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Benzannulation of isobenzopyryliums with electron-rich alkynes: a modular access to β-functionalized naphthalenes†

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Described here is a modular strategy for the rapid synthesis of β-functionalized electron-rich naphthalenes, a family of valuable molecules lacking general access previously. Our approach employs an intermolecular benzannulation of *in situ* generated isobenzopyrylium ions with various electron-rich alkynes, which were not well utilized for this type of reaction before. These reactions not only feature a broad scope, complete regioselectivity, and mild conditions, but also exhibit unusual product divergence depending on the substrate substitution pattern. This divergence allows further expansion of the product diversity. Control experiments provided preliminary insights into the reaction mechanism.

Functionalized naphthalenes are important structural motifs widely present in bioactive natural products, pharmaceuticals and functional materials.[1,2] They also serve as valuable intermediates in organic synthesis.[3] Among them, naphthalenes bearing an electron-donating group (EDG) at the β-position (*e.g.*, β-naphthols, β-naphthylamines, and β-naphthyl thioethers) are particularly versatile (Fig. 1).[2,3] For example, BINOL, which is derived from β-naphthol, is an extensively utilized synthetic precursor toward a wide range of privileged chiral ligands and catalysts.[3] While various approaches have been developed for the synthesis of naphthalenes, efficient and selective *de novo* strategies toward these β-functionalized ones still remain in high demand. Moreover, to the best of our knowledge, a general and modular approach for rapid access to all these electron-rich β-functionalized naphthalenes remains unknown.[4]

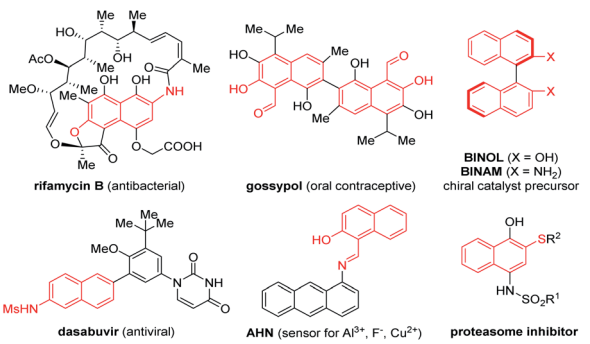
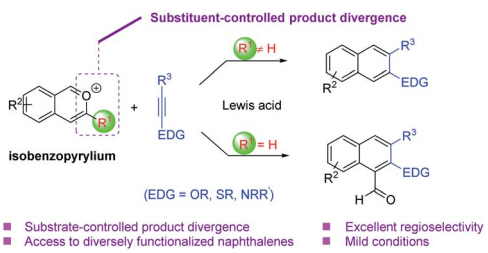


Fig. 1 Useful β-naphthol, β-naphthylamine, and β-naphthyl thioether units.

Isobenzopyrylium ions are readily accessible and versatile intermediates in organic synthesis (Scheme 1).[5] They are known to participate in cycloaddition reactions with diverse carbon–carbon double bonds or triple bonds for the synthesis of naphthalenes.[5,6] While extensive progress has been achieved in this topic, challenges still remain to be addressed. For example, the majority of these benzannulations with alkynes have to be executed at high temperature, except those intramolecular cases or with stoichiometric activators. Moreover, electron-rich alkynes have not been well explored as reaction partners for the benzannulations with isobenzopyrylium ions. Nevertheless, such reactions would provide expedient access to the valuable β-naphthol and β-napthylamine derivatives with diverse substitution patterns (Scheme 1). In this context, here we report our effort in achieving a general and modular strategy toward these electron-rich naphthalenes with high efficiency and



Scheme 1 Benzannulation of isobenzopyryliums with electron-rich alkynes.

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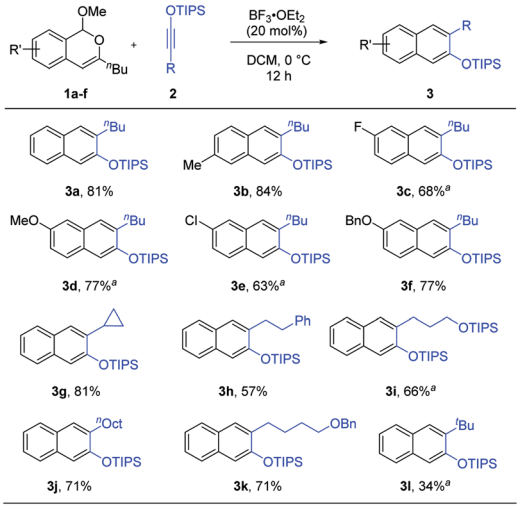
regioselectivity under mild conditions. We also observed interesting selectivity divergence controlled by the substituent of the isobenzopyrylium substrates, giving rise to different types of naphthalene products (*e.g.*, 2-hydroxy-1-naphthaldehydes, Scheme 1).

