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The Reaction of *o*-Alkynylarene and Heteroarene Carboxaldehyde Derivatives with Iodonium Ions and Nucleophiles: A Versatile and Regioselective Synthesis of 1*H*-Isochromene, Naphthalene, Indole, Benzofuran, and Benzothiophene Compounds

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Abstract: The reaction of *o*-alkynylbenzaldehydes **1** with different alcohols, silylated nucleophiles **5**, electron-rich arenes **10**, and heteroarenes **12** in the presence of the reagent IPy_2BF_4, at room temperature, gave functionalized 4-iodo-1*H*-isochromenes **2**, **6**, **11**, and **13** in a regioselective manner. When alkynes **16** and alkenes **19** and **20** were used as nucleophiles, a regioselective benzannulation reaction took place to form 1-iodonaphthalenes **17** and 1-naphthyl ketones **18**, respectively. Moreover, the latter process has been adapted to accomplish the synthesis of indole, benzofuran, and benzothiophene derivatives (**23**, **27**, and **28**, respectively). The three patterns of reactivity observed for the *o*-alkynylbenzaldehyde derivatives with IPy_2BF_4 stem from a common iodinated isobenzopyrylium ion intermediate, **A**, that evolves in a different way depending on the nucleophile present in the reaction medium. A mechanism is proposed and the different reaction pathways observed as a function of the type of nucleophile are discussed. Furthermore, the reaction of the *o*-hexynylbenzaldehyde **1b** with styrene was monitored by NMR spectroscopy. Compound **III**, a resting state for the common intermediate in the absence of acid, has been isolated. Its evolution in acid media has been also tested, thereby providing support to the proposed mechanism.

Keywords: cyclization · electrophilic addition · halogenation · iodonium ions · multicomponent reactions

Introduction

Electrophilic activation of alkynes toward intramolecular addition reactions of heteronucleophiles has become a useful method for the preparation of heterocyclic compounds.[1] In particular, the cyclization reactions of easily accessible *o*-alkynyl-substituted aniline, benzenecarboxaldehyde, phenol, or benzenecarboxylic acid derivatives have become a popular methodology for the synthesis of relevant heterocycles, such as indoles,[2] isoquinolines,[3] benzofurans,[4] and isocoumarins.[5] In those studies, the amino group of aniline and the imine functionality, easy to elaborate from the parent benzenecarboxaldehyde building block, are among the nucleophiles being frequently employed as responsible for the ultimately observed heterocyclization process. Nevertheless, the carbonyl group present in an aryl aldehyde or ketone has also been, albeit less commonly, considered as a suitable nucleophile to furnish related neutral heterocyclic compounds.[6] In this synthetic scenario, different domino processes involving electrophile-triggered cyclization of *o*-alkynylbenzaldehyde derivatives with concomitant incorporation of an additional nucleophile have recently emerged as a powerful tool for preparing benzoheterocyclic cores and polycyclic hydrocarbons. Various transition-metal catalysts have been employed for this purpose. Two major pathways have been postulated to rationalize the different types of compounds obtained, as concisely outlined in Scheme 1.

Thus, Yamamoto and his group reported an elegant cyclization of that class of acetylenic aldehydes that yielded cyclic alkenyl ethers (path a, Scheme 1) by using $Pd(OAc)_2$

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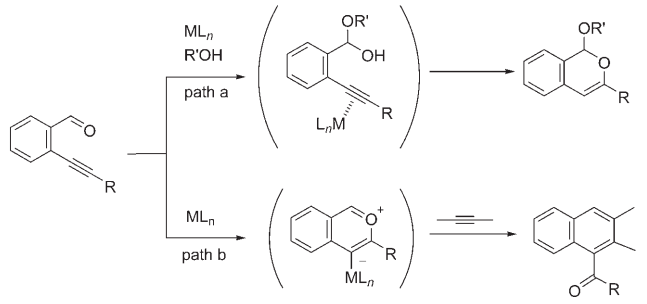


Scheme 1. Transition-metal-catalyzed cyclization reactions of *o*-alkynylbenzaldehydes. L = ligand, M = metal.

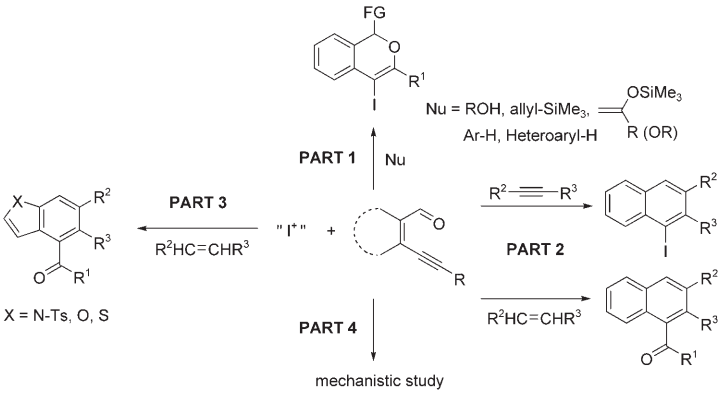
as a dual-role catalyst, which acts first as a Lewis acid to activate the carbonyl group toward the addition of the alcohol and then as a transition-metal catalyst to promote the attack of the resulting hemiacetal onto the alkyne.[7] This process was later improved through the combination of copper(I) iodide and *N*,*N*-dimethylformamide (DMF).[8]

Basic carbocyclic skeletons were also prepared from this class of precursors through related domino processes that employed alkynes as efficient partners. Therefore, substituted naphthyl ketones were prepared by $AuCl_3$-catalyzed formal [4+2] benzannulation between *o*-alkynylbenzaldehyde derivatives and alkynes (path b, Scheme 1).[9] The potential of this methodology has been rapidly recognized and nicely exploited in the synthesis of natural products.[10] When alkenes were used in this formal cycloaddition process, functionalized 1,2-dihydronaphthalenes were obtained through a [$Cu(OTf)_2$]-catalyzed reaction (Tf = trifluoromethanesulfonyl).[11] Furthermore, electron-rich heteroaromatic compounds[12] were also shown to be active components for those reaction sequences, as was, remarkably, the enol form in equilibrium with common carbonyl precursors.[13] More recently, fully intramolecular versions of these transition-metal-catalyzed [4+2] benzannulation reactions of alkynyl and alkenyl enynones and enynals have been disclosed, overall giving rise to a powerful and attractive entry for constructing polycyclic hydrocarbons.[14] Among all these studies, the initial formation of the ate isobenzopyrylium complex[15] shown in Scheme 1 (path b) was invoked. This kind of species was recognized as a key intermediate that leads to the observed naphthalene derivatives upon [4+2] cycloaddition with the corresponding unsaturated partner and further evolution.

It has been recently shown that iodonium ions can be successfully used to trigger formally related cyclization reactions of *o*-alkynylbenzenecarbaldehyde or ketone derivatives to give a wide set of 4-iodo-1*H*-isochromenes.[16] In our approach,[16a] while searching for new transformations, the reagent bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4) was routinely used as an iodine donor on the basis of its proven versatility and selectivity to act as a convenient and, in many cases, unique source of iodonium ions for a wide range of synthetically valuable transformations.[17] The iodonium approach represents an attractive and complementary alternative to the powerful metal-catalyzed entry to the heterocyclic core that is referred to above and, furthermore, this iodonium chemistry was found to be compatible with a broad range of nucleophiles. Moreover, through the use of both alkynes and alkenes as nucleophiles, it has permitted the establishment of a regioselective synthesis of naphthalenes and benzoheterocycles featuring different patterns of substitution.[18] Herein, we report a detailed study of the synthetic profile and mechanistic insights for this iodonium-promoted reaction between *o*-alkynylbenzaldehyde derivatives and different types of nucleophiles that resulted in a suitable route to access iodinated isochromenes,[16a] naphthalenes,[18a] and either benzo[*b*]pyrrole, furan, or thiophene derivatives.[18b]

Results and Discussion

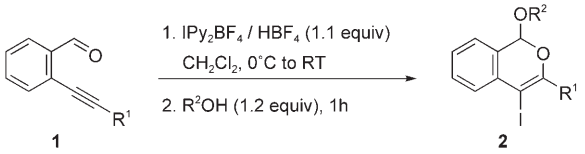
The description of the results has been arranged in different sections that offer an appropriate context for their discussion and, at the same time, that allows them to be placed in a general context. As already stated in the introduction, the momentum that the use of metal salts, particularly from precious metals, has created in this context is of great interest. Thus, whenever relevant, a comparison of the outcome of the iodonium approach with the metal-driven method has been incorporated. Also, comments on alternative iodonium donors are included. In Scheme 2, the different sections and their contents are graphically summarized.



Scheme 2. Outline of results discussion. FG = functional group, N-Ts = *N*-toluene-4-sulfonyl, Nu = nucleophile.

Cyclization of carbonyl groups onto alkynes promoted by reaction with IPy_2BF_4 and different nucleophiles: The reaction of *o*-alkynylbenzaldehyde derivatives **1** towards the versatile iodinating reagent IPy_2BF_4.and alcohols was first examined. Isochromenes **2** were regioselectively formed upon sequential treatment of a solution containing IPy_2BF_4 and HBF_4 with compounds **1** and then with different types of alcohols. The results, summarized in Table 1, show this iodocyclization reaction as being compatible with different R^1 groups in the alkyne moiety. The substitution pattern of the

Table 1. Iodocyclization of *o*-alkynylbenzaldehydes **1** with IPy_2BF_4 and trapping with alcohols.



