA, the use of InBr3 or InI3 gave lower yields. Under the same reaction conditions, the sequential indium-palladium-catalyzed procedure also proved useful with bromoalkyne 3j and the corresponding 4-phenylethynyl-2H-chromene (5b) was obtained in 83% overall yield. To the best of our knowledge, this reaction constitutes the first example of sequential one-pot transformation that includes an indium-catalyzed hydroarylation and a palladium-catalyzed copper-free Sonogashira coupling. It is remarkable that the Sonogashira coupling proceeds in higher yield in the sequential procedure than with the isolated alkenylbromide 4i or 4j (80% and 66%, Scheme 1), which suggests that indium could catalyze both transformations.

Finally, the mechanism of the indium-catalyzed IMHA of aryl propargyl ethers was investigated. Our results suggest that the reaction takes place through and electrophilic aromatic substitution promoted by π-alkyne activation through coordination with indium. A Claisen mechanism, based in a coordination with the oxygen, can be discarded since should provide the benzofuran product (not detected). Therefore, an alkynylindium compound should be generated during the electrophilic addition and, after aromatization with concomitant acid release, the last step should be protonation (Scheme 2). The catalytic cycle could be initiated either by InX3 or InX2+ as it has been reported for InCl3-catalyzed cycloisomerizations of 1,6-enynes.

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The synthesis of 4-halo-2H-chromenes (4i-k) prompted us to study the possibility of combining the indium-catalyzed hydroarylation with palladium-catalyzed cross-coupling reactions. The development of sequential metal-catalyzed reactions is an appealing trend in organic synthesis, although the combination of two metals in one-pot may lead to significant interference through either redox processes, ligand exchange or incompatible reaction conditions. Nevertheless, we attempted to combine the indium-catalyzed IMHA with a palladium-catalyzed Sonogashira coupling in one vessel. It was found that the hydroarylation reaction of bromoalkyne 3i with InCl3 (5 mol%) in toluene at 60 ºC, followed by addition of phenylethyne (2 equiv) and Pd(PPh3)2Cl2 (5 mol%) gave, after 12 h, the 4-phenylethynyl-2H-chromene 5a in 85% overall yield (two steps). Interestingly, and despite their higher reactivity in the IMHA, the use of InBr3 or InI3 gave lower yields. Under the same reaction conditions, the sequential indium-palladium-catalyzed procedure also proved useful with bromoalkyne 3j and the corresponding 4-phenylethynyl-2H-chromene (5b) was obtained in 83% overall yield. To the best of our knowledge, this reaction constitutes the first example of sequential one-pot transformation that includes an indium-catalyzed hydroarylation and a palladium-catalyzed copper-free Sonogashira coupling. It is remarkable that the Sonogashira coupling proceeds in higher yield in the sequential procedure than with the isolated alkenylbromide 4i or 4j (80% and 66%, Scheme 1), which suggests that indium could catalyze both transformations.

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To gain insight about the mechanism, the IMHA reaction was performed in the presence of a deuterium source. In this case, we found that hydroarylation of 3i using InI₃ (5 mol%) in toluene and CF₃CO₂D (2 equiv) afforded the chromene 4i-d₁ in 83% yield with significant incorporation of deuterium at the C-3 position (55/45, H/D ratio). Under the same conditions, the IMHA of internal alkyne 3a gave 4a-d₁ and deuterium was also incorporated at the C-3 position with a 40/60 H/D ratio (Scheme 3). Additionally, hydroarylation of 1a-d₁ with a deuterium label at the terminal alkyne gave 2a-d₁ without any change in the position of the deuterium. These results support the mechanism proposed in Scheme 2 and are reminiscent of deuterium experiments carried out under silver catalysis. ¹

