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Iron-Catalyzed Direct Synthesis of Densely Substituted Benzofurans and Naphthopyrans from Phenolic Compounds and Propargylic Alcohols

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Abstract: A one-pot cascade reaction for the synthesis of polysubstituted benzofurans and naphthopyrans from simple phenols and propargylic alcohols catalyzed by iron(III) is presented. The results demonstrate that the structural specificity for the formation of furan and pyran products is controlled by the structural nature of the propargylic alcohols. Namely, benzofurans could be synthesized efficiently from phenols and *secondary* propargylic alcohols in the presence of 5 mol% of iron(III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) catalyst. On the other hand, pyran derivatives were obtained exclusively when *tertiary* propargylic alcohols were employed. Mechanistic studies revealed that presumably due to the discriminated steric effect of *secondary* and *tertiary* propargylic alcohols, the Fe-catalyzed Friedel–Crafts (F–C) reaction of phenols with the two types of alcohols proceeds *via* different models. Most importantly, we have demonstrated for the first time that fully 2,3,4-substituted naphthopyrans could be synthesized efficiently *via* the iron-catalyzed one-pot cascade reaction. Consequently, the results presented herein provide straightforward pathways for versatile syntheses of valuable benzofuran and pyran derivatives from simple phenolic compounds and propargylic alcohols.

Keywords: benzofurans; iron catalyst; naphthopyrans; phenols; propargylic alcohols

Introduction

Benzofuran and pyran derivatives are valuable structural motifs in both naturally occurring and artificial compounds with interesting biological activities and photochromic properties.[1] Particularly, the 3-arylbenzofuran moiety is ubiquitous in bioactive structures.[2] The most popular methods for accessing such types of scaffolds relied mainly on the transition metal-catalyzed intramolecular annulation of the pre-prepared *ortho*-alkynylated phenol derivatives[3] or aryl alkynyl ethers.[4] While benzofurans were formed in many of these cases, Li[3f] showed that the pyran derivatives could be generated in high selectivity in the presence of $FeCl_3$ catalyst. In addition, the copper-promoted synthesis of benzofurans using *ortho*-hydroxybenzophenones or *ortho*-hydroxy-α-arylstyrenes has also been reported.[5] However, these protocols were multistep syntheses and required frequently the use of noble metals such as Pd, Pt, Au, In, and Ru as catalysts. Moreover, the formation of furan and pyran mixtures was also a concern in some cases. While improved procedures *via* the transition metal-catalyzed cascade reactions from *ortho*-halophenols[6] or *ortho*-dihaloaryl substrates[7] have been disclosed, their extensive utilizations were handicapped due to the requirement for using *ortho*-disubstituted aryl compounds as substrates. However, the commercial availability of such specially substituted substrates is very limited. In addition, undesired halogen-containing wastes are generated.

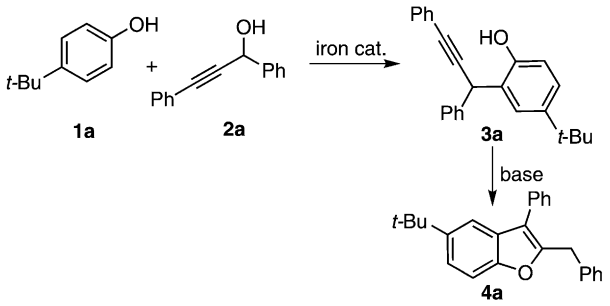
In comparison, the direct construction of benzofuran and pyran derivatives from simple phenols offers apparent advantages because of their wider availability as well as halogen-free natures. So far, the Brønsted acids such as PPTS salt,[8] TSOH,[9] and boronic acid[10] as well as Lewis acids such as zeolites,[11] indium,[12] zinc,[13] acidic alumina,[14] and ruthenium

have been used to catalyze[15] the direct synthesis of benzofurans or pyrans. However, only very limited substrate scopes were examined. Recently, Li and coworkers[16] disclosed a novel protocol for accessing benzofuran 3-carboxylates *via* the iron-catalyzed oxidative coupling of phenols and β-keto esters. This protocol represents one of the few examples for a more general and direct synthesis of benzofurans from simple phenols, although an excess of phenol substrates (3.0 equiv.) paired with the presence of stoichiometric amounts of organic peroxide (2.0 equiv. of *t*-BuOO-*t*-Bu) have to be employed, and only moderate yields were obtained.

We have constant interests in the development of new methods for the synthesis of functionalized heterocycles[17] as well as their downstream application towards the fabrication of functional materials[18] or the synthesis of complex bioactive compounds and natural products.[19] On the basis of our extensive experience on N-heterocyclic chemistry,[17–19] we recently shifted our particular attention to the development of a more efficient, general, and practical method for the construction of benzofuran as well as pyran derivatives owing to their great importance in the field of pharmaceutical and functional materials science (*vide supra*). Herein, we demonstrate that $FeCl_3 \cdot 6H_2O$ was a highly active and universally applicable catalyst for the direct synthesis of both densely substituted benzofuran and naphthopyran derivatives from phenols and propargylic alcohols *via* a one-pot operation. In addition to the broad generality and high efficacy, the methods are also atom-economic and environmentally benign since only a slight excess (1.2 equiv.) of phenol substrates was required, coupled with the generation of only a stoichiometric amount of water as wastes. More to the point, for the first time, we have established an efficient protocol for the synthesis of fully 2,3,4-functionalized naphthopyrans through a one-pot cascade reaction. Finally, the use of cheap and nontoxic iron as catalyst also represents an added advantage since in pharmaceutical industries, the content of hazardous metals in an active pharmaceutical ingredient (API) has to be strictly controlled.[20] As a result, tedious and expensive purification processes[21] as well as analysis methods[22] are often required when toxic metal catalysts are employed.

Results and Discussion

Our initial study on the feasibility of the iron-catalyzed reaction of phenol and propargylic alcohol towards the synthesis of a 3-arylated benzofuran was carried out by employing phenol **1a** and alcohol **2a** as a model reaction (Scheme 1). After numerous trials, we found that $FeCl_3 \cdot 6H_2O$ was an efficient catalyst that could affect the formation of F–C product **3a** as

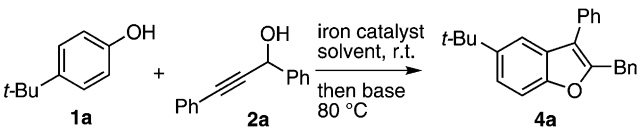


Scheme 1. Initial study on the feasibility of the reaction by a stepwise procedure.

a single product in high yield at room temperature. However, the desired benzofuran **4a** was not detected. Further investigation revealed that by *in situ* feeding of a base such as Et_3N (Table 1, entry 1) to the reaction vessel when the formation of **3a** was completed, **4a** could be obtained in 32% yield. Although the yield was not very satisfactory, the result implies that a one-pot synthesis of **4a** would be available if the reaction parameters could be properly tuned.