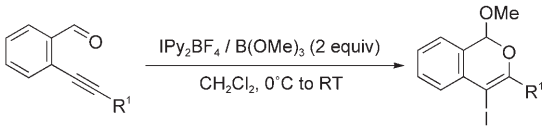
1 2

Entry	1	R^1	R^2OH	2	Yield [%][a]
1	**1a**	Ph	CH_3OH	**2a**	63
2[b]	**1a**	Ph	CH_3OH	**2a**	84
3	**1a**	Ph	$(CH_3)_2CHOH$	**2b**	61
4[c]	**1a**	Ph	$HC{\equiv}CCH_2OH$	**2c**	57
5	**1b**	*n*Bu	CH_3OH	**2d**	58
6[b]	**1b**	*n*Bu	CH_3OH	**2d**	87
7[d,e]	**1b**	*n*Bu	$(CH_3)_3COH$	**2e**	68
8	**1c**	1-cyclohexenyl	CH_3OH	**2f**	62

[a] Yield of isolated compound **2**, with respect to **1** (1 mmol scale). [b] 5 mmol of the appropriate starting material **1** were used. [c] Reaction time after R^2OH addition = 4 h. [d] Reaction was carried out without addition of HBF_4. [e] Reaction time after R^2OH addition = 6 h.

alcohol was also representatively modified. For the case with *t*BuOH, the reaction must be carried out in the absence of added HBF_4 to avoid major decomposition of the alcohol. The outcome of the process without adding HBF_4 was tested for other alcohols. The compounds depicted in Table 1 were still formed but the process was sluggish. For instance, the reaction of **1a** and IPy_2BF_4 with CH_3OH took up to 7 h to afford **2a** in a comparable yield to that indicated in Table 1 for the acid-assisted reaction. Although the yields for compounds **2** were found to be dependent on the reaction scale (Table 1, entries 1, 2, 5, and 6), essentially quantitative conversion of **1** into **2** was observed for each compound, as evidenced by NMR analysis of the crude reaction mixtures. These crude mixtures do not provide evidence for the occurrence of any significant side product. In each case, **2** was formed as a single regioisomer.

The iodinated cycloalkenyl ethers **2a**, **2d**, and **2f** can be accessed from **1** following an alternative procedure that avoids explicit addition of methanol. The reaction of **1** with a mixture of IPy_2BF_4 and $B(OMe)_3$ led to the formation of the target isochromene derivatives **2** (Scheme 3). In this



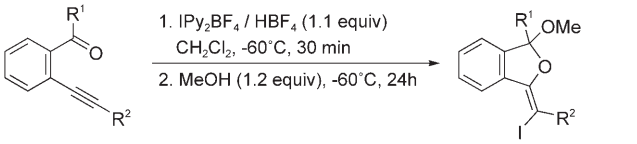
1a: R^1 = Ph
1b: R^1 = Bu
1c: R^1 = 1-Cyclohexenyl

2a: R^1 = Ph, 88%, 2h
2d: R^1 = Bu, 82%, 2h
2f: R^1 = 1-Cyclohexenyl, 79%, 3h

Scheme 3. Iodocyclization of *o*-alkynylbenzaldehydes **1** with IPy_2BF_4/B-$(OMe)_3$.

process, $B(OMe)_3$ acts both as a Lewis acid and as the source for the desired nucleophile (transferring a methoxy group) to furnish compounds **2**.

Related *o*-(alkynyl)arylketones also entered into this process. In this case, a different cyclization mode was observed. So, the reaction of *o*-(alkynyl)ketones **3a**,**b** with IPy_2BF_4 and CH_3OH, at low temperature, under the influence of acid, gave products **4a**,**b**, respectively. This selective cyclization–functionalization sequence is depicted in Scheme 4.[19] The cyclization followed the more commonly



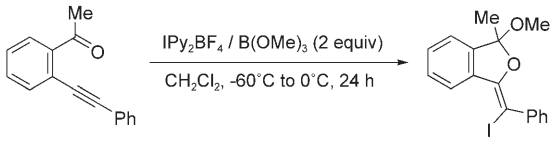
3a: R^1 = Me, R^2 = Ph
3b: R^1 = Ph, R^2 = *n*Bu

4a: R^1 = Me, R^2 = Ph, 21%
4b: R^1 = Ph, R^2 = *n*Bu, 67%

Scheme 4. Iodocyclization of *o*-(alkynyl)ketones **3a**,**b** with methanol trapping.

observed 5-*exo*-*dig* cyclization mode,[20] thereby furnishing a five-membered heterocycle, rather than the alternative six-membered ring that was previously formed from aldehydes **1** as the result of a competitive 6-*endo* cyclization path.[21]

The low yield in which product **4a** was obtained could be reasonably associated with the instability in acid media of both the enolizable ketone **3a** and the labile acetal **4a**. In this regard, the yield for that cyclization product was improved to 48% by a low-temperature reaction with the system IPy_2BF_4/$B(OMe)_3$, as depicted in Scheme 5.

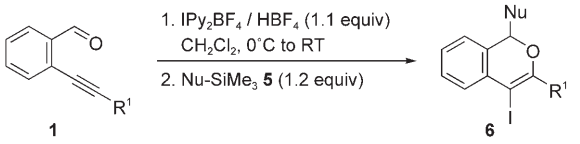


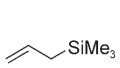
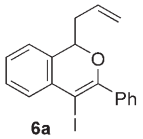
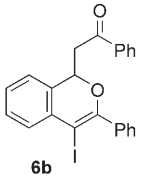
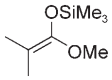
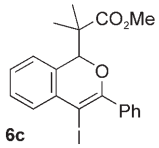
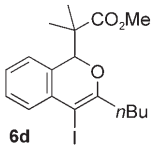
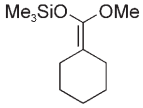
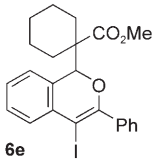
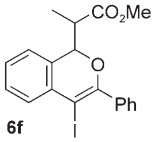
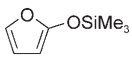
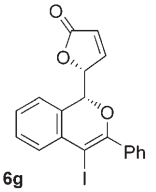
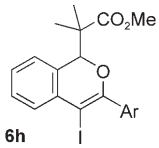
3a **4a** (48%)

Scheme 5. Iodocyclization of **3a** by employing the system IPy_2BF_4/B-$(OMe)_3$.

A sharp and differentiating feature of this iodonium-mediated cyclization approach is the possibility of conducting the process in a *sequential* manner. As a consequence of the flexibility of the experimental protocol, not only alcohols but, interestingly, also a set of carbon-based nucleophiles **5** can be successfully employed as productive nucleophilic partners for this reaction sequence. In this sense, different types of silyl-masked C-nucleophiles have been used,[22] thereby enabling a facile and straight access into more elaborate and densely functionalized heterocycles **6** (Table 2).[23] These reactions represent the first examples of formal Mukaiyama aldol[24] and Hosomi–Sakurai allylation[25] reactions formally triggered by a β-iodovinyl cation. The initial interaction of the iodonium ion with the alkyne

Table 2. Iodocyclization of **1** and trapping with silyl-masked C-nucleophiles.



R^1	t [h]	Nu-$SiMe_3$ **5**	**6**	Yield [%][a]
Ph	1	 **5a**	 **6a**	42
Ph	1	 **5b**	 **6b**	55
Ph	1	 **5c**	 **6c**	60
*n*Bu	1	**5c**	 **6d**	63
Ph	2	 **5d**	 **6e**	63
Ph	1	 **5e** (5:1)	 **6f**	55[b]
Ph	1	 **5f**	 **6g**	72[c]
Ar[d]	5	**5c**	 **6h**	53

[a] Yield of isolated compounds **6**, with respect to **1** (1 mmol scale). [b] 1:1 mixture of diastereoisomers indicated by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Compound **6g** was obtained as a single diastereoisomer. [d] Ar = 4-$NO_2C_6H_4$.

might give rise to those reactive species that, eventually, would facilitate the attack of the corresponding nucleophile onto the carbonyl group.

When 2-(trimethylsilyloxy)furan (**5f**) was employed, a single isomer **6g** was obtained in a diastereo- and regioselective process (Table 2). Its structure was established by means of NMR spectroscopy, while the relative configuration of the two formed stereogenic centers was unambiguously ascertained by means of an X-ray diffraction analysis (Figure 1). This vinylogous formal Mukaiyama aldol reaction furnished *syn*-**6g** as the only reaction product, as the result of a like approach of 2-(trimethylsilyloxy)furan (**5f**) to the iodinated isobenzopyrylium ion intermediate.[26]

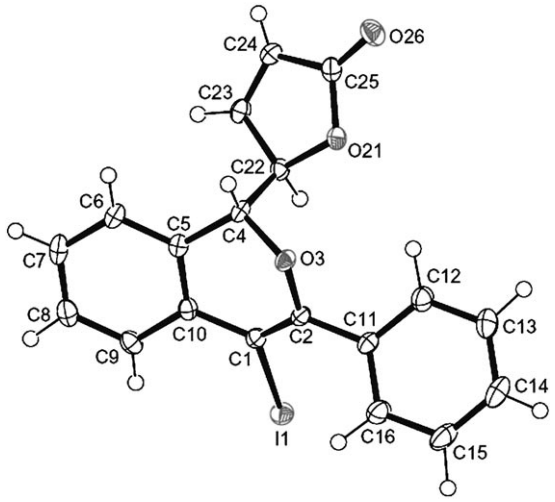
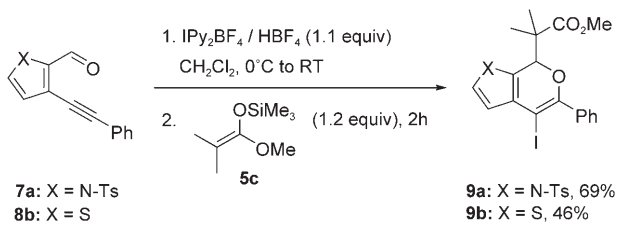


Figure 1. ORTEP drawing of **6g**.[27]

Once it was proved that formal latent enolate aldol additions can be successfully accomplished by using this iodonium technology, the possibility of using heteroarene carboxaldehyde derivatives as the starting materials was also explored. Interestingly, the cyclization–addition sequence of such systems would offer a simple entry for the synthesis of skeletons featuring fused heterocyclic cores. In this regard, when 3-alkynylpyrrole-2-carboxaldehyde (**7a**) or the related 3-alkynylthiophene-2-carboxaldehyde (**8b**) were subjected to the iodonium-mediated reaction with silylketene acetal **5c**, the 1,7-dihydropyrano[3,4-*b*]pyrrole (**9a**) and the 7*H*-thieno[2,3-*c*]pyran (**9b**), respectively, were accessed in a straightforward manner (Scheme 6).

