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Indium-Catalyzed Intramolecular Hydroarylation of Aryl Propargyl Ethers

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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.[1] 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,[2] platinum,[3] ruthenium,[4] rhodium,[5] gold,[6] and silver.[7] More recently, non-precious metals such as iron,[8] gallium,[9] and indium[10] have been suggested as promising alternatives in terms of economy and reactivity.

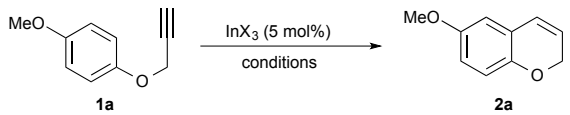
In the context of a research program aimed at developing new metal-catalyzed reactions using indium[11] and gold,[12] we report here the indium-catalyzed intramolecular hydroarylation of aryl propargyl ethers. Although this transformation can be performed with various precious metals, there are still limitations associated with the substrate (*i.e.*, terminal alkynes), regioselectivity (*6-endo vs. 5-exo*), side reactions such as ether cleavage or alkene isomerization and the economy of the transformation.[3a] Gold(I) catalysis is probably the best choice, although silver cocatalysis or highly active complexes are required.[6] On the other hand, IMHA of aryl propargyl ethers provides a straightforward synthesis of 2*H*-chromenes, a structural unit that is present in a vast number of naturally occurring and pharmaceutically active compounds.[13] 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.[14] 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.[15] Indium-catalyzed addition to alkynes has been described in inter- and intramolecular reactions involving 1,3-dicarbonyls,[16] in cycloisomerization reactions of alkynyl anilines.[17] Furthermore, indium catalysis has been used in intramolecular hydroarylations during the synthesis of phenanthrenes and derivatives from alkynylated biphenyl derivatives.[10] 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.[18] In addition, indium also offers significant advantages in terms of cost and low toxicity.[14,15]

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-methoxy-2*H*-chromene, **2a**) 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,[19] 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_2Cl_2 but not with coordinating solvents such as THF or MeOH (entries 6–9).

Table 1. Indium-catalyzed hydroarylation of aryl propargyl ether **1a**.

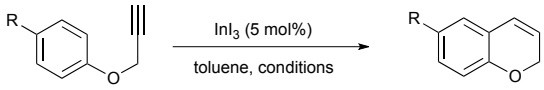


1a **2a**

Entry	InX_3	Solvent	T (°C)	t (h)	Yield(%)[a,b]
1	$InCl_3$	Toluene	rt	48	— (100)
2	$InCl_3$	Toluene	100	24	— (100)
3	$InBr_3$	Toluene	rt	16	58
4	InI_3	Toluene	rt	4	85
5	$In(OTf)_3$	Toluene	100	24	—
6	InI_3	CH_2Cl_2	rt	4	83
7	InI_3	THF	80	24	— (100)
8	$InBr_3$	MeOH	80	24	15 (85)[c]
9	InI_3	MeOH	80	24	— (100)

[a] Isolated yield. [b] Recovered starting material in parentheses. [c] Conversion determined by ^{1}H NMR.

Table 2. Indium-catalyzed IMHA with phenyl-substituted propargyl ethers.



1a–f **2a–f**

Entry	R	T (°C)	t (h)	2*H*-Chromene	Yield (%)[a]
1	OMe (**1a**)	rt	4	**2a**	85
2	Me (**1b**)	rt	12	**2b**	63
3	CO_2Me (**1c**)	100	24	**2c**	90
4	NO_2 (**1d**)	100	24	**2d**	98
5	CN (**1e**)	100	24	**2e**	63
6	Br (**1f**)	100	24	**2f**	70

[a]Isolated yield.