**Scheme 2.** Plausible mechanism for the indium-catalyzed intramolecular hydroarylation.

**Scheme 3.** Indium-catalyzed IMHA using deuterated compounds or solvents.

**Conclusions**

Indium(III) halides are efficient catalysts for the intramolecular hydroarylation of aryl propargyl ethers. The reaction proceeds with terminal and internal alkyne bearing electron-rich and electron-deficient substituents in the benzenes and alkynes affording the 6-endo cyclization product regioselectively. The indium-catalyzed IMHA of haloalkynes can also be combined with palladium-catalyzed Sonogashira coupling in a sequential one-pot transformation. These results highlight indium as one of the best metals for IMHA in terms of cost, lack of toxicity, and intrinsic effectiveness. In addition, mechanistic studies carried out with deuterium support an electrophilic aromatic substitution pathway.

**Experimental**

**General methods**

All reactions were carried out in flame-dried glassware, under argon atmosphere, using standard gastight syringes, cannula and septa. Toluene and THF were distilled from sodium/ benzophenone. Dichloromethane was distilled from calcium hydride. Dry acetonitrile, DMF and MeOH and other commercially available reagents were used as received. Reaction temperatures refer to external bath temperatures. Butyllithium was titrated prior to use. Indium(III) iodide (99.999%), indium(III) bromide (99%), indium(III) chloride (99.999%) and indium(III) trifluoromethanesulfonate were purchased from Aldrich and used as received under argon. NBS was recrystallized from water. Reactions were monitored by TLC using pre-coated silica gel plates (Alugram® Xtra SIL G/UV₂₅₄, 0.20 mm thick), UV light as the visualizing agent and ethanolic phosphomolybdic acid as the developing agent. Organic extracts were dried with anhydrous MgSO₄, filtered, and concentrated by using a rotary evaporator under reduced pressure. Flash column chromatography was performed with 230–400 mesh silica gel packed in glass columns. ¹H and ¹³C NMR spectra were recorded in CDCl₃ or MeOD-d₄ at 300 MHz and 75 MHz, respectively, in a Bruker Avance 300 spectrometer at ambient temperature, and calibrated to the solvent peak. DEPT data were used to assign carbon types. The low resolution EIMS were measured on a Thermo Finnigan Trace MS spectrometer at 70 eV. The HRMS were measured on a Thermo Finnigan MAT 95XP spectrometer or in a QSTAR LC/MS Turbo Spray. IR spectra were taken with a Bruker Vector 22 and with ATR (“attenuated total reflectance”). Melting points were measured in a Stuart Scientific melting point apparatus SMP3 and are uncorrected.

**General procedure for the indium-catalyzed IMHA of aryl propargyl ethers 1a–f.**

In a Schlenk tube with InI₃ (18 mg, 0.037 mmol) a solution of the aryl propargyl ether 1a–f (100 mg scale) in dry toluene (5 mL) was added. The reaction was monitored by TLC under the reaction conditions described in Table 2. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (EiOAc/hexanes) to afford, after concentration and high-vacuum drying, the corresponding 2H-chromenes (2a–f).

**6-Methoxy-2H-chromene (2a).**

According to the general procedure, the reaction of 1a (120 mg, 0.742 mmol) with InI₃ afforded, after purification by column chromatography (Rₙ = 0.24, 5% EiOAc/hexanes, 1% Et₃N), 2a as a colorless oil (94 mg, 0.631 mmol, 85%): ¹H NMR (300 MHz, CDCl₃) δ 6.74-6.66 (m, 2H), 6.56 (d, J = 2.8 Hz, 1H), 6.46 (d, J = 9.8 Hz, 1H), 5.84 (dt, J = 9.8, 3.6 Hz, 2H), 4.77 (dd, J = 3.6, 1.8 Hz, 2H), 3.77 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 154.1 (C), 148.0 (C), 124.7 (CH), 123.1 (C), 123.0 (CH), 116.2 (CH), 114.1 (CH), 111.8 (CH), 65.4 (CH), 55.7 (CH₃); IR (ATR) νmax 2997, 2832, 1724, 1490 cm⁻¹; MS (EI) m/z 162 [M⁺] (80), 161 [M - H]⁻ (100); HRMS (EI) calcd for C₁₀H₁₀O₂ [M⁺] 162.0675, found 162.0670.