We also explored the possibility of conducting the kind of transformation depicted in both Table 2 and Scheme 6 by

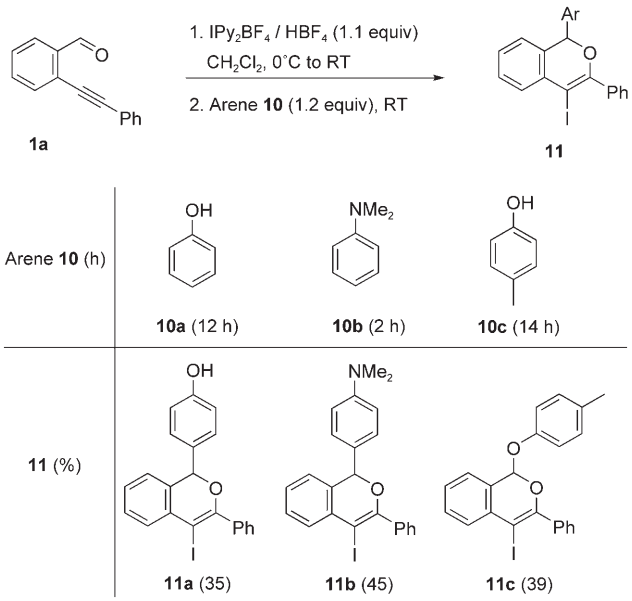


Scheme 6. Synthesis of fused heterocyclic compounds by iodocyclization with nucleophilic trapping.

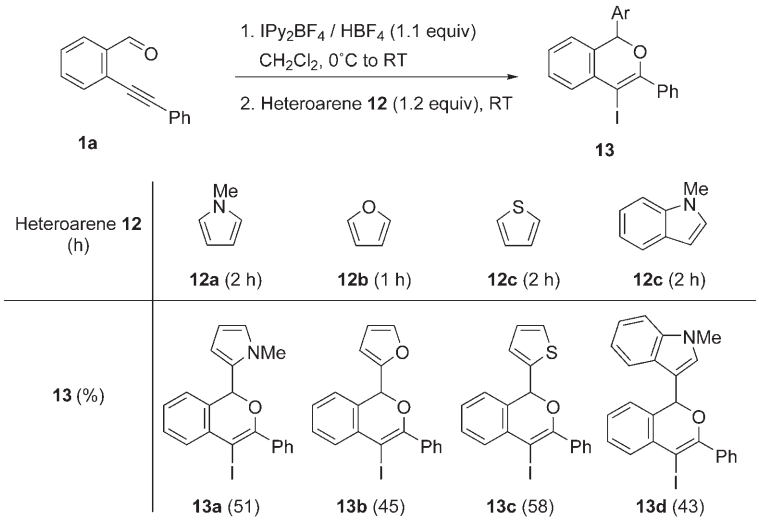
using iodine as the source for the required iodonium ions, because soon after our initial discovery this was shown by Larock and co-workers to be efficient in promoting the cyclization of *o*-alkynylcarbonyl derivatives with primary alcohols as nucleophiles.[16] We tested the reaction of **7a** with **5c** in the presence of I_2 and K_2CO_3, with CH_2Cl_2 as the solvent, at room temperature.[28] However, Mukaiyama aldol products were formed that arose from direct attack of the latent enolate on the carbonyl functionality, without the participation of the alkyne component. Thus, for processes that require a sequential protocol, the nature of the iodonium donor plays a key role in allowing the desired transformation to take place, as is the case for the given examples. In this context, IPy_2BF_4 was proven to behave as the iodonium donor of choice in terms of broad scope.

This iodonium-promoted entry to 1*H*-isochromene rings allows electron-rich arenes to be used as the ultimately incorporated nucleophile (Scheme 7).

Overall, arylation of the carbonyl group with nucleophiles lacking net charges was achieved.[16a] For arenes **10a**,**b**, reaction exclusively at the *para*-position was noted. In keeping with this trend, adduct **11c**, which arose from an O- rather than a C-alkylation process, was isolated as the only product when 4-methylphenol (**10c**) was employed. For the purpose of incorporating **10b** into the target isochromene skeleton, iodine was shown to be an alternative reagent that allowed a more efficient process to occur.[16b] However, no report on the related reaction of phenol was disclosed.



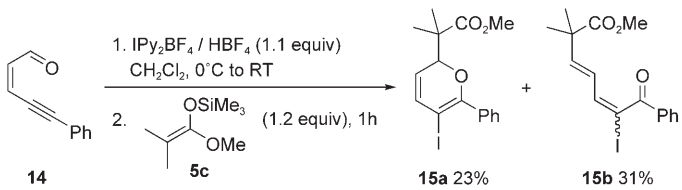
Scheme 7. Electron-rich arenes as nucleophiles in the iodocyclization reaction.



Scheme 8. Reaction of *o*-alkynylbenzaldehyde **1a** with heteroarenes.

As depicted in Scheme 8, the same type of reaction can be accomplished by using five-membered heteroarene rings (*N*-methylpyrrol (**12a**), furan (**12b**), and thiophene (**12c**)), as well as *N*-methylindole (**12d**). These heteroaromatic compounds reacted selectively across the C2-position in the case of the heteroarenes **12a–c**, whereas the C3-position was involved for indole **12d**, to yield the corresponding isochromene derivatives **13a–d**, as expected from their reactions with an electrophile. These examples contribute to enlarge the previously noted scope of this process and its synthetic impact.[16]

The iodonium-induced cyclization of enynal **14** in the presence of the silylketene acetal **5c** was investigated. Under the standard reaction conditions, the formation of the corresponding 2*H*-pyran derivative **15a** along with an open-chain product (**15b**) was realized (Scheme 9). The cyclic product **15a** was formed according to the 6-*endo*-*dig* cyclization mode, as previously observed for the case of the related benzene carboxaldehyde derivatives. The acyclic product **15b** could be the result of the evolution of **15a** in acid media, although a thermal electrocyclic ring-opening reaction of **15a** cannot be ruled out as a viable alternative



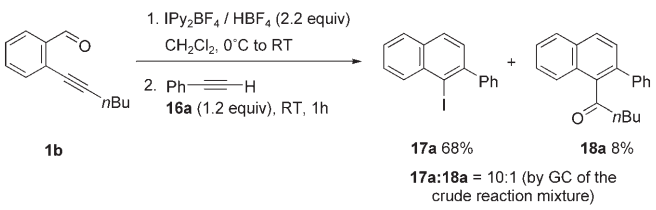
Scheme 9. Cyclization of the 4-alkynyl-2-pentenal **14**.

at present.[29] These results proved the compatibility of this methodology with substrates other than arene or heteroarene carboxaldehyde derivatives.

As a conclusion of this initial section, the iodonium-induced reaction of *o*-alkynylbenzaldehydes with alcohols represents a useful and complementary addition to the metal-catalyzed approach to trigger related cyclizations. The election of the iodonium donor has been shown to influence the reaction outcome and, in some cases, it is crucial for accomplishing the desired transformation. For the case of primary alcohols, for reactions up to the 1 mmol scale, higher yields were accomplished by following the modification with I_2 introduced by Larock than our method with IPy_2BF_4; however, virtually comparable results were obtained when the reaction with IPy_2BF_4 was conducted on a 5 mmol scale. Interestingly, the initially reported IPy_2BF_4-triggered cyclization offers a significant advantage in terms of the scope of the nucleophile. Thus, not only can a larger set of alcohols, arenes, and heteroarenes be used as nucleophiles, but, remarkably, a wide collection of silylated nucleophiles can participate as masked C-nucleophile partners in this process, thereby offering smooth access to a variety of interesting derivatives of the target isochromene skeleton.

Benzannulation reaction through iodonium-initiated [4+2] cycloaddition of *o*-alkynylbenzaldehydes with both alkynes and alkenes: A further step in the study of the reactivity of *o*-alkynylbenzaldehydes **1** with iodonium ions was the use of alkynes and alkenes as nucleophiles. The cyclization reaction with these unsaturated substrates afforded regioselectively substituted naphthalenes,[30] thereby giving rise to novel benzannulation processes. Interestingly, the reaction with alkynes yielded 1-iodonaphthalene derivatives **17**, while related naphthyl ketone derivatives **18** were obtained when alkenes were used (Scheme 10). This unique and tunable manifold has not been previously observed with alternative reagents. These results, put together with those in the previous section, set up the basis for a rapid entry to the assembly of carbo- and heterocyclic scaffolds by mixing an *o*-substituted benzaldehyde derivative that is accessible on a multigram basis with IPy_2BF_4 and a nucleophile. The latter can be chosen from a wide diversity of commercially available, or easy to prepare, compounds.