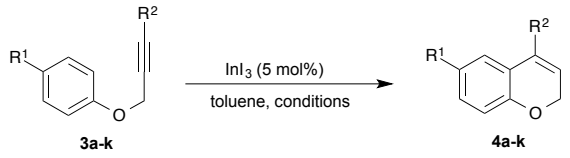
These promising results led us to survey the scope of the indium-catalyzed IMHA with functionalized aryl propargyl ethers (Table 2). The metal-catalyzed hydroarylation reaction is usually sensitive to electronic effects and limitations can arise with electron-deficient benzenes. Using InI_3 (5 mol%) as catalyst and toluene as solvent, we found that the presence of a methoxy group on the benzene is not essential, since the reaction with *p*-tolyl propargyl ether **1b** gave the 6-*endo* product **2c** in 63% yield at rt in 12 h (entry 2). This transformation showed a higher conversion by ^{1}H NMR, but isolated yield is usually lower due to decomposition by traces of acids. When an ester group was incorporated into the benzene (**1c**), InI_3 was ineffective at rt but at 100 °C the hydroarylation took place in 24 h and the 2*H*-chromene **2c** was isolated in 90% yield (entry 3). In a similar way, reaction of *p*-nitrophenyl 2-propynyl ether (**1d**) at 100 °C for 24 h gave the desired 6-nitro-2*H*-chromene (**2d**) in 98% yield as a single product (entry 4). The IMHA reaction with arenes functionalized with other electron-withdrawing groups such as cyano **1e** or bromo **1f** proceeded at 100 °C for 24 h in high yields (entries 5 and 6). Overall, it has been demonstrated that indium(III) hydroarylation can be performed efficiently with aryl 2-propynyl ethers (terminal alkynes) substituted with electron-rich and electron-deficient functional groups. These results are better than those obtained on using other metals catalysts, such as ruthenium(II),[4] platinum(II),[3d] and gallium(III),[9] in terms of efficiency and regioselectivity. It is interesting to note that, in contrast to gold(I) catalysis,[6] indium(III) provides the *6-endo* product exclusively and neither the ether cleavage nor isomerization byproducts were isolated. These results support a mechanism based on an electrophilic aromatic substitution process.

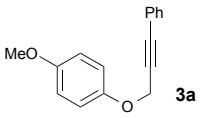
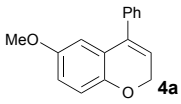
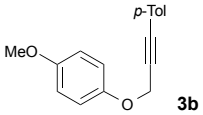
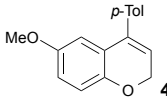
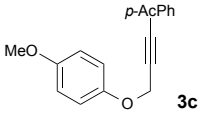
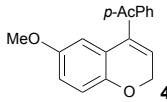
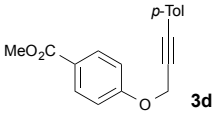
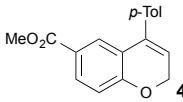
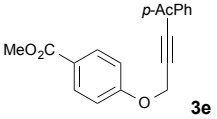
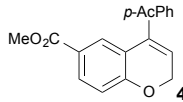
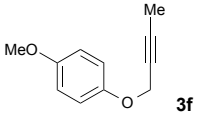
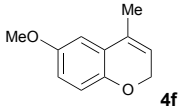
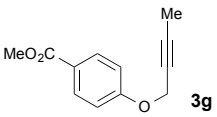
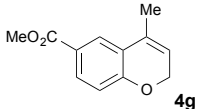
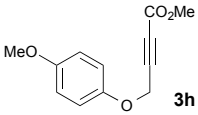
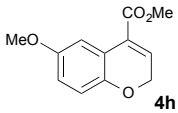
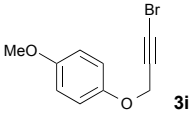
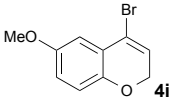
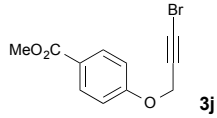
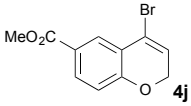
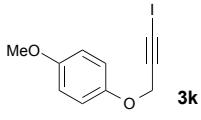
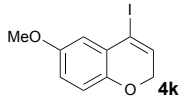
Given our success in the intramolecular hydroarylation with terminal alkynes, we turned our attention to internal alkynes that would allow the synthesis of 4-substituted 2*H*-chromenes and, with this aim in mind, a variety of internal alkynes were prepared (Table 3). Hydroarylation of 4-methoxyphenyl 3-phenyl-2-propynyl ether (**3a**) proceeded with $InBr_3$ or InI_3 (5 mol%) at rt and the corresponding 4-phenyl-2*H*-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 ^{1}H NMR spectroscopy. The electronic effects were analyzed with electron-donating and -withdrawing substituents in the benzene and alkyne. Aryl propargyl ethers **3b** and **3c** bearing a methoxy group in the benzene and *p*-tolyl or *p*-acetylphenyl groups in the alkyne reacted efficiently on using InI_3 (85% and 78%, respectively, entries 2 and 3). Internal alkynes **3d** and **3e**, both substituted with a methyl carboxylate 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 alkyne 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).

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.[20] Interestingly, it was found that reaction of 3-bromo-2-propynyl aryl ether **3i** with InI_3 (5 mol%) proceeded at rt in 6 h to give the 4-bromo-2*H*-chromene (**4i**) in 95% yield as a single product. On the other hand, the reaction with $InCl_3$ 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 $InCl_3$ (entry 11). In general, it has been shown that 4-halo-2*H*-chromenes can be efficiently prepared from the corresponding haloalkynes **3i**–**k** and that these compounds are more reactive than aryl alkynyl ethers **3a**–**e**.