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According to the general procedure, the reaction of 1b (108 mg, 0.742 mmol) with InI$_3$ afforded, after purification by column chromatography (R$_f$ = 0.25, 2% EtOAc/hexanes, 1% Et$_3$N), compound 2b as a colorless oil (68 mg, 0.467 mmol, 63%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.92 (dd, $J$ = 8.5, 1.7 Hz, 1H), 6.79 (d, $J$ = 1.7 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.1, 178.0, 177.0420, found 177.0415.  

**Methyl 2H-chromene-6-carboxylate (2c).** According to the general procedure, the reaction of 1c (141 mg, 0.742 mmol) with InI$_3$ afforded, after purification by column chromatography (R$_f$ = 0.24, 10% EtOAc/hexanes, 1% Et$_3$N), 2e as a viscous white oil (127 mg, 0.668 mmol, 90%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.79 (dd, $J$ = 8.5, 2.1 Hz, 1H), 7.64 (d, $J$ = 2.1 Hz, 1H), 7.76 (d, $J$ = 8.5 Hz, 1H), 6.43 (d, $J$ = 9.9 Hz, 1H), 5.76 (dt, $J$ = 9.9, 3.4 Hz, 1H), 4.92 (dd, $J$ = 3.4, 2.0 Hz, 2H), 3.87 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.7 (C), 158.1 (CH), 131.2 (CH), 128.2 (CH), 123.8 (CH), 123.1 (C), 122.2 (CH), 121.5 (C), 115.6 (CH), 66.1 (CH$_3$), 51.8 (CH$_2$); IR (ATR) $\nu$$_{max}$ 2951, 2848, 1713, 1612, 1493 cm$^{-1}$; MS (EI) $m/z$ 176 [M$^+$] (100); HRMS (EI) calcld for C$_6$H$_4$NO$_2$ [M$^+$] 176.0462, found 176.0470.

**6-Nitro-2H-chromene (2d).** According to the general procedure, the reaction of 1d (128 mg, 0.742 mmol) with InI$_3$ afforded, after purification by column chromatography (R$_f$ = 0.28, 10% EtOAc/hexanes, 1% Et$_3$N), 2e as a light yellow solid (129 mg, 0.727 mmol, 98%); mp 134-135 $^\circ$C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.02 (dd, $J$ = 8.9, 2.7 Hz, 1H), 7.85 (d, $J$ = 2.7 Hz, 1H), 6.80 (d, $J$ = 8.9 Hz, 1H), 6.45 (dt, $J$ = 9.8, 1.7 Hz, 1H), 5.88 (dd, $J$ = 10.0, 3.4 Hz, 1H), 5.01 (dd, $J$ = 3.4, 2.0 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.5 (C), 141.8 (C), 125.3 (CH), 123.7 (CH$_2$), 122.9 (CH), 122.1 (CH$_2$), 121.7 (C), 116.0 (CH$_3$), 106.7 (CH$_2$); IR (ATR) $\nu$$_{max}$ 2920, 2850, 1505, 1400 cm$^{-1}$; MS (EI) $m/z$ 176 [M$^+$] (7), 83 [M - C$_6$H$_4$NO$_2$]$^-$ (100); HRMS (EI) calcld for C$_6$H$_4$NO$_2$ [M$^+$] 177.0420, found 177.0415.