Reaction with alkynes for the synthesis of 1-iodonaphthalenes: As reported previously,[18a] our initial studies addressed the effect that the amount of added HBF_4, as well as that of the R^1 group attached to the triple bond in **1**, has over the reaction outcome and the product distribution. An optimization stage showed that **1b** (R = *n*Bu) reacts with phenylacetylene (**16a**), IPy_2BF_4, and HBF_4 (2.2 equiv, for activating the iodinating reagent) to yield regioselectively 1-iodo-2-phenylnaphthalene (**17a**) as the major reaction product (Scheme 11). Besides **17a**, the naphthyl ketone **18a** was found to be present in the crude reaction mixture as a minor byproduct of this new transformation.[31]

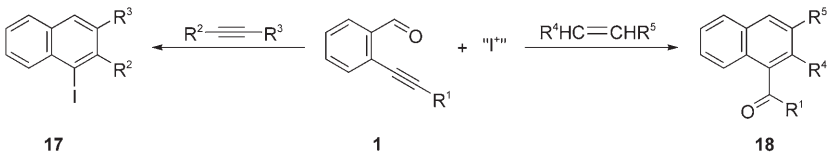


Scheme 11. Synthesis of 1-iodo-2-phenylnaphthalene (**17a**).

By using the reaction conditions described above for **17a**, the generality of the reaction was explored by modifying the alkyne. The results are summarized in Table 3. These transformations proceeded in a regioselective manner and both aryl- and alkyl-substituted terminal alkynes **16** (Table 3, entries 1–6) reacted productively with **1b** to furnish 1-iodonaphthalenes **17** as the major reaction products in moderate yield after isolation.[32] Internal alkynes react in a similar way to afford 1,2,3-substituted naphthalene derivatives in a selective manner. With the internal alkynes **16g**,**h** (Table 3, entries 7 and 8), the transformation is more selective toward the formation of the 1-iodonaphthalene derivatives **17g**,**h** and no significant amounts of the related naphthyl ketones were isolated after chromatographic purification of the crude reaction mixture (see Table 3, footnote [b]).

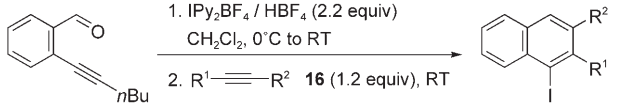
Reaction with alkenes for the synthesis of naphthyl ketones: The scope of this approach to access naphthalene derivatives was significantly broadened by the proof that alkenes are good partners in the cycloaddition reactions. The reactive iodonium ion allows both unsaturated functionalities to become involved in this multicomponent process. The reaction between *o*-alkynylbenzaldehydes **1** and olefins **19**, in the presence of IPy_2BF_4 and HBF_4 (1.1 equiv), resulted in a general method for the regioselective preparation of naphthyl ketone derivatives **18** as the sole reaction products. The reaction with alkenes complements the one previously observed with alkynes, in terms of the reaction product. The results obtained for this new cyclization reaction with olefins are summarized in Tables 4 and 5.

This novel approach to the benzannulation reaction was found to be independent of the aliphatic or aromatic nature of the R^1 group in **1**, as both types of substituents gave satisfactory results (Table 4, entries 1 and 2). Additionally, the reaction took place with a high degree of selectivity, with all of the as-



Scheme 10. Iodonium-triggered reactions of *o*-alkynylbenzene carboxaldehyde with alkynes and alkenes.

Table 3. Iodonium-promoted reaction of *o*-alkynylbenzaldehyde **1b** with alkynes **16**.

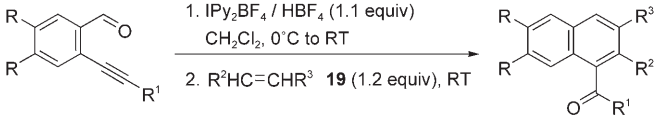


1b **17**

Entry	**16**	R^1	R^2	*t* [h]	**17**	Yield [%][a,b]
1	**16a**	Ph	H	1	**17a**	68
2	**16b**	*n*Pr	H	1	**17b**	60
3	**16c**	*p*-Me-C_6H_4	H	1	**17c**	61
4	**16d**	*p*-NO_2-C_6H_4	H	3	**17d**	35
5	**16e**	*p*-OMe-C_6H_4	H	0.5	**17e**	42
6	**16f**	2-thienyl	H	2	**17f**	26
7	**16g**	Ph	Me	0.5	**17g**	65
8	**16h**	Ph	CO_2Et	3	**17h**	44

[a] Yield of isolated compounds **17**, with respect to **1b** (1 mmol scale). [b] In all cases the crude reaction mixture contained variable amounts of the corresponding ketone **18** (see Scheme 9): Entry (GC ratio **17**:**18**) from crude reaction mixture: 1 (10:1), 2 (8:1), 3 (7.5:1), 4 (5:1), 5 (2.5:1), 6 (2:1), 7 (15:1), and 8 (17:1). These 1-naphthyl ketones are described in the Supporting Information.

Table 4. The iodonium-promoted reaction of *o*-alkynylbenzaldehydes **1** with alkenes **19**.



1 **18**

Entry	**1**	R^1	R	**19**	R^2	R^3	*t* [h]	**18**	Yield [%][a]
1	**1b**	*n*Bu	H	**19a**	Ph	H	2	**18a**	70
2	**1a**	Ph	H	**19a**	Ph	H	1	**18b**	78
3	**1a**	Ph	H	**19b**	*n*-Bu	H	2	**18c**	73
4	**1a**	Ph	H	**19c**	Ph	Me	1	**18d**	65
5	**1a**	Ph	H	**19d**	Ph	CO_2Me	19	**18e**	74
6	**1a**	Ph	H	**19e**	Et	Me	2	**18f**	61[b]
7	**1d**	*n*Bu	OMe	**19a**	Ph	H	0.5	**18g**	52

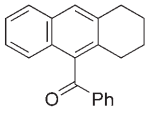
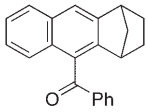
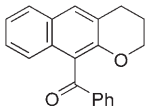
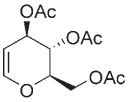
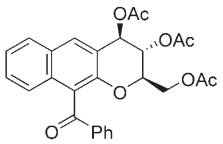
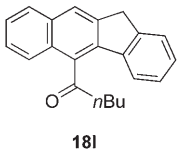
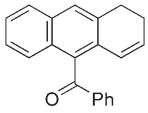
[a] Yield of isolated compounds **18**, with respect to **1** (1 mmol scale). [b] 1.7:1 mixture of regioisomers indicated by GC analysis of the crude reaction mixture. Major regioisomer: R^2 = Et and R^3 = Me.

sayed olefins **19**, that is, both aliphatic- and aromatic-substituted terminal olefins, as well as internal alkenes, being suitable components for the cyclization process (Table 4, entries 3–7).

As depicted in Table 5, cycloalkenes **20** reacted nicely, thereby opening up a reliable alternative for the rapid assembly of 2,3-disubstituted 1-naphthyl ketones. Fused polycycles can be synthesized by using this process. This finding is of interest, as the alternative gold-catalyzed approach to access 1-naphthyl ketones would recognize a cycloalkyne as a precursor and those being required to prepare **18h–m** turn out not to be accessible. Electron-rich cycloalkenes, such as the enol ether **20c** (Table 5, entry 3) and the glucal derivative **20d** (Table 5, entry 4), were also employed and cocyclized, thereby giving access to the tricycle **18j** and the hybrid core present in **18k**, respectively.

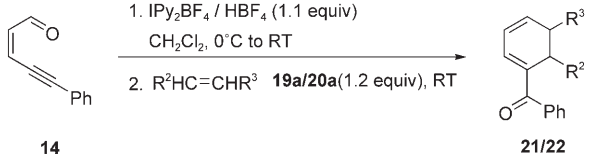
The fact that, under the standard reaction conditions, conjugated dienes, such as 1,3-cyclohexadiene (**20f**), undergo a benzannulation reaction at only one double bond is also worth noting (Table 5, entry 6).

Table 5. Benzannulation reaction of *o*-alkynylbenzaldehydes **1** with cyclic alkenes **20**.[a]

Entry	**1**	R^1	**20**	*t* [h]	**18**	Yield [%][b]
1	**1a**	Ph	 **20a**	2	 **18h**	70
2	**1a**	Ph	 **20b**	1.5	 **18i**	44
3	**1a**	Ph	 **20c**	1	 **18j**	49
4	**1a**	Ph	 **20d**	12	 **18k**	35
5	**1b**	*n*Bu	 **20e**	3	 **18l**	40
6	**1a**	Ph	 **20f**	2	 **18m**	63

[a] The reaction was performed by using *o*-alkynylbenzaldehydes **1** (1 equiv) and alkenes **20** (1.2 equiv) in the presence of IPy_2BF_4 (1 equiv) and HBF_4 (1.1 equiv) in CH_2Cl_2 at room temperature. [b] Yield of isolated compounds **18**, with respect to **1** (1 mmol scale).

When a nonaromatic aldehyde, such as enynal **14**, was employed the benzoannulation reaction also occurred. Thus, the reaction of **14** with either styrene (**19a**) or cyclohexene (**20a**) afforded the corresponding dienes **21** and **22**, respectively (Scheme 12). These examples illustrate that the originally developed benzannulation process could be adapted to prepare polysubstituted carbocycles featuring a 1,3-diene functionality.