Thus, we carried out a detailed optimization of the reaction conditions. The key of our efforts was fo-

Table 1. Optimization of the reaction conditions for the one-pot synthesis of benzofuran from phenols and propargylic alcohols.[a]



Entry	Catalyst (mol%)	Base	Solvent	Yield[b]
1	$FeCl_3 \cdot 6H_2O$ (5)	Et_3N	MeCN	32%
2	$FeCl_3 \cdot 6H_2O$ (5)	DBACO	MeCN	76%
3	$FeCl_3 \cdot 6H_2O$ (5)	$KHCO_3$	MeCN	75%
4	**$FeCl_3 \cdot 6H_2O$ (5)**	**K_2CO_3**	**MeCN**	**77%**
5	$FeCl_3 \cdot 6H_2O$ (5)	K_2CO_3	CH_2Cl_2	n.r.[c]
6	$FeCl_3 \cdot 6H_2O$ (5)	–	DMF	n.r.[d]
7	$FeCl_3 \cdot 6H_2O$ (2)	–	MeCN	–[e]
8	$FeCl_3$ (5)	K_2CO_3	MeCN	79%
9	$FeCl_2 \cdot 4H_2O$ (5)	–	MeCN	n.r.[d]
10	$FeSO_4 \cdot 7H_2O$ (5)	–	MeCN	n.r.[d]

[a] *Reaction conditions:* **1a** (0.24 mmol, 1.2 equiv.), **2a** (0.2 mmol, 1.0 equiv.), $FeCl_3 \cdot 6H_2O$ (5 mol%) in MeCN (3 mL) at room temperature until **2a** had disappeared as monitored by TLC, then base (1.0 equiv.) was recharged *in situ* and heated at 80 °C for 2–26 h.

[b] Isolated yield.

[c] Conversion of **1a** and **2a** to **3a** (see Scheme 1) was competed, but **4a** was not formed.

[d] Conversion of **1a** and **2a** to **3a** did not proceed.

[e] Conversion of **3a** to **4a** was not performed because only about 50% of **3a** was obtained for the F–C reaction after 16 h.

cused on the screening of an appropriate combination of iron catalyst, base, and solvent that enables the F–C and the following furan ring formation cyclization to occur efficiently through a one-pot operation. Some representative results are summarized in Table 1. A screening of base (entries 1–4) showed that organic DABCO (1,4-diazabicyclo[2.2.2]octane) and inorganic $KHCO_3$ and K_2CO_3 were effective, affording the desired product **4a** in *ca.* 80% yield (entries 2–4). The solvent exhibits a dramatic effect on this transformation. For instance, the formation of **4a** was sluggish when CH_2Cl_2 was used, although the F–C reaction for forming **3a** was completed (entry 5). Alternatively, the F–C reaction was completely suppressed when DMF was employed (entry 6). A brief examination of the loading amount of catalyst showed that the F–C reaction rate was remarkably slowed down when $FeCl_3{\cdot}6H_2O$ was decreased from 5 mol% to 2 mol% (entry 7). About 50% of F–C product **3a** was isolated when the reaction was carried out for a long time on a 1-mmol scale. Finally, a comparison of the catalytic activity of several iron catalysts showed that $FeCl_3$ was equally efficient to $FeCl_3{\cdot}6H_2O$ (entry 4 *vs.* 8), whereas Fe(II) catalysts such as $FeCl_2{\cdot}4H_2O$ and $FeSO_4{\cdot}7H_2O$ were ineffective (entries 9 and 10). Based on an overall consideration of the investigated parameters, we could establish the optimized conditions for the one-pot synthesis of benzofuran **4a** from phenol **1a** and **2a**, that is: 1.2:1 equiv. of **1a** and **2a** in the presence of 5 mol% of $FeCl_3{\cdot}6H_2O$ catalyst at room temperature in MeCN for 3 h, then K_2CO_3 (1.0 equiv.) was recharged *in situ* and the reaction mixture was stirred at 80 °C for an additional 4 h. Under these conditions, **4a** could be obtained in 77% isolated yield (entry 4). These conditions are high-yielding, atom-efficient, and environmentally more begin in terms of the substrates and catalyst being used and the water as the only by-product.

With the optimized conditions established, we examined the substrate scope of this methodology under the optimized conditions. As shown in Table 2, complete conversion as well as high yields were observed for the reaction of a rich range of substituted phenolic compounds **1a–1k** with propargylic alcohol **2a** (entries 1–11), except for 4-halo-substituted phenols **1f** and **1g** (entries 6 and 7). Strangely, incomplete F–C reaction was observed for these two substrates either when elongating the reaction time or elevating the reaction temperature. In addition, the reaction also exhibited good compatibility for an array of propargylic alcohols with various combinations of aromatic and aliphatic substituents. Namely, alcohols **2b**, **2c**, and **2d**, whose structures were modified by electron-donating OMe, or electron-withdrawing Br and Cl moieties on the phenyl periphery, could be converted to the corresponding 3-arylated benzofurans **4l–4o** in good isolated yields (entries 12–15). Moreover, alcohols with an alkyl group at the alkynyl terminals, e.g., **2e–2g**, were also well tolerated (entries 16–19). Finally, the TMS-substituted **2h** was also a viable substrate, affording the desilylated benzofurans **4t** and **4u** in high yields (entries 20 and 21). The structures of all the products were characterized by their NMR spectroscopies (see the Supporting Information). Structures of products **4a**, **4i**, and **4n** were also confirmed by their single X-ray analyses[23] (Figure 1). It is worth noting that in all these transformations, the corresponding pyran derivatives were not isolated.