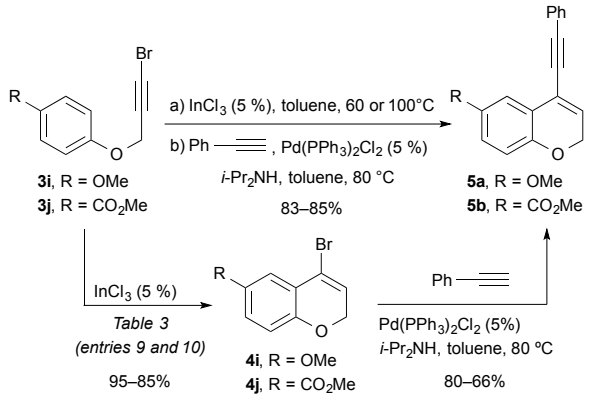
Table 3. Indium-catalyzed hydroarylation with internal alkynes.



Entry	Aryl propargyl ether	conditions	2*H*-Chromene	Yield (%)[a]
1	 **3a**	rt, 16h	 **4a**	65[b] 79
2	 **3b**	rt, 16h	 **4b**	85
3	 **3c**	100 °C, 36 h	 **4c**	78
4	 **3d**	100 °C, 72 h	 **4d**	45(38)[c]
5	 **3e**	100 °C, 72 h	 **4e**	38(45)[c]
6	 **3f**	rt, 16 h	 **4f**	97
7	 **3g**	100 °C, 24 h	 **4g**	75
8	 **3h**	100 °C, 4 h	 **4h**	98
9	 **3i**	rt, 6 h 60 °C, 4 h	 **4i**	95 95[d]
10	 **3j**	100 °C, 24 h	 **4j**	95 85[d]
11	 **3k**	rt, 16 h 60 °C, 1 h	 **4k**	30 95[d]

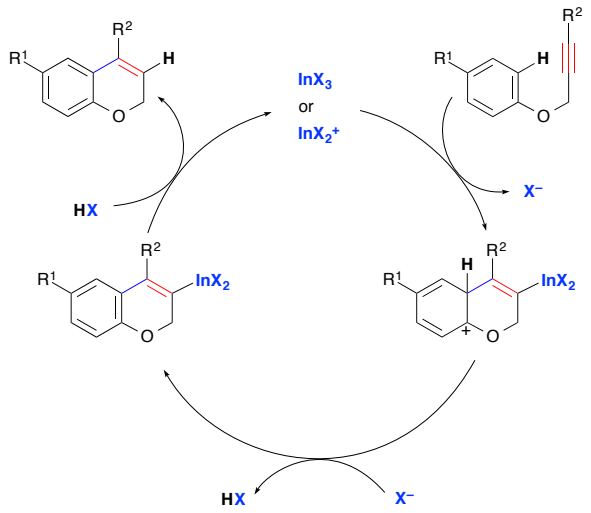
[a] Isolated yields, recovered starting material in parentheses; [b] Using 5 mol% $InBr_3$; [c] 10 mol% InI_3 was used; [d] 5 mol% $InCl_3$ was used.

The synthesis of 4-halo-2*H*-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.[21] 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 $InCl_3$ (5 mol%) in toluene at 60 ºC, followed by addition of phenylethyne (2 equiv) and $Pd(PPh_3)_2Cl_2$ (5 mol%) gave, after 12 h, the 4-phenylethynyl-2*H*-chromene **5a** in 85% overall yield (two steps). Interestingly, and despite their higher reactivity in the IMHA, the use of $InBr_3$ or InI_3 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-2*H*-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.[22]



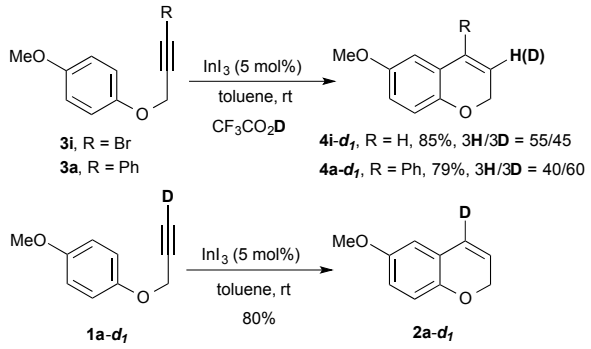
Scheme 1. Sequential indium-catalyzed hydroarylation/palladium-catalyzed Sonogashira coupling.