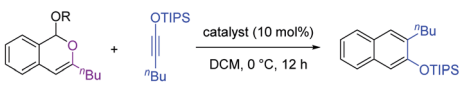
We began our study with isochromene **1a** as the isobenzopyrylium precursor. Siloxy alkyne **2a** was first employed as the model electron-rich alkyne in view of the extraordinary versatility of this type of alkyne in various cyclization reactions, including benzannulation.[7–9] Various Brønsted and Lewis acids were evaluated as catalysts for this reaction. Unfortunately, most of them did not show obvious catalytic activity toward the formation of a naphthalene product (Table 1). These reactions either had little conversion or resulted in a mixture of undesired products. Nevertheless, further screening led to the identification of AgOTf and $BF_3\cdot OEt_2$ as capable catalysts (entries 5–6), with the latter being superior, leading to the formation of naphthalene **3a** as the major product (75% yield, entry 6). Increasing the catalyst loading to 20 mol% further improved the product yield to 85% (with an isolated yield of 81%, entry 7). Further increasing the catalyst loading proved to be not beneficial (entry 8). Notably, the use of substrate **1a′** bearing an ethoxy leaving group also provided an equally good result. Other solvents, such as toluene and MeCN, were also evaluated, but all gave lower product yields. Finally, it is worth noting that the mild conditions used here are in sharp contrast to the typical high temperature required for the previously known catalytic intermolecular benzannulations involving isobenzopyryliums and alkynes.[5d]

With the optimized conditions, the generality of this process was examined (Scheme 2). A range of isochromenes **1** and siloxy alkynes **2** participated in this benzannulation to form the desired silylated β-naphthols **3** with moderate to good efficiency. Notably, these products were all generated as a single isomer. This is particularly noteworthy when compared with the cases using phthalazines, which gave a mixture of regioisomers if the phthalazine was unsymmetrically substituted.[8g] The excellent regioselectivity observed in our reaction is likely attributed to the significant polarization of both cycloaddition partners. While alkyl-substituted siloxy alkynes reacted efficiently, unfortunately aryl-substituted ones led to low yield.



Scheme 2 Reaction scope. Reaction scale: **1** (0.5 mmol), **2** (0.6 mmol), DCM (5 mL), 12 h, and isolated yield. [a] Run for 24 h.

Table 1 Evaluation of reaction conditions



Entry	Catalyst	Yield[a] (%)
1	$MeSO_3H$	<5[b]
2	$HNTf_2$	<5[c]
3	$Sc(OTf)_3$	<5[c]
4	$TiCl_4$	<5[b]
5	AgOTf	30[c]
6	$BF_3\cdot OEt_2$	75
7	**$BF_3\cdot OEt_2$ (20 mol%)**	**85 (81)[d]**
8	$BF_3\cdot OEt_2$ (1.0 equiv.)	83
9	$BF_3\cdot OEt_2$ (20 mol%), with **1a′**	(75)[d]

[a] Reaction scale: **1a** (0.05 mmol), **2a** (0.06 mmol), catalyst (10 mol%), and DCM (0.5 mL). Yield is based on the analysis of the ^1H NMR spectrum of the crude product using CH_2Br_2 as the internal standard. [b] Unreacted substrates account for the major remainder of the mass balance. [c] An unidentifiable mixture accounts for the major remainder of the mass balance. [d] Yield in parentheses is isolated yield.

During the above scope study, we found that the reaction of 3-unsubstituted isochromene **1g** and siloxy alkyne **2a** did not form the desired product **3a**. Instead, 2-hydroxy-1-naphthaldehyde **4a** was formed as the major product (64% yield, eqn (1)). Careful analysis of this product structure indicated that the original leaving part in **1a** (in the case of **3a**) was not completely cleaved from the molecule. Instead, only the C–O bond cleavage took place, which led to a dangling aldehyde group. Another important observation is that the TIPS group was lost in the naphthalene product. It was proposed that the methoxide leaving group in **1a** might help remove this silyl group and assist the above C–O bond cleavage. In contrast, in the formation of **3a**, this methoxide group was a part of the whole leaving unit during rearomatization and thus unavailable for desilylation (*vide infra*).