During the optimization of the reaction conditions, we noted that a sequential addition of $FeCl_3{\cdot}6H_2O$ catalyst and K_2CO_3 is essential for effective synthesis of benzofurans. To clarify each role played by the Lewis acid and K_2CO_3 base, we carried out some control experiments. The results showed that the propargylation of **1a** and **2a** occurred smoothly in the presence of 5 mol% of $FeCl_3{\cdot}6H_2O$ at room temperature to give **3a** in 85% isolated yield [Eq. (1)]. In stark contrast, a simultaneous addition of $FeCl_3{\cdot}6H_2O$ and K_2CO_3 base to the reaction system suppressed completely the formation of **3a** [Eq. (2)], indicating that the base exhibits a significant detrimental effect on

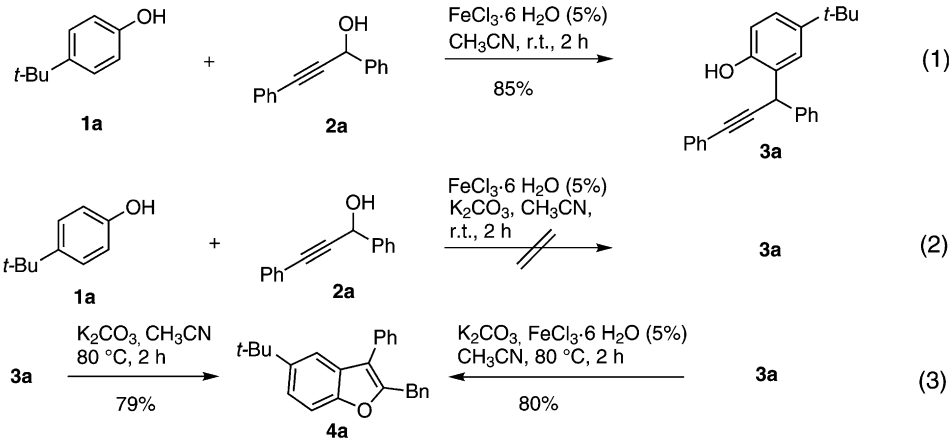
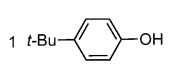
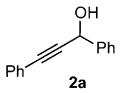
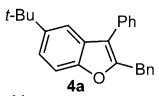
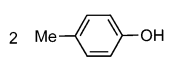
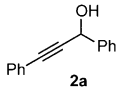
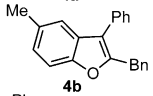
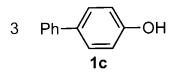
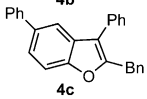
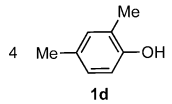
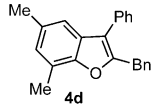
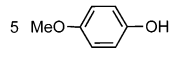
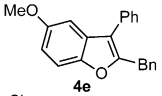
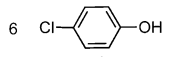
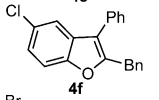
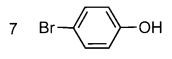
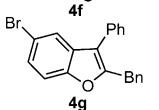
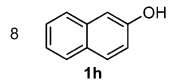
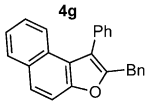
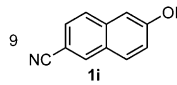
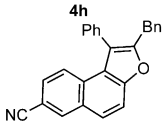
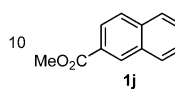
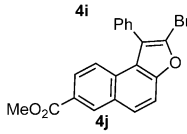
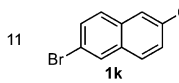
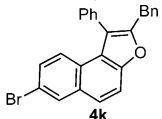
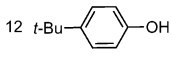
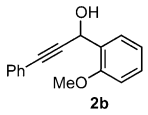
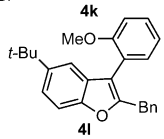
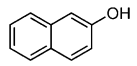
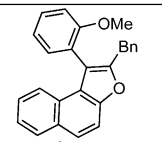
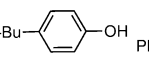
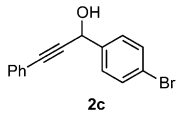
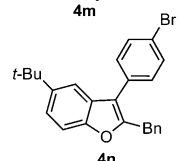
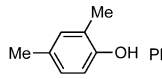
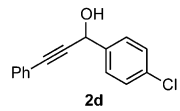
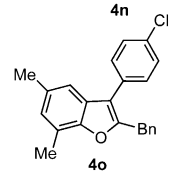
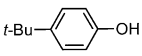
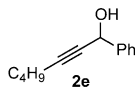
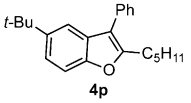
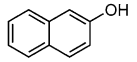
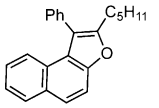


Table 2. Diverse synthesis of 3-arylated benzofurans from various phenols and propargylic alcohols.[a]

Entry	Phenol (**1**)	Alcohol (**2**)	t_1/t_2 [h]	Product (**4**)	Yield[b]
1	 **1a**	 **2a**	3/4	 **4a**	77%
2	 **1b**	 **2a**	6/10	 **4b**	82%
3	 **1c**	**2a**	4/11	 **4c**	75%
4	 **1d**	**2a**	8/12	 **4d**	71%
5	 **1e**	**2a**	6/10	 **4e**	80%
6	 **1f**	**2a**	24/22	 **4f**	14%
7	 **1g**	**2a**	72/24	 **4g**	38%
8	 **1h**	**2a**	4/8	 **4h**	81%
9	 **1i**	**2a**	5/3	 **4i**	87%[c]
10	 **1j**	**2a**	17/10	 **4j**	82%[c]
11	 **1k**	**2a**	5/13	 **4k**	87%
12	 **1a**	 **2b**	16/2	 **4l**	49%[c]
13	 **1h**	**2b**	10/10	 **4m**	71%
14	 **1a**	 **2c**	8/14	 **4n**	74%
15	 **1d**	 **2d**	10/20	 **4o**	79%
16	 **1a**	 **2e**	3/2	 **4p**	63%
17	 **1h**	**2e**	7/3	 **4q**	68%
18	**1a**	**2f**	3/24	**4r**	53%
19	**1a**	**2g**	48/24	**4s**	51%
20	**1a**	**2h**	4/2	**4t**	70%
21	**1h**	**2h**	7/3	**4u**	81%

[a] *Reaction conditions:* phenol **1** (0.6 mmol, 1.2 equiv.), proparyl alcohol **2** (0.5 mmol, 1.0 equiv.), $FeCl_3{\cdot}6H_2O$ (5 mol%) in MeCN (3 mL) at room temperature until **2** had disappeared as monitored by TLC, then K_2CO_3 (1.0 equiv.) was recharged *in situ* and heated at 80 °C.