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 alkenylindium 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 InX_3 or InX_2^+ as it has been reported for $InCl_3$-catalyzed cycloisomerizations of 1,6-enynes.[23]



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

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 InI_3 (5 mol%) in toluene and CF_3CO_2D (2 equiv) afforded the chromene **4i-*d*$_1$** 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-*d*$_1$** and deuterium was also incorporated at the C-3 position with a 40/60 H/D ratio (Scheme 3). Additionally, hydroarylation of **1a-*d*$_1$** with a deuterium label at the terminal alkyne gave **2a-*d*$_1$** 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.[7]



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 alkynes 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 acetone, 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 (99.998%), indium(III) bromide (99%), indium(III) chloride (99.99%) 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/UV$_{254}$, 0.20 mm thick), UV light as the visualizing agent and ethanolic phosphomolybdic acid as the developing agent. Organic extracts were dried with anhydrous $MgSO_4$, 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. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or MeOD-d_4 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 InI_3 (18 mg, 0.037 mmol) a solution of the aryl propargyl ether **1a–1f** (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 (EtOAc/hexanes) to afford, after concentration and high-vacuum drying, the corresponding 2*H*-chromenes (**2a–f**).

6-Methoxy-2*H*-chromene (2a).[24]

According to the general procedure, the reaction of **1a** (120 mg, 0.742 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.24, 5% EtOAc/hexanes, 1% Et_3N), **2a** as a colorless oil (94 mg, 0.631 mmol, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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_2), 55.7 (CH_3); IR (ATR) ν_{max} 2997, 2832, 1724, 1490 cm^{-1}; MS (EI) *m/z* 162 $[M]^+$ (80), 161 $[M - H]^+$ (100); HRMS (EI) calcd for $C_{10}H_{10}O_2$ $[M]^+$ 162.0675, found 162.0670.

6-Methyl-2*H*-chromene (2b).[24]

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_3N), **2b** as a colorless oil (68 mg, 0.467 mmol, 63%): ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, J = 8.1, 1.7 Hz, 1H), 6.79 (d, J = 1.7 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.40 (d, J = 9.8 Hz, 1H), 5.77 (dt, J = 9.8, 3.6 Hz, 1H), 4.80 (dd, J = 3.6, 1.8 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9 (C), 130.5 (C), 129.5 (CH), 127.1 (CH), 124.7 (CH), 122.2 (C), 122.0 (CH), 115.4 (CH), 65.5 (CH_2), 20.5 (CH_3); IR (ATR) ν_{max} 3019, 2922, 2825, 2729, 1491 cm^{-1}; MS (EI) *m/z* 146 $[M]^+$ (44), 145 $[M - H]^+$ (100); HRMS (EI) calcd for $C_{10}H_{10}O$ $[M]^+$ 146.0726, found 146.0726.

Methyl 2*H*-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_3N), **2c** as a viscous white oil (127 mg, 0.668 mmol, 90%): ^1H NMR (300 MHz, $CDCl_3$) δ 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), 5.78 (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, $CDCl_3$) δ 166.7 (C), 158.1 (C), 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) ν_{max} 2951, 2848, 1713, 1612, 1493 cm^{-1}; MS (EI) *m/z* 190 $[M]^+$ (53), 189 $[M - H]^+$ (92), 83 $[M - C_5H_7O_2]^+$ (100) ; HRMS (EI) calcd for $C_{11}H_{10}O_3$ $[M]^+$ 190.0624, found 190.0614.

6-Nitro-2*H*-chromene (2d).[6d]

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_3N), **2e** as a light yellow solid (129 mg, 0.727 mmol, 98%): mp 134-135 ºC; ^1H NMR (300 MHz, $CDCl_3$) δ 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 (dt, J = 10.0, 3.4 Hz, 1H), 5.01 (dd, J = 3.4, 2.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (C), 141.8 (C), 125.3 (CH), 123.7 (CH), 122.9 (CH), 122.1 (CH), 121.7 (C), 116.0 (CH), 66.7 (CH_2); IR (ATR) ν_{max} 2920, 2850, 1505, 1400 cm^{-1}; MS (EI) *m/z* 176 $[M - H]^+$ (7), 83 $[M - C_4H_4NO_2]^+$ (100); HRMS (EI) calcd for $C_9H_7NO_3$ $[M]^+$ 177.0420, found 177.0415.

2*H*-Chromene-6-carbonitrile (2e).[6d]

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_3N), compound **2e** as a white solid (74 mg, 0.467 mmol, 63%): mp 65-67 ºC; ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) ν_{max} 2922, 2872, 2222, 1647, 1488 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_8NO$ $[M + H]^+$ 158.0600, found 158.0601.