**2H-Chromene-6-carbonitrile (2e).** According to the general procedure, the reaction of 1e (117 mg, 0.742 mmol) with InI$_3$ afforded, after purification by column chromatography (R$_f$ = 0.30, 10% EtOAc/hexanes, 1% Et$_3$N), compound 2e as a white solid (74 mg, 0.467 mmol, 63%); mp 65-67 $^\circ$C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.19 (d, $J$ = 2.0 Hz, 1H), 6.77 (d, $J$ = 8.4 Hz, 1H), 6.36 (dt, $J$ = 10.0, 1.7 Hz, 1H), 5.83 (dt, $J$ = 10.0, 3.4 Hz, 1H), 4.94 (dd, $J$ = 3.4, 2.0 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 157.7 (C), 133.4 (CH), 130.2 (CH), 123.5 (CH), 122.7 (CH), 122.6 (C), 119.0 (C), 116.6 (CH), 104.4 (C), 66.3 (CH$_2$); IR (ATR) $\nu$$_{max}$ 2922, 2872, 2222, 1647, 1488 cm$^{-1}$; HRMS (ESI) calcld for C$_6$H$_4$NO$_2$ [M$^+$] 158.0600, found 158.0601.

**6-Bromo-2H-chromene (2f).** According to the general procedure, the reaction of 1f (153 mg, 0.742 mmol) with InI$_3$ afforded, after purification by column chromatography (R$_f$ = 0.26, 20% EtOAc/hexanes, 1% Et$_3$N), compound 2f as a colorless oil (81 mg, 0.462 mmol, 78%); mp 96-98 $^\circ$C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.98 (d, $J$ = 8.3 Hz, 2H), 7.45 (d, $J$ = 8.3 Hz, 2H), 6.86 (d, $J$ = 8.8 Hz, 1H), 6.73 (dd, $J$ = 8.8, 3.0 Hz, 1H), 6.51 (d, $J$ = 3.0 Hz, 1H), 5.90 (t, $J$ = 4.0 Hz, 1H), 4.79...
According to the general procedure, the reaction of 3d (129 mg, 0.462 mmol) with InI₃ afforded, after purification by column chromatography (Rᵣ = 0.26, 20% EtOAc/hexanes), compound 4h as a yellow oil (100 mg, 0.453 mmol, 98%): ¹¹B NMR (300 MHz, CDCl₃) δ 7.55 (d, J = 2.8 Hz, 1H), 6.89 (t, J = 4.2 Hz, 1H), 6.80-6.72 (m, 2H), 4.77 (d, J = 4.2 Hz, 2H), 3.84 (s, 3H), 3.76 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 161.5 (C), 154.2 (C), 148.0 (C), 132.8 (CH), 127.1 (C), 120.2 (C), 116.7 (C), 115.4 (CH), 111.5 (CH), 64.6 (CH₃), 55.7 (CH₃), 51.9 (CH₃); IR (ATR) νmax 2955, 2886, 2836, 1717, 1574, 1487, 1434 cm⁻¹; MS (EI) m/z 220 [M⁺] (93), 205 [M-C₇H₅]⁺ (83); HRMS (EI) calecd for C₁₂H₁₂O₃ [M⁺] 220.0730, found 220.0729.

4-Bromo-6-methoxy-2H-chromene (4i). ²⁵

According to the general procedure, the reaction of 3i (111 mg, 0.462 mmol) with InI₃ afforded, after purification by column chromatography (Rᵣ = 0.25, 5% EtOAc/hexanes), compound 4i as a colorless oil (106 mg, 0.439 mmol, 95%): ¹¹B NMR (300 MHz, CDCl₃) δ 6.97 (t, J = 1.7 Hz, 1H), 6.73 (d, J = 1.7 Hz, 2H), 6.18 (t, J = 4.0 Hz, 1H), 4.72 (d, J = 4.0 Hz, 2H), 3.79 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 154.3 (C), 148.3 (C), 124.3 (CH), 122.7 (C), 118.0 (C), 116.5 (CH), 115.8 (CH), 112.3 (CH), 66.7 (CH₃), 55.8 (CH₃); IR (ATR) νmax 2954, 2906, 2832, 2722, 1687, 1621, 1574, 1480, 1427 cm⁻¹; MS (EI) m/z 242 [M⁺] [⁷Br]⁺ (54), 240 [M⁺] [⁸Br]⁺ (56); HRMS (EI) calecd for C₁₂H₁₀OBr [M⁺] 239.9780, found 239.9790.