[b] Isolated yield.

[c] F–C reaction of **1** and **2** was carried out in 6 mL MeCN at 80 °C.

the F–C reaction. On the other hand, the base-mediated furan ring formation from **3a** to benzofuran **4a** can proceed in equally good yields either in the presence or in the absence of $FeCl_3{\cdot}6H_2O$ [Eq. (3), 79% and 80%, respectively]. These results clearly suggested that the F–C reaction and the followed cycloaddition were affected independently by $FeCl_3{\cdot}6H_2O$ Lewis acid and K_2CO_3 base.

On the other hand, since several proton transfer processes were involved in the tandem reaction, for a better understanding of the mechanism, we investigated the detailed proton transfer behaviour employ-

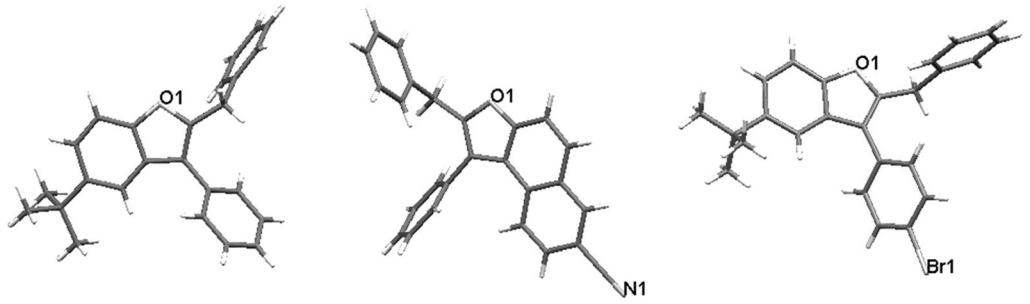
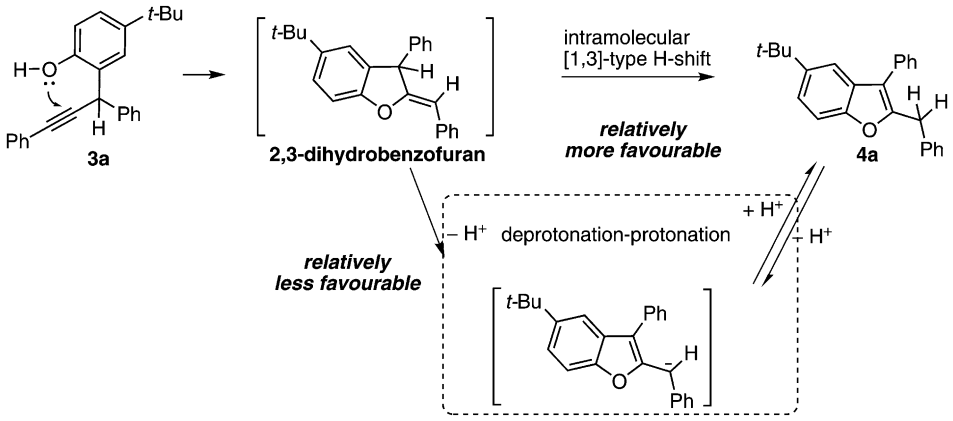


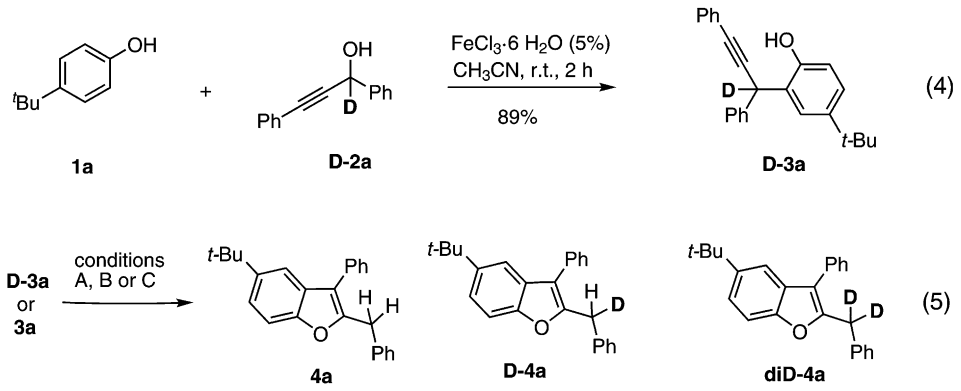
Figure 1. X-ray crystal structures of compounds **4a** (*left*), **4i** (*middle*), and **4n** (*right*)

ing an isotopic labelling technique. Accordingly, the reaction of phenol **1a** with the deuterated propargylic alcohol **D-2a** afforded **D-3a** in 89% yield as a single product [Eq. (4)]. This result indicates that no proton exchange at the propargylic position took place in the F–C reaction although the connection of two aryl groups and an alkynyl group makes the methine proton rather acidic. Interestingly, the furan ring formation of **D-3a** in the presence of base afforded a 2:3 mixture of **4a** and **D-4a** in 84% total yield with the deuterated **D-4a** being the major product as determined by the ^{1}H NMR analysis [Eq. (5), conditions A]. Alternatively, external addition of a large excess of H_2O (5.0 equiv.) as a competitive proton source resulted in a slight increase of the undeuterated product **4a** [Eq. (5), conditions B], forming a 5:4 mixture of **4a** and **D-4a** in 77% total yield. The dideuterated product **diD-4a** was not observed under both conditions **A** and **B**. These observations imply that both intramolecular [1,3]-type proton shift and intermolecular transfer *via* the deprotonation–protonation process from the propargylic position of the 2,3-dihydrobenzofuran intermediate to the benzylic position should be possible (Scheme 2). However, transfer *via* an intramolecular manner should be relatively more favourable because even in the presence of a large excess of H_2O, the yield of the undeuterated **4a** did not increase significantly. On the other hand, when undeuterated **3a** was reacted in the presence of 5.0 equiv. of D_2O as an external proton source [Eq. (5), conditions C), a 1:3.6:3 mixture of **4a**:**D-4a**:**diD-4a** was obtained. Notably, the formation of a substantial amount of **diD-4a** suggests that protonation and deprotonation of **4a** occur reversibly in the reaction processes.