19a: R^2 = Ph, R^3 = H (1h) **21:** R^2 = Ph, R^3 = H, 50%

20a: R^2, R^3 = -$CH_2CH_2CH_2CH_2$- (12h) **22:** R^2, R^3 = -$CH_2CH_2CH_2CH_2$-, 25%

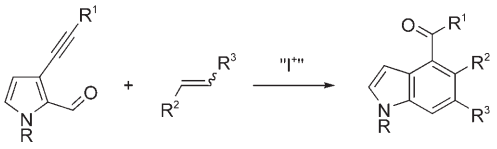
Scheme 12. Formation of cycloalkyldienes upon iodonium-mediated annulation of enynals.

Synthesis of indoles and other benzo-fused heterocycles by related benzannulation processes: Although many efforts have been devoted to the study of the reactivity of *o*-alkynylbenzaldehyde systems, no attempt to apply the new reactivity found for these systems to target the synthesis of relevant benzo-fused heterocycles has been disclosed, to the best of our knowledge.

The indole skeleton is a "privileged" structure present in many natural products and drugs; thus, the search for new methodologies to obtain this scaffold with different substitution patterns has been the subject of much interest in the last few decades.[33,34] However, out of the many processes developed for the synthesis of indoles, only a few alternatives are well suited for obtaining highly substituted benzo-functionalized derivatives that, at the same time, are compatible with access to the 2,3-unsubstituted motif in the target ring.[35,36] Moreover, the synthetic sequence involving the construction of a benzene ring onto a pyrrole to generate the corresponding indole has been rarely considered.[37]

The novel strategy presented above for the synthesis of the naphthalene skeleton, based on the key role of iodonium ions as efficient promoters of the cycloaddition reaction between *o*-alkynylbenzaldehyde and alkenes, could provide a suitable alternative for the synthesis of the indole structure if the appropriate starting material is chosen, in which the aldehyde and alkyne functions would be connected through a pyrrole ring (Scheme 13). We have successfully developed the application of this iodonium-based methodology for the synthesis of 2,3-unsubstituted indoles, by relying on pyrrole-3-carboxaldehyde derivatives as valuable synthetic precursors.[18b]

Initial studies were conducted on the study of the reaction of *N*-tosyl-protected 3-alkynylpyrrol-2-carboxaldehydes **7a** (R = Ph) and **7b** (R = *n*Bu) with several alkenes. These studies quickly proved the feasibility of the proposed iodonium-



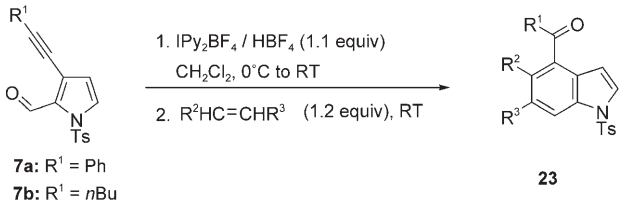
Scheme 13. Iodonium-mediated benzannulation approach for preparing indoles.

mediated entry to both 4,5-disubstituted and 4,5,6-trisubstituted indoles **23**, depending on the degree of substitution of the starting alkene. Thus, indoles **23** were regioselectively obtained from **7a**,**b** upon treatment with the system IPy_2BF_4/HBF_4 and further treatment with the corresponding alkene. The results are summarized in Table 6.

Both simple alkyl- and aryl-substituted acyclic olefins are compatible substrates for this process and give the desired indoles in moderate to satisfactory yields after isolation. Cycloalkenes also undergo this transformation and lead to tri- and tetracyclic compounds. Among the alkenes used in the reaction, 2,3-dihydropyran (**20c**), indene (**20e**), and 1,2-dihydronaphthalene (**20h**) furnished structurally complex indole derivatives in a regioselective and relatively simple process (Table 6, entries 3, 7, and 8). For simple cycloalkenes, it was found that cyclopentene (**20g**; Table 6, entry 6) could participate in the reaction under slightly modified conditions (0.5 equiv HBF_4, 60 °C, dichloroethane). Under these modified reaction conditions other cyclic olefins, such as cyclohexene, failed to react, with the starting material being recovered unaltered after the reaction workup. These modified reaction conditions were tested with a set of representative alkenes and proved to be superior to those previously employed (1.1 equiv of HBF_4, room temperature, dichloromethane) in that they gave an improvement in the reaction yields. Thus, **23e** was obtained in 61 % yield under the new reaction conditions; this represents an increased yield over that obtained by using the standard reaction conditions (Table 6, entry 5).

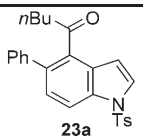
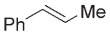
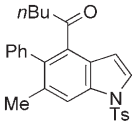
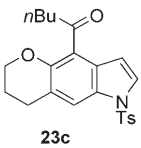
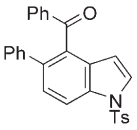
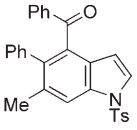
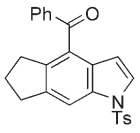
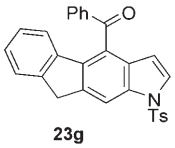
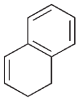
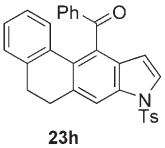
During the study of the scope of this new methodology for the synthesis of the indole core, we tried to find alternatives to overcome the lack of reactivity evidenced by simple cycloalkenes, such as cyclohexene, and by terminal aliphatic alkenes, such as 1-hexene, for producing the expected indole derivatives. Interestingly, we found that enamines can be used as good reaction partners for assembling indoles, thereby offering an alternative to override these limitations. Enamines derived from both aldehydes and ketones were recognized as active components for this reaction, although they gave different compounds, as a function of their own structural features. The reaction of the enamine **24a**, derived from pyrrolidine and cyclohexanone, offers a viable alternative for the assembly of indole **23i** and nicely covers the failure of cyclohexene to access this indole through the iodonium-driven stepwise cycloaddition approach. Thus, in dichloromethane, at room temperature, the sequential reaction of the 3-alkynylpyrrol-2-carboxaldehyde **7a** with IPy_2BF_4 followed by the addition of the enamine **24a** af-

Table 6. Indoles **23** from reaction of pyrroles **7**, alkenes and IPy_2BF_4.



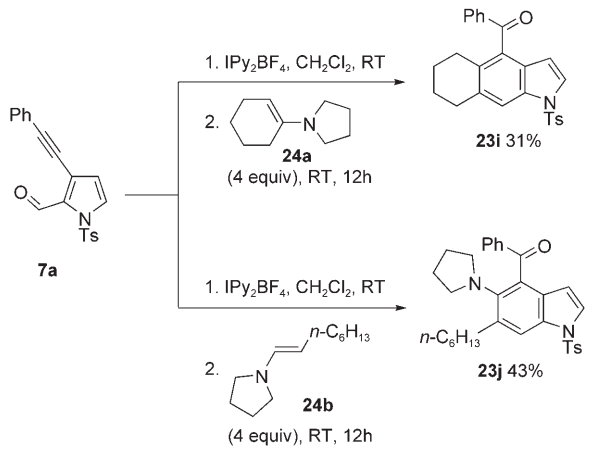
7a: R^1 = Ph
7b: R^1 = *n*Bu

23

Entry	Alkene	*t* [h]	**23**	Yield [%][a]
1	 **19a**	2	 **23a**	62
2	 **19c**	3	 **23b**	45
3	 **20c**	2	 **23c**	41
4	**19a**	1	 **23d**	72
5	**19c**	3	 **23e**	48 (61[b])
6	 **20g**	2	 **23f**	37[b]
7	 **20e**	1	 **23g**	36
8	 **20h**	4	 **23h**	42

[a] Yield of isolated compounds **23**, with respect to **7** (1 mmol scale). [b] The reaction was performed with HBF_4 (0.5 equiv) in $ClCH_2CH_2Cl$ at 60 °C in a sealed tube.

forded the indole **23i** (Scheme 14).[38] However, reaction of **7a** with the enamine **24b**, derived from hexanal, under the same experimental conditions furnished the indole **23j**, which retains the amine functionality from the enamine attached to the indole skeleton (Scheme 14). This differentiated behavior could be anticipated as a function of the structure of the enamine according to our proposal to rationalize the mechanism of these benzannulation reactions and will be discussed in the next section.



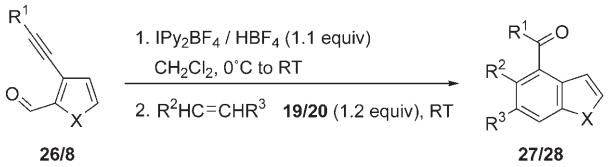
Scheme 14. Enamines as efficient partners in the iodonium-promoted entry to indoles **23**.