Methyl 4-bromo-2H-chromene-6-carboxylate (4j).

According to the general procedure, the reaction of 3j (124 mg, 0.462 mmol) with InI₃ afforded, after purification by column chromatography (Rᵣ = 0.28, 10% EtOAc/hexanes), compound 4j as a white solid (112 mg, 0.416 mmol, 90%): mp 104–106 °C; ¹¹B NMR (300 MHz, CDCl₃) δ 8.04 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 8.5, 2.0 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H) 6.15 (t, J = 3.8 Hz, 1H), 4.87 (d, J = 3.8 Hz, 2H), 3.88 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 163.3 (C), 158.1 (C), 132.5 (CH), 128.8 (CH), 123.8 (CH), 123.5 (C), 121.2 (C), 117.2 (C), 115.8 (CH), 66.3 (CH₃), 52.0 (CH₃); IR (ATR) νmax 3070, 2954, 2909, 2860, 1708, 1604, 1327 cm⁻¹; MS (EI) m/z 270 [M⁺] [⁸Br]⁺ (39), 268 [M⁺] [⁷Br]⁺ (38); HRMS (EI) calecd for C₁₂H₉O₂Br [M⁺] 267.9730, found 267.9738.

4-Iodo-6-methoxy-2H-chromene (4k).

According to the general procedure, the reaction of 3k (133 mg, 0.462 mmol) with InC₃I₃ afforded, after purification by column chromatography (Rᵣ = 0.32, 10% EtOAc/hexanes), compound 4k as a yellow oil (126 mg, 0.434 mmol, 95%): ¹¹B NMR (300 MHz, CDCl₃) δ 6.85 (d, J = 2.6 Hz, 1H), 6.75-6.65 (m, 2H), 5.63 (t, J = 4.0 Hz, 1H), 4.68 (d, J = 4.0 Hz, 2H), 3.80 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 154.4 (C), 147.7 (C), 133.4 (CH), 124.2 (C), 116.6 (2 × CH), 115.7 (CH), 93.1 (C), 67.5 (CH₃), 55.8 (CH₃); IR (ATR) νmax 2932, 2832, 1682, 1608, 1514, 1487, 1428 cm⁻¹; HRMS (EI) calecd for C₁₀H₇O₄I [M⁺] 287.9642, found 287.9631.
6-Methoxy-4-(phenylethynyl)-2H-chromene (5a).
To a solution of 3i (100 mg, 0.415 mmol, 1.0 equiv.) in dry toluene (5 mL), InCl₃ (3.0 mg, 0.021 mmol, 0.05 equiv.) was added and the mixture was stirred at 60 °C for 1 h. Then, a solution of phenyl acetylene (91 µL, 0.830 mmol, 2.0 equiv.) in dry toluene (5 mL) and [Pd(PPh₃)₄]Cl₂ (14.6 mg, 0.021 mmol, 0.05 equiv.) in dry toluene (5 mL) was added. After stirring for 16 h at 80 °C the mixture was cooled to rt and the solvent was concentrated. Purification by flash chromatography on silica gel (Rₛ = 0.29, 5% EtOAc/hexanes), gave compound 5a as a brown oil (99 mg, 0.377 mmol, 83%).

HRMS (EI) m/z 290 [M⁺] calcd 290.0937, found 290.0937.

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Notes and references
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2. Electronic Supplementary Information (ESI) available: Experimental details for the preparation of aryl propargyl ethers 1a-f and 3a-k, full characterization and copies of the ¹H and ¹³C NMR for all compounds used is included. See DOI: 10.1039/b000000x/