Having investigated the generality and mechanism for the one-pot synthesis of benzofuran derivatives from phenols and secondary propargylic alcohols, our attention was shifted to further expand the utility of this methodology. Thus, the reaction of phenols with primary and *tertiary* propargylic alcohols was inspected. Initial studies showed that unlike the *secondary* alcohols, the primary propargylic alcohols were sluggish for the Fe(III)-catalyzed F-C reaction. Alternatively, the use of the mesylated surrogates, for example, **5**, led to the etherified products **6a** and **6b** (Scheme 3). For the *tertiary* alcohol **7a**, we observed two considerably different outcomes depending on the structural features of phenols. Namely, elimination of *tertiary* alcohol **7a** to **8a** occurred as the major reaction when phenol **1a** was used as nucleophile. However, 2-naphthol **1h** reacted very efficiently with **7a** to give the naphthopyran **9a** in 94% yield in the presence of only $FeCl_3{\cdot}6H_2O$ catalyst without the assistance of base.



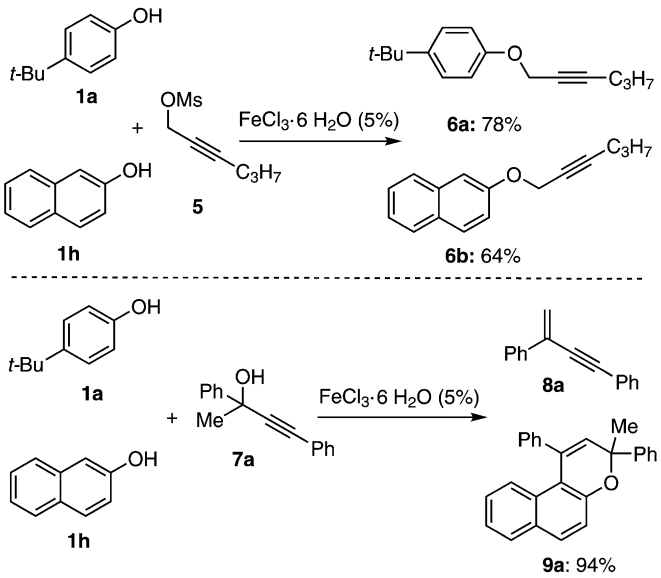
Scheme 2. Proposed H-transfer process for the aromatization of the 2,3-dihydrobenzofuran intermediate.



Conditions A: **D-3a**, K_2CO_3 (1.0 equiv.), $FeCl_3$ (5 mol%), 4 Å MS, CH_3CN, 80 °C; total yield: 84%; molar ratio: **4a**:**D-4a** = 2:3.
Conditions B: **D-3a**, K_2CO_3 (1.0 equiv.), $FeCl_3$ (5 mol%), H_2O (5.0 equiv.), CH_3CN, 80 °C; total yield: 77%; molar ratio: **4a**:**D-4a** = 5:4.
Conditions C: **3a**, K_2CO_3 (1.0 equiv.), $FeCl_3$ (5 mol%), D_2O (5.0 equiv.), CH_3CN, 80 °C; total yield: 84%; molar ratio: **4a**:**D-4a**:**diD-4a** = 1:3.6:3.

The structure of **9a** was unambiguously confirmed by the X-ray single crystal analysis[23] (Figure 2, *left*). This result implies that the reaction of *tertiary* alcohols with naphthol for the formation of naphthopyran proceeds *via* a different reaction model from that of *secondary* alcohols for the formation of 3-arylated benzofurans (see Table 2).

Based on our results for the synthesis of benzofurans (*vide supra*) together the few related literature reports[10] concerning the Brønsted acids, e.g., boronic acid-catalyzed reaction of *tertiary* propargylic alcohols with aryl nucleophiles, we proposed two tentative pathways for the formation of naphthopyran **9a** (Scheme 4). Most probably, **7a** would form an allenyl



Scheme 3. Reaction of phenols with primary and tertiary propargylic alcohols in the presence of Fe(III) catalyst.

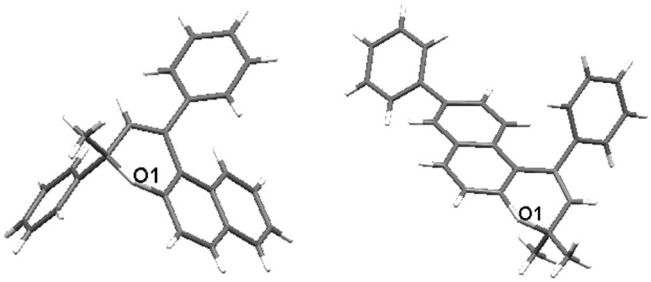
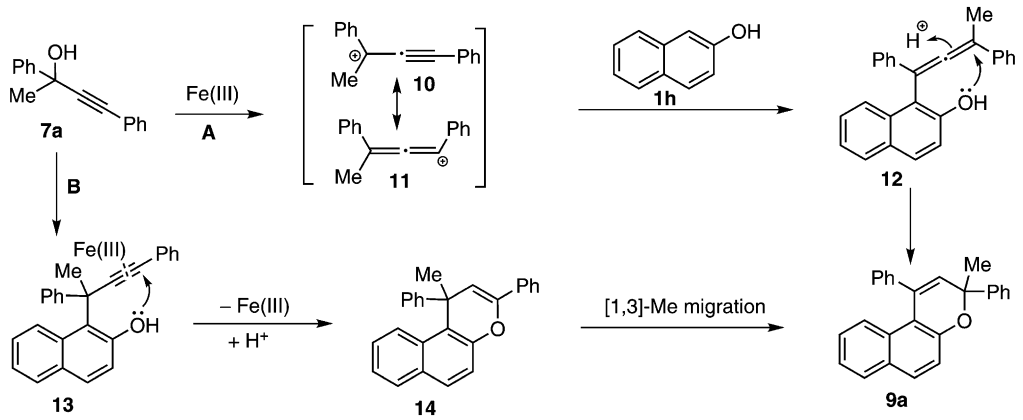


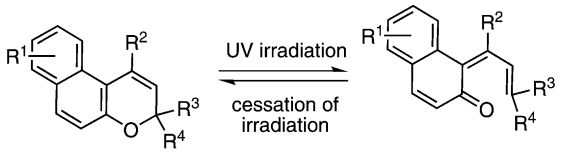
Figure 2. X-ray crystal structures of compounds **9a** (*left*) and **9l** (*right*).