6-Bromo-2*H*-chromene (2f).[25]

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 = 0.25, 2% EtOAc/hexanes, 1% Et_3N), compound **2f** as a colorless oil (110 mg, 0.519 mmol, 70%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (dd, J = 8.5, 2.4 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.34 (dt, J = 9.9, 1.6 Hz, 1H), 5.79 (dt, J = 9.9, 3.5 Hz, 1H), 4.82 (dd, J = 3.5, 1.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (C), 131.6 (CH), 129.0 (CH), 124.1 (C), 123.5 (CH), 123.2 (CH), 117.4 (CH), 113.2 (C), 65.6 (CH_2); IR (ATR) ν_{max} 2955, 2916, 2848, 2755, 1479, 1421, 1232 cm^{-1}; MS (EI) *m/z* 212 $[M, {}^{81}Br]^+$ (55), 210 $[M, {}^{79}Br]^+$ (100); HRMS (EI) calcd for C_9H_7BrO $[M]^+$ 209.9675, found 209.9668.

General procedure for indium-catalyzed IMHA with internal alkynes 3a–3k.

In a Schlenk tube with InI_3 (11 mg, 0.023 mmol) a solution of the alkyne **3a**–**3k** (0.462 mmol) in dry toluene (5 mL) was added. The reaction was monitored by TLC under the reaction conditions described in Table 3. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes) to afford, after concentration and high-vacuum drying, the corresponding *2H*–chromenes **4a–k**.

6-Methoxy-4-phenyl-2*H*-chromene (4a).[25]

According to the general procedure, the reaction of **3a** (110 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.33, 5% EtOAc/hexanes), compound **4a** as a white solid (87 mg, 0.365 mmol, 79%): mp 62–64 ºC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.36 (m, 5H), 6.87 (d, J = 8.7 Hz, 1H), 6.74 (dd, J = 8.7, 3.0 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 5.87 (t, J = 4.0 Hz, 1H), 4.81 (d, J = 4.0 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0 (C), 148.6 (C), 138.1 (C), 137.2 (C), 128.6 (2 × CH), 128.4 (2 × CH), 127.8 (CH), 124.5 (C), 120.9 (CH), 116.6 (CH), 114.1 (CH), 111.6 (CH), 65.2 (CH_2), 55.7 (CH_3); IR (ATR) ν_{max} 2997, 2939, 2832, 1736, 1576, 1486 cm^{-1}; MS (EI) *m/z* 238 $[M]^+$ (46), 237 $[M - H]^+$ (52); HRMS (EI) calcd for $C_{16}H_{14}O_2$ $[M]^+$ 238.0988, found 238.0984.

6-Methoxy-4-(*p*-tolyl)-2*H*-chromene (4b).

According to the general procedure, the reaction of **3b** (117 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.28, 2% EtOAc/hexanes), compound **4b** as a light yellow solid (99 mg, 0.393 mmol, 85%): mp 82–84 ºC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.19 (m, 4H), 6.85 (d, J = 8.7 Hz, 1H), 6.72 (dd, J = 8.7, 3.0 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 5.83 (t, J = 4.0 Hz, 1H), 4.78 (d, J = 4.0 Hz, 2H), 3.66 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9 (C), 148.7 (C), 137.6 (C), 137.1 (C), 135.2 (C), 129.1 (2 × CH), 128.4 (2 × CH), 124.6 (C), 120.4 (CH), 116.6 (CH), 114.1 (CH), 111.6 (CH), 65.1 (CH_2), 55.7 (CH_3), 21.2 (CH_3); IR (ATR) ν_{max} 2995, 2939, 2832, 1486, 1463, 1425 cm^{-1}; MS (EI) *m/z* 252 $[M]^+$ (100); HRMS (EI) calcd for $C_{17}H_{16}O_2$ $[M]^+$ 252.1145, found 252.1139.

1-(4-(6-Methoxy-2*H*-chromen-4-yl)phenyl)ethanone (4c).[7]

According to the general procedure, the reaction of **3c** (129 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.26, 20% EtOAc/hexanes), compound **4c** as a yellow solid (101 mg, 0.360 mmol, 78%): mp 96–98 ºC; ^1H NMR (300 MHz, $CDCl_3$) δ 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

(d, J = 4.0 Hz, 2H), 3.63 (s, 3H), 2.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6 (C), 154.0 (C), 148.6 (C), 143.0 (C), 136.5 (2 × C), 128.8 (2 × CH), 128.5 (2 × CH), 123.8 (C), 122.0 (CH), 116.9 (CH), 114.5 (CH), 111.4 (CH), 65.0 (CH_2), 55.7 (CH_3), 26.6 (CH_3); IR (ATR) ν_{max} 2959, 2910, 2835, 1679, 1600, 1505, 1429 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}O_3$ $[M + H]^+$ 281.1172, found 281.1166.

Methyl 4-(*p*-tolyl)-2*H*-chromene-6-carboxylate (4d).