In this context, we attempted to promote the same indolization process by using **7a**, molecular iodine (1.2 equiv) as the source of the required iodonium ion, and **24a** as the enamine. The reaction was conducted in CH_2Cl_2 in the presence of a base (K_2CO_3, 1 equiv). Unfortunately, no cyloaddition was observed. This is in sharp contrast with the outcome of the reaction of **7a** with styrene (**19a**), which was satisfactorily verified by using I_2/K_2CO_3 and gave **23d** in a comparable 62 % yield.[39]

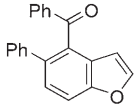
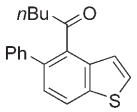
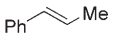
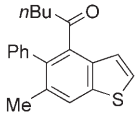
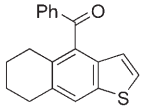
The deprotection of the *N*-tosyl-masked compound to afford the corresponding 1*H*-indole derivative was also tested.[40] Thus, the free-NH indole **25** was easily obtained from **23e** upon reaction with NaOH in boiling ethanol.[41] We have also expanded the scope of this approach to tackle the synthesis of related heterocycles other than indole. These results are depicted in Table 7, which illustrates the feasibility of using this transformation to prepare both benzofuran **27** and benzothiophenes **28a–c**, simply by starting from either the corresponding furan **26** or thiophene derivatives **8a**,**b**. Although the products were isolated only in moderate yields, this method represents a valuable alternative for the synthesis of these systems, the preparation methods of which are scarce and more limited when compared to those for the synthesis of indoles.[42]

Reaction mechanism: In this article, three different three-component processes are reported from the reaction of *o*-alkynylbenzaldehyde derivatives with the reagent IPy_2BF_4, with the observed pathway depending on the nature of the added nucleophile. A plausible mechanism that accounts for these transformations would assume the formation of a benzo[*c*]pyrylium cation **A** as a common intermediate (Scheme 15). Thus, as the initial step, we propose the attack of the iodonium ion, liberated from the IPy_2BF_4 by treatment with HBF_4, onto the alkyne, assisted by the neighbor-

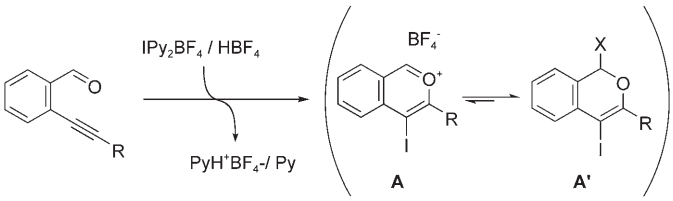
Table 7. Synthesis of benzofuran **27** and benzothiophene **28** following a common approach.



26/8 **27/28**

Entry	Alkynyl aldehyde **26/8**	Alkene **19/20**	*t* [h]	Benzoheterocycle **27/28**	Yield [%][a]
1	**26**: X = O, R^1 = Ph	 **19a**	6	 **27**	36
2	**8a**: X = S, R^1 = *n*Bu	 **19a**	3	 **28a**	44
3	**8a**: X = S, R^1 = *n*Bu	 **19c**	8	 **28b**	39
4	**8b**: X = S, R^1 = Ph	 **20a**	24	 **28c**	31

[a] Yield of isolated compounds **27/28**, with respect to **26/8** (1 mmol scale).



Scheme 15. Proposed common intermediate for the iodonium-induced functionalization reactions of *o*-alkynylbenzene carbaldehydes.

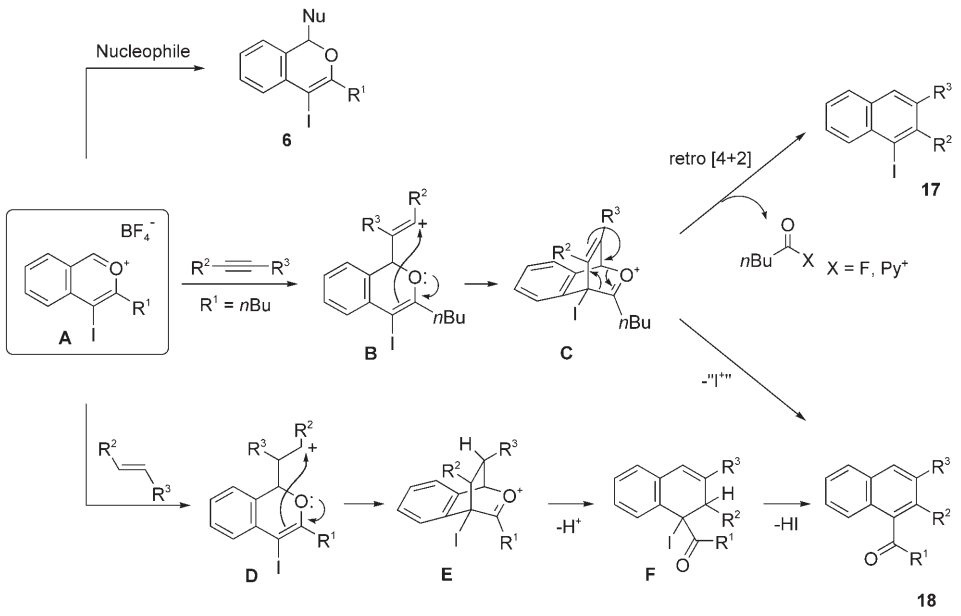
ing carbonyl group, to furnish the reactive species **A**. This intermediate **A** could be in equilibrium with species **A′** which might reversibly incorporate some of the nucleophiles already present in the reaction media (pyridine, fluoride; Scheme 15). Subsequent incorporation of the externally added nucleophile would give rise to the corresponding products, as will be discussed in the following paragraphs.

A possible evolution of the species **A**/**A′** that accounts for the observed products is outlined in Scheme 16. For simple nucleophiles such as alcohols, silyl-masked nucleophiles, electron-rich arenes, and heteroarenes, the addition of the nucleophile to species **A** would directly furnish the formation of the observed compounds **6**.

When an alkyne is added to the reaction media, stepwise reaction through an intermediate **B**, resulting from the nucleophilic attack of the alkyne onto **A**, followed by intramolecular trapping of the cationic species by the β-iodoenol ether fragment would lead to the polycyclic intermediate **C**. In this framework, the ability of the alkyne substituents to stabilize the developing positive charge along the reaction path would explain the high regioselectivity observed for the overall process. From **C**, a formal retro-[4+2] cycloaddition reaction would explain the formation of the major reaction products, the 1-iodonaphthalenes **17**. This seems to be a high-energy process because of the generation of a labile acylium ion; it could be facilitated by previous nucleophilic attack of fluoride (liberated from BF_4^-) on the charged carbonyl moiety, followed by the retro-[4+2] cycloaddition. Alternatively, the loss of an iodonium ion from **C** would afford the naphthyl ketones **18**, which are observed as minor reaction products. To provide evidence for this mechanistic proposal, the reaction mixture obtained after the reaction of **1b** with the corresponding alkyne was quenched with 1-octanol and, besides the desired naphthalene compound, octylpentanoate was found to be present in the crude reaction mixture. The formation of this ester provides additional evidence for the participation of an intermediate of type **C** during the process of formation of the iodonaphthalenes **17**.

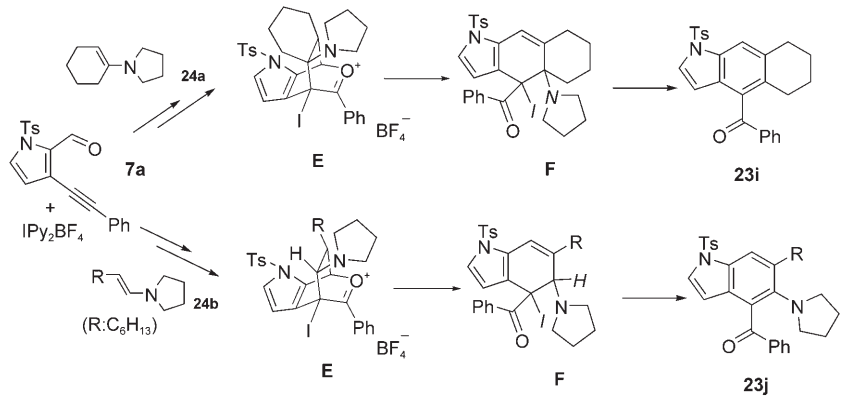
The formation of only naphthyl ketones when alkenes were used as nucleophiles could be explained by a mechanistic pathway based on the previous experience of the parent-alkyne transformation. Thus, the participation of a new reaction intermediate **E** formed by the nucleophilic attack of the alkene onto **A** is proposed. Evolution of the intermediate **E** by loss of a proton would produce the polycyclic compound **F**. The loss of an HI molecule and concomitant aromatization would yield the obtained naphthyl ketones **18**, the only reaction products observed for this transformation.

This mechanism could also be invoked to account, in a straightforward manner, for the synthesis of indoles and other benzoheterocycles by the reaction of corresponding aldehyde–heterocycle derivative with alkenes. Interestingly, when enamine **24a** was used as a more reactive surrogate for cyclohexene, the indole **23i** was formed with concomitant loss of the amine fragment present in **24a**. The formation of the product **23i** can also be rationalized by the mechanism proposed. In this case, the intermediate of type **F** lacked the hydrogen atom in the β-position with respect to iodine that was required for the β-elimination reaction, eventually resulting in the aromatization process; instead,



Scheme 16. Proposed pathways for transforming the benzo[*c*]pyrylium cation **A**. Py^+ = pyridinium.

an alternative cleavage of the β-amino functionality present in **F** drove the process and the indole **23i** was the observed reaction product (Scheme 17).



Scheme 17. Product diversity as a function of the enamine.

By contrast, for the reaction of the enamine **24b**, the resulting intermediate **F** showed a hydrogen atom attached to the same carbon atom as the pyrrolidine fragment (R^2 = pyrrolidine), thereby allowing the aromatization step to occur through loss of HI and resulting in the formation of **23j**, which still retained the amine incorporated in the indole framework.