carbocation (**10**) or propagylic cation (**11**) under the effect of Fe(III) (path **A**). Subsequently, the F–C reaction of 2-naphthol **1h** with the cation occurs at the less hindered side to provide the *ortho*-allenylphenol **12**. Attributed to the high reactivity as well as the strained linear configuration of allene moiety, the cyclization takes place smoothly *via* a regiospecific 6-*endo*-dig selectivity to give pyran **9a**. As another possible way, **7a** and **1h** undergoes a sequential F–C reaction (**13**, path **B**) and cycloaddition to give pyran **14**, in which the exclusive 6-*endo*-dig selectivity for **14** can be explained by the steric effect of a quaternary carbon adjacent to the alkynyl group. Finally, 1,3-migration of the Me group in **14** furnishs **9a**. To clarify the exact mechanism, we investigated the reaction of **1h** with dimethylpropargylic alcohol **7b** (Table 3, entry, 2). Only product **9b** was obtained in high yield while the Me-migrated isomer, i.e., **9a** was not detected. Moreover, we could also obtain the single X-ray crystal structure of **9l**[23] (Figure 2, *right*) derived from **7b** and naphthol **1l** (Table 3, entry 12). These results unambiguously confirmed that the naphthopyrans are formed through pathway **A**.



Scheme 4. Possible pathway for the formation of naphthopyran **9a**.

Having clarified the mechanism for the generation of naphthopyran **9a**, we then examined the general applicability of the method because naphthopyran frameworks are of special interest as photochromophores. This structural motif exhibits reversible colour changes through the photo-induced ring-opening of the pyran ring and the recyclization reaction upon the cessation of irradiation [Eq. (6)]. Such a facile and unique structural interconversion gives rise to a significant colour change between the two states before and after irradiation and, thereby, making it particularly attractive in a wide range of application areas such as ophthalmic glasses, electronic displays, optical switches, and memory devices, et al.[8,9,14]



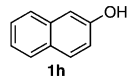
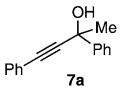
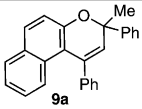
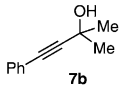
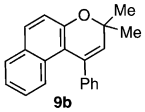
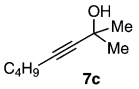
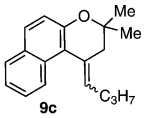
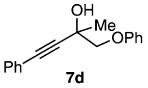
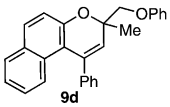
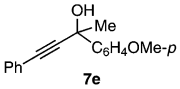
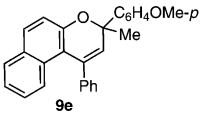
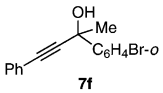
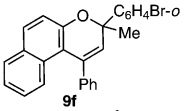
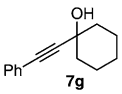
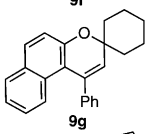
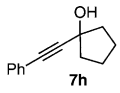
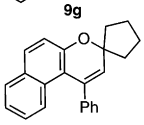
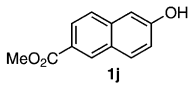
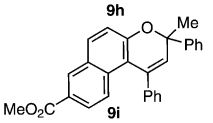
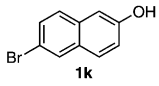
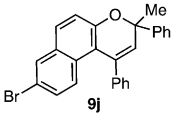
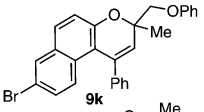
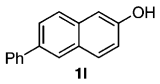
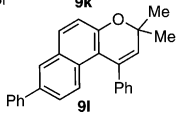
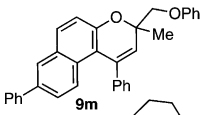
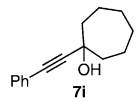
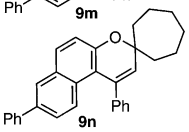
(6)

As illustrated in Table 3, we have clearly demonstrated that $FeCl_3 \cdot 6H_2O$ is a highly efficient catalyst that allows for the direct synthesis of various naphthopyrans from naphthols and *tertiary* propargylic alcohols *via* the one-pot procedure under mild and very simple conditions-just by stirring a slight excess of naphthol (1.2 equiv.) and propargylic alcohol in the presence of 5 mol% of Fe(III) catalyst at 80 °C without the need of any other additives. A rich range of propargylic alcohols substituted by a variety of combinations of aromatic, aliphatic, and cyclic substituents (entries 1–8) was well tolerated, affording the 2,2,4-trisubstituted naphthopyrans in high yields. In addition, various naphthols decorated by different functional groups such as ester (**1j**), bromo (**1k**), and phenyl (**1l**) were also viable substrates (entries 9–14). Importantly, the flexible incorporation of various functional groups such as phenoxy (**9d**, **9k**, and **9m**), methoxy (**9e**), ester (**9i**), and bromo (**9f**, **9j**, and **9k**) groups facilitate further diversifying the structures of the derived naphthopyrans.

Finally, based on the mechanistic studies for the formation of naphthopyrans (Scheme 4), we reasoned that the synthesis of more functionalized pyran derivatives, i.e., introducing a functional group at the 3-position of the pyran ring would also be possible through a one-pot cascade reaction. As illustrated in Scheme 5, by choosing appropriately a second electrophile (E^+X^-) which can be captured by the *ortho*-allenylphenol intermediate **12** during the cycloaddition reaction, the 3-functionalized naphthopyran derivatives **15** might be obtained.

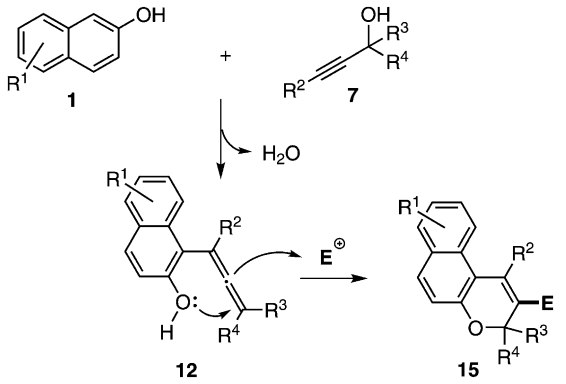
Accordingly, the reaction of naphthol **1h**, **7b**, and a second electrophile such as aldehyde, allylic bromide, MeI, NBS, NIS, and I_2 was examined under the identical conditions for the synthesis of naphthopyrans **9a**–**9n** (Table 3). The preliminary results showed that the presence of aldehyde, allylic bromide, and MeI did not afford the desired 3-functionalized products and only **9b** was obtained in over 80% yield. On the other hand, the addition of NBS and NIS resulted in an intractable mixture. Delightedly, when I_2 was employed, the desired 3-iodo-substituted product **15b** (Scheme 6) was obtained in 10% yield together with 46% of 3-protonated **9b**. Encouraged by this preliminary result, we carried out further optimization of the reaction conditions. An extensive trial of various reaction parameters led eventually to the discovery of mild and efficient conditions for the one-pot synthesis of **15b**, i.e., by employing naphthol **1h** (1.0 equiv.), *tertiary* propargylic alcohol **7b** (3.0 equiv.), and I_2 (2.0 equiv.) as substrates, and 10 mol% of $FeCl_3 \cdot 6H_2O$ as catalyst in toluene (3 mL) at 25 °C for 10 h, **15b** could be obtained in 81% isolated yield with only a trace amount of **9b** being observed in TLC (Table 4, entry 2). The structure of **15b** was confirmed by single crystal X-ray analysis[23] (Figure 3). The excess of **7b**