According to the general procedure, the reaction of **3d** (129 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.22, 2% EtOAc/hexanes), compound **4d** as a light yellow solid (58 mg, 0.208 mmol, 45%): mp 84–86 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.5, 2.1 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.27 (br s, 4H), 6.91 (d, J = 8.5 Hz, 1H), 5.80 (t, J = 3.9 Hz, 1H), 4.95 (d, J = 3.9 Hz, 2H), 3.83 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (C), 158.8 (C), 137.9 (C), 136.4 (C), 134.7 (C), 131.1 (CH), 129.3 (2 × CH), 128.3 (2 × CH), 127.5 (CH), 123.1 (C), 123.0 (C), 119.8 (CH), 116.2 (CH), 65.8 (CH_2), 51.9 (CH_3), 21.3 (CH_3); IR (ATR) ν_{max} 2951, 2923, 2850, 2225, 1713, 1605, 1507, 1436 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}O_3$ $[M + H]^+$ 281.1172, found 281.1169.

Methyl 4-(4-acetylphenyl)-2*H*-chromene-6-carboxylate (4e).

According to the general procedure, the reaction of **3e** (142 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.21, 20% EtOAc/hexanes), compound **4e** as a white solid (54 mg, 0.175 mmol, 38%): mp 119–121 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 2H), 7.87 (dd, J = 8.5, 2.1 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.5 Hz, 1H), 5.86 (t, J = 3.9 Hz, 1H), 4.96 (d, J = 3.9 Hz, 2H), 3.81 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6 (C), 166.5 (C), 158.7 (C), 142.4 (C), 136.7 (C), 135.8 (C), 131.5 (CH), 128.7 (2 × CH), 127.2 (CH), 123.2 (C), 122.4 (C), 121.3 (CH), 116.4 (CH), 65.7 (CH_2), 51.9 (CH_3), 26.7 (CH_3); IR (ATR) ν_{max} 2955, 2842, 1717, 1679, 1603, 1575 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}O_4$ $[M + H]^+$ 309.1121, found 309.1121.

6-Methoxy-4-methyl-2*H*-chromene (4f).[25]

According to the general procedure, the reaction of **3f** (81 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.41, 5% EtOAc/hexanes), compound **4f** as a light yellow oil (79 mg, 0.448 mmol, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77-6.66 (m, 3H), 5.62 (dd, J = 3.6, 1.8 Hz, 1H), 4.68 (dd, J = 3.5, 1.8 Hz, 2H), 3.77 (s, 3H), 2.02 (dd, J = 3.3, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C), 148.1 (C), 130.3 (C), 125.2 (C), 119.4 (CH), 116.0 (CH), 113.3 (CH), 109.7 (CH), 65.3 (CH_2), 55.8 (CH_3), 17.9 (CH_3); IR (ATR) ν_{max} 2943, 2919, 2832, 2733, 1577, 1490, 1425 cm^{-1}; MS (EI) m/z 176 $[M]^+$ (62), 161 $[M\text{-}CH_3]^+$ (87); HRMS (EI) calcd for $C_{11}H_{12}O_2$ $[M]^+$ 176.0832, found 176.0827.

Methyl 4-methyl-2*H*-chromene-6-carboxylate (4g).

According to the general procedure, the reaction of **3g** (94 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.25, 5% EtOAc/hexanes), compound **4g** as a yellow oil (71 mg, 0.347 mmol, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.79 (m, 2H), 6.78 (d, J = 8.9 Hz, 1H), 5.59 (m, 1H), 4.85 (dd, J = 3.4, 1.7 Hz, 2H), 3.88 (s, 3H), 2.06 (dd, J = 3.4, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9 (C), 158.3 (C), 131.0 (CH), 129.5 (CH), 125.3 (CH), 123.5 (C), 122.8 (C), 118.6 (CH), 115.5 (CH), 66.0 (CH_2), 51.9 (CH_3), 18.0 (CH_3); IR (ATR) ν_{max} 2951, 2844, 1711, 1607, 1492, 1437 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{12}O_3$ $[M + H]^+$ 205.0859, found 205.0861.

Methyl 6-methoxy-2*H*-chromene-4-carboxylate (4h).

According to the general procedure, the reaction of **3h** (102 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.26, 20% EtOAc/hexanes), compound **4h** as a yellow oil (100 mg, 0.453 mmol, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (C), 154.2 (C), 148.0 (C), 132.8 (CH), 127.1 (C), 120.2 (C), 116.7 (CH), 115.4 (CH), 111.5 (CH), 64.6 (CH_2), 55.7 (CH_3), 51.9 (CH_3); IR (ATR) ν_{max} 2996, 2951, 2834, 1717, 1574, 1487, 1434 cm^{-1}; MS (EI) m/z 220 $[M]^+$ (93), 205 $[M\text{-}CH_3]^+$ (83); HRMS (EI) calcd for $C_{12}H_{12}O_4$ $[M]^+$ 220.0730, found 220.0729.