The reaction of the *o*-alkynylbenzaldehyde **1b** with styrene was monitored by NMR spectroscopy with the aim of finding new evidence to support the mechanism proposed. For this NMR study, the reaction was carried out in the absence of tetrafluoroboric acid; thus, **1b** (1 equiv) was added to a solution of IPy_2BF_4 (1 equiv) in CD_2Cl_2 and ^1H and ^{13}C NMR spectra were recorded at 25 °C after different reaction times (Figure 2).[43] After 6 h, a complete transformation of **1b** (Figure 2, spectrum A) into the corresponding adduct resulting from the incorporation of pyridine into the benzo[*c*]pyrilium cation **I** (Figure 2, spectrum B) was observed. The ^1H NMR chemical shift of the hydrogen atom sited in the α-position to the oxygen atom ($\delta = 7.90$ ppm) indicates the formation of the proposed pyrilium salt derivative **I**. At this point, styrene (1.2 equiv) was added to the NMR tube and a progressive transformation of the benzo[*c*]-pyrilium cation **I** into a new compound **III** was observed, while the styrene signals decreased in intesnity (Figure 2, spectrum C). The transformation of **I** into **III** was complete in three days (Figure 2, spectrum D).[44] The disappearance of compound **I** could be monitored through the slow disappearance of the characteristic singlet at $\delta = 7.90$ ppm; the transformation gave rise a new set of ^1H NMR signals, the further analysis of which led to the structural characterization of compound **III**.[45]

This NMR experiment was repeated in dichloromethane for a 1 mmol scale reaction and a compound was isolated as an orange solid after simple evaporation of the solvent. Surprisingly, when this orange solid, with the structure assigned to compound **III** (Figure 3 shows its ^1H NMR spectrum), was dissolved in $CDCl_3$, ^1H NMR monitoring revealed that the corresponding naphthyl ketone **18a** was gradually formed in a process that was finished in 14 h. Most probably, the traces of acid present in the deuterated solvent catalyzed the transformation of **III** into **18a**. It did not occur during the NMR studies of the reaction, probably due to the presence of pyridine molecules in the reaction media, arising from the IPy_2BF_4 reagent; these molecules would preclude this possibility by neutralizing the traces of acid present in the deuterated solvent.

The proposed sequence for the formation and evolution of the different intermediates observed during the NMR studies is depicted in Scheme 18. The structure of **III** was determined by one- and two-dimensional NMR spectrosco-

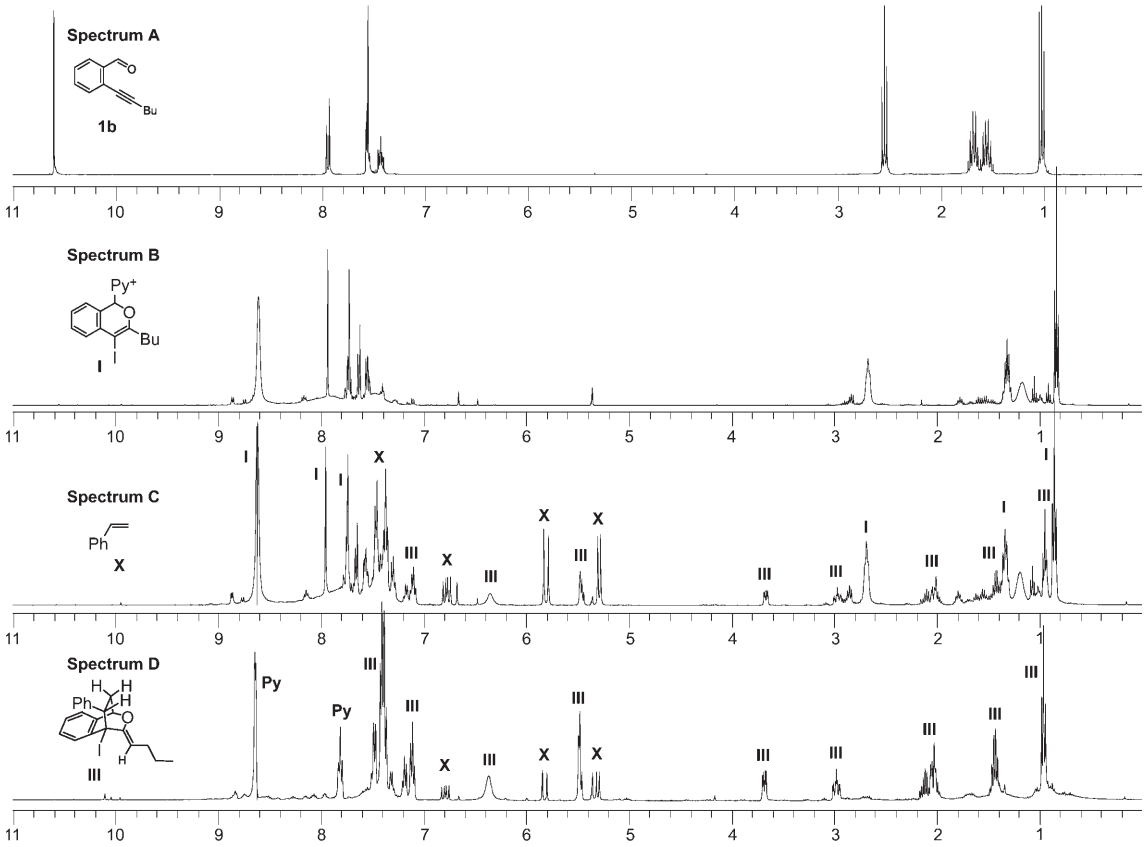


Figure 2. NMR study of the iodocyclization of the *o*-alkynylbenzaldehyde **1b** with styrene.

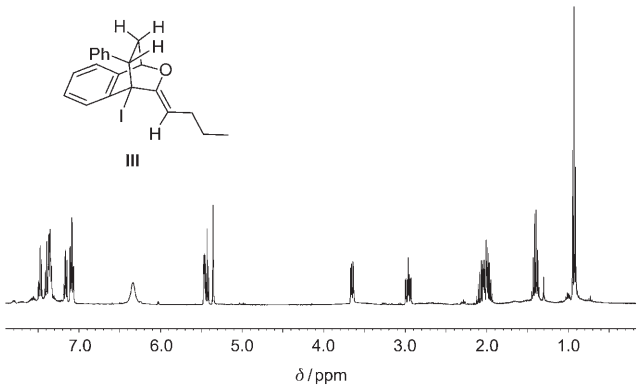
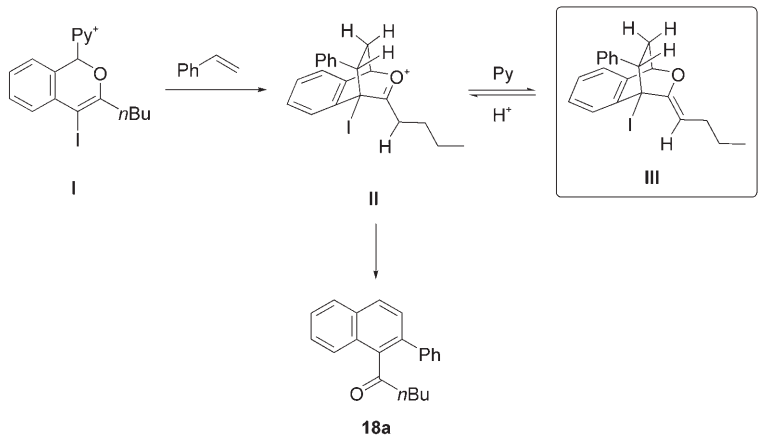


Figure 3. ^{1}H NMR spectrum of compound **III**.

py, as well as mass spectrometry experiments. As is shown, the formation of **III** could be driven by the basic reaction conditions, since pyridine could cause isomerization of the double bond of intermediate **II** to an exocyclic position. Finally, when intermediate **III** is exposed to acid media, the transformation to the observed naphthyl ketone **18a** would occur through rapid equilibration with its isomer **II**.

Conclusion

In summary, new metal-free protocols for the synthesis of different types of substituted isochromenes, naphthalenes, and benzoheterocycles have been developed. The combination of *o*-alkynylbenzaldehyde derivatives, iodonium ions, and either alcohols, silylated nucleophiles, alkynes, or alkenes occurs in a predictable manner to produce the corresponding family of compounds. The synthesis of benzo-fused heterocycles with interesting di- and trisubstitution patterns and featuring the 2,3-unsubstituted ring motif has been established. Significant mechanistic insights have been gained and are reported that should contribute to further expand the opportunities raised by this synthetic strategy. In this synthetic scenario, an iodonium ion acts as an electrophilic promoter and allows the incorporation of a synthetically useful iodine atom in some of the final products, thereby offering a valuable complement to related transition-metal-based cyclizations and opening many synthetic possibilities for the use of the assembled iodinated rings as building blocks in diversity-oriented synthesis, just by relying on well-established metal-catalyzed cross-coupling reactions.



Scheme 18. Different reaction pathways in the presence and absence of added acid.

Experimental Section

General: All reactions were conducted by using oven-dried glassware under an atmosphere of nitrogen. Dichloromethane and 1,2-dichloroethane were distilled from CaH_2 before use. Ethanol and the solvents used in column chromatography, hexane and ethyl acetate, were obtained from commercial suppliers and used without further distillation. TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator (Merck). Flash chromatography was carried out over silica gel. NMR spectra were measured at room temperature on Bruker AC-200 MHz, Bruker DPX-300 MHz, Bruker AV-300 MHz, and Bruker AV-400 MHz spectrometers. 2D-NMR experiments were recorded on a Bruker AV-400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance used as the internal standard (deuterochloroform: $\delta = 7.26$ ppm in ^{1}H NMR spectra, $\delta = 77.00$ ppm in ^{13}C NMR spectra). Carbon multiplicities were assigned by DEPT techniques. High-resolution mass spectra were recorded on a Finnigan-Matt 95 mass spectrometer by using EI at 70 eV. Infrared spectra were obtained on a Unicam Mattson 3000 FTIR spectrometer; only the most significant IR absorptions are given. Elemental analyses were carried out on Perkin–Elmer 2400 and Carlo Erba 1108 microanalyzers. Melting points were measured on a Büchi Totoli apparatus.