Table 3. Diverse syntheses of various naphthopyrans.[a]

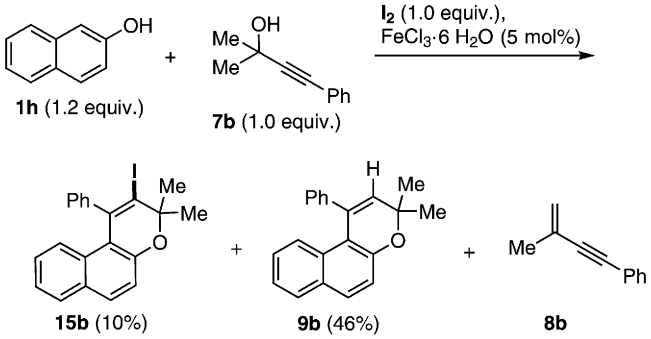
Entry	Phenol (**1**)	Alcohol (**7**)	Product (**9**)	Yield[b]
1	 **1h**	 **7a**	 **9a**	94%
2		 **7b**	 **9b**	87%
3		 **7c**	 **9c**	66%
4		 **7d**	 **9d**	74%
5		 **7e**	 **9e**	79%
6		 **7f**	 **9f**	77%
7		 **7g**	 **9g**	71%
8		 **7h**	 **9h**	38%
9	 **1j**	**7a**	 **9i**	90%
10	 **1k**	**7a**	 **9j**	92%
11	**1k**	**7d**	 **9k**	70%
12	 **1l**	**7b**	 **9l**	94%
13	**1l**	**7d**	 **9m**	70%
14	**1l**	 **7i**	 **9n**	67%

[a] *Reaction conditions:* naphthol **1** (0.6 mmol, 1.2 equiv.), proparyl alcohol **7** (0.5 mmol, 1.0 equiv.), $FeCl_3{\cdot}6H_2O$ (5 mol%) in MeCN (3 mL) at 80 °C.

[b] Isolated yield.



Scheme 5. Proposed mechanism for the synthesis of 2,2,3,4-tetrasubstituted naphthopyrans *via* a one-pot cascade procedure.



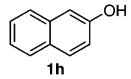
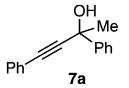
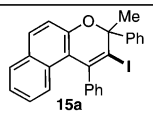
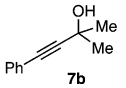
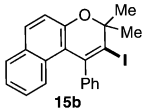
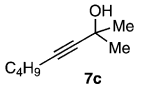
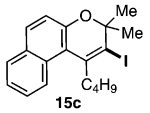
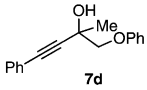
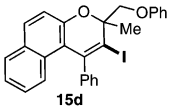
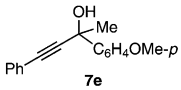
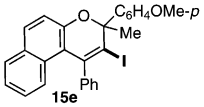
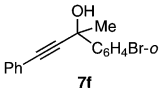
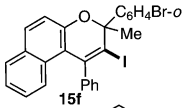
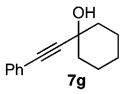
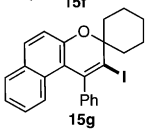
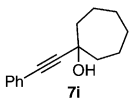
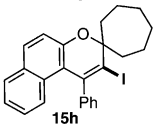
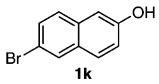
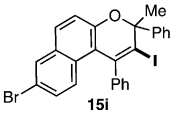
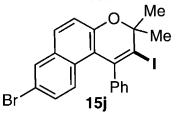
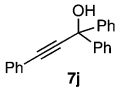
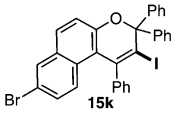
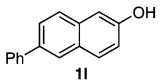
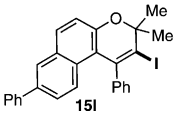
Scheme 6. Initial experiment for the synthesis of 3-iodinated naphthopyran.

was mainly eliminated to **8b** (Scheme 6) and can be recovered easily by column chromatography.

With the mild, high-yielding conditions for the one-pot synthesis of 3-iodinated naphthopyran **15b** established, we then examined the generality of this methodology by varying the structure of propargylic alcohols and naphthols. As shown in Table 4, an array of *tertiary* propargylic alcohols substituted by a flexible combination of various aromatic and alphatic, as well as the heteroatom-hybrid substituents reacted smoothly to afford the 3-iodinated pyrans in high yields (**15a**–**15f**), albeit a moderated yield was observed for the cyclic alcohols (**15g** and **15h**). In addition, several substituted naphthols (**1k** and **1l**) were also viable substrates, affording the desired products in excellent yields (**15i**–**15l**).