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

According to the general procedure, the reaction of **3i** (111 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.25, 5% EtOAc/hexanes), compound **4i** as a colorless oil (106 mg, 0.439 mmol, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 55.8 (CH_3); IR (ATR) ν_{max} 2954, 2906, 2832, 2722, 1687, 1621, 1574, 1480, 1427 cm^{-1}; MS (EI) m/z 242 [M, ^{81}Br]$^+$ (54), 240 [M, ^{79}Br]$^+$ (56); HRMS (EI) calcd for $C_{10}H_9O_2Br$ $[M]^+$ 239.9780, found 239.9790.

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

According to the general procedure, the reaction of **3j** (124 mg, 0.462 mmol) with InI_3 afforded, after purification by column chromatography (R_f = 0.28, 10% EtOAc/hexanes), compound **4j** as a white solid (112 mg, 0.416 mmol, 90%): mp 104–106 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 2.0 Hz, 1H), 7.85 (dd, 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 52.0 (CH_3); IR (ATR) ν_{max} 3070, 2954, 2909, 2860, 1708, 1640, 1327 cm^{-1}; MS (EI) m/z 270 [M, ^{81}Br]$^+$ (39), 268 [M, ^{79}Br]$^+$ (38); HRMS (EI) calcd for $C_{11}H_9O_3Br$ $[M]^+$ 267.9730, found 267.9738.

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

According to the general procedure, the reaction of **3k** (133 mg, 0.462 mmol) with $InCl_3$ (5.1 mg, 0.023 mmol) afforded, after purification by column chromatography (R_f = 0.32, 10% EtOAc/hexanes), compound **4k** as a yellow oil (126 mg, 0.439 mmol, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, J = 2.6 Hz, 1H), 6.75-6.65 (m, 2H), 6.53 (t, J = 4.0 Hz, 1H), 4.68 (d, J = 4.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 55.8 (CH_3); IR (ATR) ν_{max} 2932, 2832, 1682, 1608, 1514, 1487, 1428 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9O_2I$ $[M]^+$ 287.9642, found 287.9631.

6-Methoxy-4-(phenylethynyl)-2*H*-chromene (5a).

To a solution of **3i** (100 mg, 0.415 mmol, 1.0 equiv.) in dry toluene (5 mL), $InCl_3$ (4.60 mg, 0.021 mmol, 0.05 equiv.) was added and the mixture was stirred at 60 ºC for 1 h. Then, a solution of phenyl acetylene (91 µL, 0.830 mmol, 2.0 equiv.), *i*-Pr_2NH (1.15 mL, 8.30 mmol, 20.0 equiv.) and $Pd(PPh_3)_2Cl_2$ (14.6 mg, 0.021 mmol, 0.05 equiv.) in dry toluene (5 mL) was added. After stirring for 16 h at 80 ºC the mixture was cooled to rt and the solvent was concentrated. Purification by flash chromatography (R_f = 0.29, 5% EtOAc/hexanes), gave compound **5a** as a brown oil (99 mg, 0.377 mmol, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.51 (m, 2H), 7.39-7.34 (m, 3H), 7.13 (d, J = 2.6 Hz, 1H), 6.76-6.73 (m, 2H), 6.24 (t, J = 4.1 Hz, 1H), 4.82 (d, J = 4.1 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 (C), 147.6 (C), 131.7 (2 × CH), 128.6 (2 × CH), 128.4 (CH), 122.8 (C), 122.2 (C), 119.5 (C), 116.5 (CH), 114.9 (CH), 111.1 (CH), 92.2 (C), 84.7 (C), 65.3 (CH_2), 55.8 (CH_3); IR (ATR) ν_{max} 2955, 2923, 2855, 1623, 1560, 1492, 1432 cm^{-1}; MS (EI) *m/z* 262 $[M]^+$ (10); HRMS (EI) calcd for $C_{18}H_{14}O_2$ $[M]^+$ 262.0988, found 262.0983.

Methyl 4-(phenylethynyl)-2*H*-chromene-6-carboxylate (5b).