The crystallographic structure determination for **6g** was performed on a Bruker SMART 1000 diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), at 120 K. Spectroscopic data for all of the compounds described may be found in the Supporting Information.

General procedure for the synthesis of 4-iodo-1*H*-isochromenes 2, 6, 11, and 13 by using IPy_2BF_4 and HBF_4: IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled at 0 °C and tetrafluoroboric acid (54% solution in diethyl ether; 0.15 mL, 1.1 mmol, 1.1 equiv) was added. After 10 min, 2-alkynylbenzaldehyde **1** (1 mmol, 1 equiv) was added and the solution was stirred for 30 min at room temperature. After this time, the appropriate nucleophile (alcohols, silylated compounds **5**, arenes **10**, or heteroarenes **12**; 1.2 mmol, 1.2 equiv) was added and the solution was stirred further until the benzaldehyde starting material disappeared (the reaction times are given in the text). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford pure compounds **2**, **6**, **11**, and **13**.

For the reaction of the pyrrole and thiophene derivatives **7a** and **8b**, the same procedure was used to obtain the corresponding biheterocyclic compounds **9a**,**b**.

Reaction of *o*-alkynylbenzaldehyde 1b with IPy_2BF_4 and *tert*-butyl alcohol: *o*-(1-Hexynyl)benzaldehyde (**1b**; 0.19 g, 1 mmol, 1 equiv) was added to a solution of IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) in dry dichloromethane (10 mL) and the resultant solution was stirred at room temperature for 1 h. After this time, *tert*-butyl alcohol (115 μL, 1.2 mmol, 1.2 equiv) was added and the solution was stirred until the benzaldehyde starting material had disappeared (6 h). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford pure compound **2d** (275 mg, 68%).

General procedure for the synthesis of 4-iodo-1-methoxy-1*H*-isochromenes 2a,d,f by using IPy_2BF_4 and trimethylborate: Trimethylborate (0.22 mL, 2 mmol, 2 equiv) was added to a solution of IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at 0 °C. After 10 min, the appropriate 2-alkynylbenzaldehyde **1a–c** (1 mmol, 1 equiv) was added and the solution was stirred at room temperature until the aldehyde starting material had disappeared. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford pure compounds **2a**,**d**,**f**.

Reaction of *o*-(alkynyl)ketones 3a,b with IPy_2BF_4 and alcohols

*a) Reaction of **3a**,**b** by using the system IPy_2BF_4/HBF_4*: Tetrafluoroboric acid (54% solution in diethyl ether; 0.15 mL, 1.1 mmol, 1.1 equiv) was added to a stirred solution of IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at −60 °C. After 10 min, the appropriate *o*-(alkynyl)ketone **3a**,**b** (1 mmol, 1 equiv) was added. After the mixture was stirred for 30 min, methanol (48 μL, 1.2 mmol, 1.2 equiv) was added and the resulting solution was stirred at −60 °C for 24 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford pure compounds **4a**,**b**.

*b) Reaction of **3a** by using the system $IPy_2BF_4/B(OMe)_3$*: Trimethylborate (0.22 mL, 2 mmol, 2 equiv) was added to a solution of IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at −60 °C. After 10 min, 2-(phenylethynyl)acetophenone (**3a**, 0.22 g, 1 mmol, 1 equiv) was added and the resultant solution was allowed to reach 0 °C for 24 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. Flash column chromatography (neutral aluminum oxide, hexane/EtOAc) of the crude residue gave the pure compound **4a** (182 mg, 48%).

Reaction of enynal 14 with IPy_2BF_4 and silylketene acetal 5c: IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled at 0 °C and tetrafluoroboric acid (54% solution in diethyl ether; 0.15 mL, 1.1 mmol, 1.1 equiv) was added. After 10 min, the enynal **14** (0.16 g, 1 mmol, 1 equiv) was added and the solution was stirred for 30 min at room temperature. After this time, the silylketene acetal **5c** (243 μL, 1.2 mmol, 1.2 equiv) was added and the solution was stirred further until the aldehyde starting material had disappeared (1 h). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatog-

raphy (neutral aluminum oxide, hexane/EtOAc) to afford pure compounds **15a** (23%, 90 mg) and **15b** (31%, 120 mg).

General procedure for the reaction of *o*-(1-hexynyl)benzaldehyde (1b) and alkynes 16 by using IPy_2BF_4 and HBF_4: IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled to 0°C and tetrafluoroboric acid (54% solution in diethyl ether; 0.30 mL, 2.2 mmol, 2.2 equiv) was added. After 10 min, **1b** (0.19 g, 1 mmol, 1 equiv) was added and the solution was stirred for 30 min at room temperature. After this time, the corresponding alkyne **16** (1.2 mmol, 1.2 equiv) was added and the solution was further stirred at room temperature (reaction times are given in Table 3). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to afford pure 1-iodonaphthalenes **17** with variable amounts of the corresponding naphthyl ketones **18** as minor products.

General procedure for the reaction of *o*-alkynylbenzaldehyde 1 and alkenes 19 and 20 by using IPy_2BF_4 and HBF_4: Tetrafluoroboric acid (54% solution in diethyl ether, 0.15 mL, 1.1 mmol, 1.1 equiv) was added to a stirred solution of IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at 0°C. After 10 min, the appropriate *o*-(alkynyl)benzaldehyde **1** (1 mmol, 1 equiv) was added. After the mixture was stirred for 30 min at room temperature, the corresponding alkene **19** or **20** (1.2 mmol, 1.2 equiv) was added and the resulting solution was stirred at room temperature until the benzaldehyde starting material had disappeared (reactions times are given in Tables 4 and 5). The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to afford pure compounds **18**.

Reaction of enynal 14 with alkenes by using IPy_2BF_4 and HBF_4: IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (10 mL). The solution was cooled to 0°C and tetrafluoroboric acid (54% solution in diethyl ether; 0.15 mL, 1.1 mmol, 1.1 equiv) was added. After 10 min, the enynal **14** (0.16 g, 1 mmol, 1 equiv) was added and the solution was stirred for 30 min at room temperature. After this time, the corresponding alkene **19a** or **20a** (1.2 mmol, 1.2 equiv) was added and the solution was stirred further until the aldehyde starting material had disappeared. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (50 mL) and water (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to afford the corresponding diene **21** or **22**.

General procedure for the synthesis of benzoheterocycles 23, 27, and 28 by using IPy_2BF_4 and HBF_4: IPy_2BF_4 (112 mg, 0.3 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (5 mL). The solution was cooled to 0°C and tetrafluoroboric acid (54% solution in diethyl ether; 45 μL, 0.33 mmol, 1.1 equiv) was added. After 10 min, the appropriate *N*-tosyl-protected 3-alkynylpyrrole-2-carboxaldehyde **7a**,**b**, 3-phenylethynyl-furan-2-carboxaldehyde (**26**), or 3-alkynylthiophene-2-carboxaldehyde **8a**,**b** (0.3 mmol, 1 equiv) was added and the solution was stirred for 30 min at room temperature. After this time, the alkene **19**/**20** was added and the solution was further stirred until the starting material had disappeared as determined by TLC analysis (reaction times are given in Tables 6 and 7). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (20 mL) and water (20 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to afford the pure compounds.

Procedure for the synthesis of the indole 23f by using IPy_2BF_4 and HBF_4: IPy_2BF_4 (115 mg, 0.31 mmol, 1 equiv) was dissolved in dry 1,2-dichloroethane (5 mL) in a sealed tube. The solution was cooled to 0°C and tetrafluoroboric acid (54% solution in diethyl ether; 21 μL, 0.15 mmol, 0.5 equiv) was added. After 10 min, 3-phenylethynyl-*N*-tosylpyrrole-2-carboxaldehyde (**7a**; 108 mg, 0.31 mmol, 1 equiv) was added and the solution was stirred for 30 min at room temperature. After this time, cyclopentene (**20g**; 110 μL, 1.24 mmol, 4 equiv) was added and the solution was further stirred at 60°C for 2 h. The reaction mixture was allowed to reach room temperature and was then quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (25 mL) and water (25 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to afford pure compound **23f** (47 mg, 37%).

General procedure for the synthesis of the indoles 23i and 23j by using IPy_2BF_4: IPy_2BF_4 (115 mg, 0.31 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (5 mL) and 3-phenylethynyl-*N*-tosylpyrrole-2-carboxaldehyde (**7a**; 108 mg, 0.31 mmol, 1 equiv) was added at room temperature. After the solution has been stirred for 30 min, the corresponding enamine [1-pyrrolidino-1-cyclohexene (**24a**; 199 μL, 1.24 mmol, 4 equiv) or 1-pyrrolidino-1-hexene (**24b**; 224 mg, 1.24 mmol, 4 equiv)] was added and the solution was further stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and vigorously stirred. The organic layer was washed with a 5% aqueous solution of $Na_2S_2O_3$ (25 mL) and water (25 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to afford pure compound **23i** (41 mg, 31%) or pure compound **23j** (70 mg, 43%).

Procedure for the synthesis of compound III: IPy_2BF_4 (0.37 g, 1 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (4 mL) and *o*-(1-hexynyl)benzaldehyde (**1b**; 0.19 g, 1 mmol, 1 equiv) was added at room temperature. After the solution had been stirred for 6 h, styrene (**19a**; 114 μL, 1 mmol, 1 equiv) was added and the solution was stirred further at room temperature for 3 days. The solvent was removed under pressure to afford the pure compound **III** as an orange solid in quantitative yield.

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[45] A full assignment of the ^1H and ^{13}C NMR spectra of compounds **I** and **III** is reported in the Supporting Information.

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