Thus, we have established a novel protocol for the synthesis of 2,2,3,4-tetrasubstituted naphthopyran derivatives *via* the iron-catalyzed one-step cascade reaction. To the best of our knowledge, such a protocol has never been reported previously. Of even more interest than this newly developed methodology, the iodinated naphthopyrans **15** are anticipated to be attractive compounds in the field of photochromic materials, because the intrinsically high reactivity of

Table 4. Iron-catalyzed efficient synthesis of 3-iodinated nathopyrans **15** *via* the iron-catalyzed one-pot three-component reaction.[a]

Entry	Phenol (**1**)	Alcohol (**7**)	Product (**15**)	Yield[b]
1	 **1h**	 **7a**	 **15a**	92%
2		 **7b**	 **15b**	81%
3		 **7c**	 **15c**	60%
4		 **7d**	 **15d**	83%
5		 **7e**	 **15e**	73%
6		 **7f**	 **15f**	75%
7		 **7g**	 **15g**	33%
8		 **7i**	 **15h**	43%
9	 **1k**	**7a**	 **15i**	72%
10	**1k**	**7b**	 **15j**	75%
11	**1k**	 **7j**	 **15k**	92%
12	 **1l**	**7b**	 **15l**	86%

[a] *Reaction conditions:* phenol **1** (0.3 mmol, 1.0 equiv.), proparyl alcohol **7** (0.9 mmol, 3.0 equiv.), I_2 (0.6 mmol, 2.0 equiv.), $FeCl_3{\cdot}6H_2O$ (10 mol%) in toluene (3 mL) at 25 °C.

[b] Isolated yield.

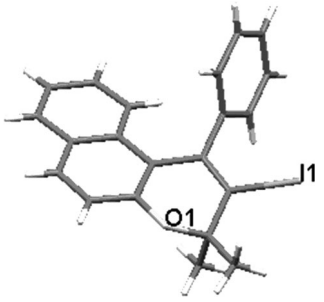


Figure 3. X-ray crystal structure of compound **15b**.

C_{sp2}–I bond gives it highly potential for the flexible incorporation of various functional groups at the C-3 position in **15** *via* the transition metal-catalyzed cross-couplings. As a result, the introduction of a substituent at such a position is highly anticipated to influence through the steric, electronic, and/or conjugating effects the photochemical as well as physical properties of the derived compounds and, thereby, offering opportunities for the development of new photochromic materials. In fact, it has been observed that a subtle change of the substituents at the 2-position of naphthopyrans resulted in a profound change of photochromic properties as seen in some literature reports.[8,14] However, the 3-substituted analogues have been less investigated due to the lack of a general method for their synthesis.

Conclusions

In summary, we have demonstrated that, by employing the iron catalyst, both densely substituted benzofurans and naphthopyrans could be synthesized directly from simple phenolic compounds and propargylic alcohols. Benzofurans were synthesized *via* a two-step one-pot procedure involving the $FeCl_3{\cdot}6H_2O$-catalyzed F–C reaction followed by a base-mediated furan ring formation. More importantly, naphthopyrans can be obtained *via* a single step tandem reaction in the presence of only a catalytic amount of Fe(III) catalyst without the assistance of any other external additives. Such a general and efficient method has been rarely reported. The chemospecific formation of furan and pyran motifs proceeded through different reaction models as controlled by the structural features of the *secondary* and *tertiary* propargylic alcohols. In addition, the methods are also atom-economic and environmentally benign because only a slight excess of phenol substrates (1.2 equiv.) was used and only water was produced as stoichiometric waste. Most interestingly, for the first time, we have established an efficient protocol for the synthesis of fully 2,3,4-substituted naphthopyrans *via* a one-pot reaction. The introduction of an iodo func-

tional group at the 3-position should provide a new entry for the development of naphthopyran-based photochromic materials. The design and synthesis of some 3-substituted naphthopyrans and study of their photochromic properties are currently underway in our laboratory.

Experimental Section

General Methods

All solvents were purified according to the standard methods prior to use. Phenols and iron catalysts were purchased from J&K Chemical Ltd or Alfa Aesar, and were used without further purification. $FeCl_3{\cdot}6H_2O$ of 99% purity from ACROS company was used; the $FeCl_3$ used for optimization of the reaction conditions was purchased from Alfa Aesar company and had 98% purity. Propargylic alcohols were prepared according to the known methods.[24] Unless otherwise noted, the ^1H NMR spectra were recorded at 400 or 600 MHz in $CDCl_3$ and the ^{13}C NMR spectra were recorded at 100 or 150 MHz in $CDCl_3$, respectively, with TMS as internal standard. All shifts are given in ppm. All coupling constants (J values) are reported in Hertz (Hz). X-ray crystallographic analyses were performed on a Bruker SMART APEX II CCD diffractometer with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) operated at 2.0 kW (50 kV, 40 mA). The structures were solved by direct methods using the program SHELXL-97 and refined anisotropically by full matrix least squares on F2 values with SHELXL-97. High resolution mass spectra was measured by using IonSpec7.0T MALDI-FTICRMs. Column chromatography was performed on silica gel 100 mesh. See the Supporting Information for characterization data, and copies of ^1H NMR and ^{13}C NMR spectra of the products.

General Procedure for the One-Pot Synthesis of Benzofurans (4)

A MeCN solution (3 mL) of phenol **1** (0.6 mmol), propargylic alcohol **2** (0.5 mmol), and $FeCl_3{\cdot}6H_2O$ (6.8 mg, 0.025 mmol) was stirred at 25 °C in a sealed Schlenck tube until the propargylic alcohol had disappeared as monitored by TLC. Then, K_2CO_3 (69 mg, 0.5 mmol) was recharged *in situ* to the reaction vessel and the mixture was further stirred at 80 °C for additional hours. After the completion of the reaction as monitored by TLC, 30 mL of DCM were added and the mixture was filtered, concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (petroleum ether/DCM = 10/1, v/v) to give the desired pure product.

General Procedure for the Synthesis of Naphthopyrans (9)

A MeCN solution (3 mL) of propargylic alcohol **7** (0.5 mmol), 2-naphthol **1** (0.6 mmol), and $FeCl_3{\cdot}6H_2O$ (6.8 mg, 0.025 mmol) was stirred in a sealed Schlenck tube at 80 °C. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (petroleum ether/DCM = 10/1, v/v) to give the desired product.

General Procedure for the One-Pot Three-Component Synthesis of 3-Iodinated Naphthopyrans (15)

A toluene solution (3 mL) of propargylic alcohol **7** (0.9 mmol), 2-naphthol **1** (0.3 mmol), I_2 (152 mg, 0.6 mmol), and $FeCl_3{\cdot}6H_2O$ (8.1 mg, 0.03 mmol) was stirred in a sealed Schlenck tube at 25 °C. After the completion of the reaction as monitored by TLC, ethyl acetate (30 mL) was added and the mixture was washed successively with saturated aqueous $Na_2S_2O_3$ solution and brine for three times. The organic layer was then dried over Na_2SO_4, filtered, and concentrated. The mixture was purified by silica gel chromatography (petroleum ether/DCM = 10/1, v/v) to give the desired product.

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