To a solution of **3j** (100 mg, 0.372 mmol) in dry toluene (5 mL), $InCl_3$ (8.20 mg, 0.037 mmol) was added and the resulting mixture was stirred at 100 ºC for 24 h, cooled to 80 ºC, and a solution of phenyl acetylene (82 µL, 0.743 mmol), *i*-Pr_2NH (1.04 mL, 7.43 mmol) and $Pd(PPh_3)_2Cl_2$ (13 mg, 0.019 mmol) in toluene (5 mL) was added. The mixture was stirred at 80 ºC for 24 h, cooled to rt and the solvent was concentrated. Purification by flash chromatography (R_f = 0.22, 10% EtOAc/hexanes), afforded **5b** as a viscose brown-orange oil (90 mg, 0.310 mmol, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 2.1 Hz, 1H), 7.87 (dd, J = 8.5, 2.1 Hz, 1H),7.60-7.52 (m, 2H), 7.42-7.32 (m, 3H), 6.82 (d, J = 8.5 Hz, 1H), 6.19 (t, J = 4.0 Hz, 1H), 4.98 (d, J = 4.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 157.6 (C), 131.8 (2 × CH), 128.7 (CH), 128.4 (2 × CH), 127.5 (CH), 126.9 (CH), 123.4 (C), 122.6 (C), 120.6 (C), 118.8 (C), 115.8 (CH), 92.9 (C), 84.0 (C), 66.0 (CH_2), 51.9 (CH_3); IR (ATR) ν_{max} 2951, 2924, 2853, 1715, 1613, 1570, 1492, 1437 cm^{-1}; MS (EI) *m/z* 290 $[M]^+$ (100); HRMS (EI) calcd for $C_{19}H_{14}O_3$ $[M]^+$ 290.0937, found 290.0931.

1-Methoxy-4-((3-*d*)prop-2-yn-1-yloxy)benzene (1a-*d*$_1$).

n-BuLi (0.9 mL, 2.03 mmol, 2.25 M in hexanes) was added to a solution of **1a** (316 mg, 1.95 mmol) in dry THF (10 mL) at -78 ºC. After stirring for 1 h, D_2O (70 µL, 3.90 mmol, 2 equiv.) was added and the reaction mixture was warmed to rt. The crude was diluted with H_2O (5 mL) and extracted with EtOAc (2 × 15 mL). The organic phase was dried, filtered and concentrated to afford **1a-*d*$_1$** as light yellow oil (R_f = 0.27, 10% EtOAc/hexanes, 291 mg, 1.78 mmol, 83%, 96%-D), which was used in next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dt, J = 9.3, 3.4 Hz, 2H), 6.85 (dt, J = 9.3, 3.4 Hz, 2H), 4.64 (s, 2H), 3.77 (s, 3H).

6-Methoxy-2*H*-(4-*d*)chromene (2a-*d*$_1$).

A solution of **1a-*d*$_1$** (104 mg, 0.637 mmol, 1.0 equiv.) and InI_3 (16 mg, 0.032 mmol, 0.05 equiv.) in dry toluene (5 mL) was stirred at rt for 12 h. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (R_f= 0.32, 5% EtOAc/hexanes, 1% Et_3N), to afford **2a-*d*$_1$** as a colorless oil (83 mg, 0.509 mmol, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (br s, 1H), 6.67 (d, J = 2.7 Hz, 1H), 6.54 (d, J = 2.7 Hz, 1H), 5.83-5.80 (m, 1H), 4.76 (d, J = 3.6 Hz, 2H), 3.76 (s, 3H).

4-Bromo-6-methoxy-2*H*-(3-*d*)chromene (4i-*d*$_1$).

A solution of **3i** (95 mg, 0.394 mmol, 1.0 equiv.), TFA-*d*$_1$ (61 µL, 0.788 mmol, 2.0 equiv.) and InI_3 (9.7 mg, 0.019 mmol, 0.05 equiv.) in dry toluene (5 mL) was stirred for 12 h at rt. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (R_f = 0.36, 5% EtOAc/hexanes, 1% Et_3N), to afford **4i-*d*$_1$** as a colorless oil (79 mg, 83%, 3H/3D 55:45): ^{1}H NMR (300 MHz, $CDCl_3$) 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), 4.71 (d, J = 4.0 Hz, 2H), 3.79 (s, 3H).

6-Methoxy-4-phenyl-2*H*-(3-*d*)chromene (4a-*d*$_1$).[7]

A solution of **3a** (75 mg, 0.315 mmol, 1.0 equiv.), TFA-*d*$_1$ (48 µL, 0.629 mmol, 2.0 equiv.) and InI_3 (8.0 mg, 0.016 mmol, 0.05 equiv.) in dry toluene (5 mL) was stirred for 12 h at rt. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (R_f = 0.32, 5% EtOAc/hexanes, 1% Et_3N), to afford **4a-*d*$_1$** as a colorless oil (47 mg, 63%, 3H/3D 40:60)): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.36 (m, 5H), 6.87 (d, J = 8.7 Hz, 1H), 6.74 (dd, J = 8.7, 3.0 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 5.87 (t, J = 4.0 Hz, 1H), 4.81 (d, J = 4.0 Hz, 2H), 3.69 (s, 3H).

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Notes and references

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