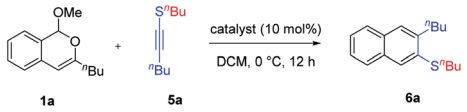
In fact, such 2-hydroxy-1-naphthaldehyde products, resembling the highly versatile salicylaldehyde family, are indeed a useful substructure of bioactive molecules, such as gossypol (Fig. 1).[2b] They can also serve as key intermediates toward functional materials, such as molecular sensors (*e.g.*, AHN, Fig. 1).[2e] In view of these important applications, considerable efforts were next devoted to further improving the reaction efficiency (see the ESI for details†). Finally, we found that the reaction yield of **4a** could be improved to 85% with 2.0 equivalents of $BF_3\cdot OEt_2$ and one equivalent of 2,4,6-collidine as the additive. We believe that the role of collidine is to help reversibly stabilize the isobenzopyrylium intermediate and prevent its decomposition during the reaction progress.[9b]

(1)

The above protocol for the synthesis of 2-hydroxy-1-naphthaldehydes is general for a range of 3-substituted isobenzopyryliums (Scheme 3). The reaction efficiency was not affected by electron-donating or electron-withdrawing groups. Various siloxy alkynes were also suitable reaction partners, including aryl- and alkyl-substituted ones. Again, these products were all formed as a single regioisomer. While the majority of these reactions were highly chemoselective toward the formation of aldehydes **4**, it is worth noting that ^{t}Bu- and TBS-substituted alkynes resulted in a mixture of **3** and **4**, with the former being major. This is likely due to the substantial steric hindrance in close proximity to the silyl group, whose cleavage was obstructed and thus the driving force for the subsequent C–O bond cleavage was weakened, thereby altering the pathway to preferentially form **3** (*vide infra*). Finally, the structures of **4a** and **4b** were unambiguously confirmed by X-ray crystallography.

The divergent reaction patterns observed with siloxy alkynes prompted us to explore other electron-rich alkynes. Thioalkyne **5a** was next employed for the reaction with **1a**. Indeed, direct extension with $BF_3\cdot OEt_2$ as the catalyst successfully resulted in regioselective formation of β-naphthyl thioethers **6a** in about 70% yield (Table 2, entries 1 and 2). Further screening of other catalysts was performed to further improve the reaction efficiency (see the ESI for details†). While Brønsted acids led to a significant drop in the yield, we were pleased to find that the Lewis acid $AgNTf_2$ exhibited excellent catalytic activity, furnishing **6a** in 89% yield (entry 6).

Table 2 Condition optimization[a]

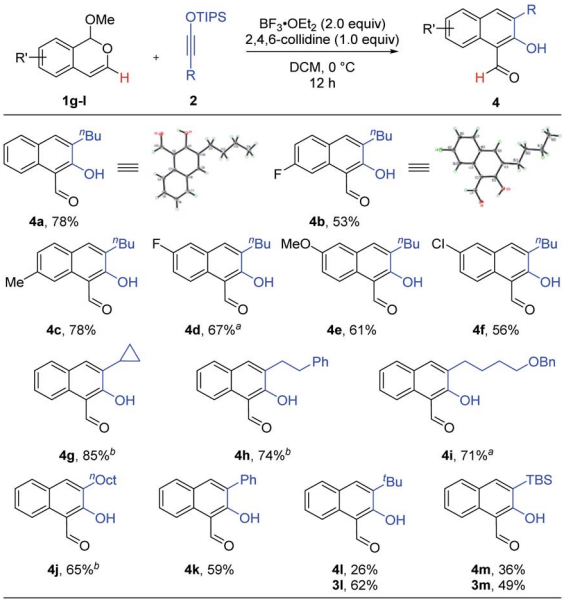


Entry	Catalyst	Yield[b] (%)
1	$BF_3\cdot OEt_2$	70
2	$BF_3\cdot OEt_2$ (20 mol%)	72 (68)[b]
3	$HNTf_2$	20
4	$MeSO_3H$	7
5	AgOTf	80
6	**$AgNTf_2$**	**89 (83)[b]**

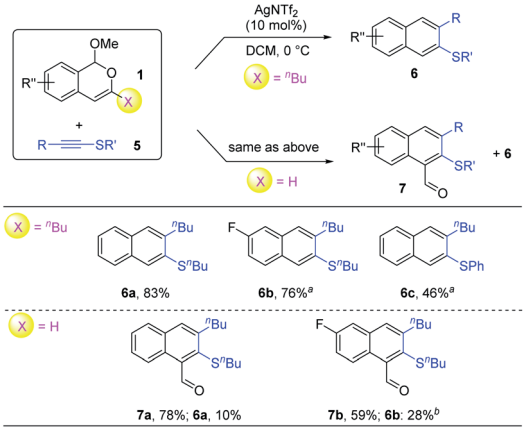
[a] Reaction scale: **1a** (0.05 mmol), **5a** (0.06 mmol), catalyst (10 mol%), and DCM (0.5 mL). The yields are based on NMR analysis of the crude product using CH_2Br_2 as the internal standard. [b] Isolated yield.

With the above conditions, we carried out a brief examination of the reaction scope (Scheme 4). Interestingly, a similar selectivity divergence was also observed with thioalkynes. Indeed, under identical conditions, the 3-butyl-substituted and 3-unsubstituted isobenzopyryliums all reacted efficiently, with the former leading to only 2-naphthyl thioethers **6**, but the latter preferentially to 2-sulfenyl-1-naphthaldehydes **7**. It is worth noting that only one regioisomer was observed in all these products.

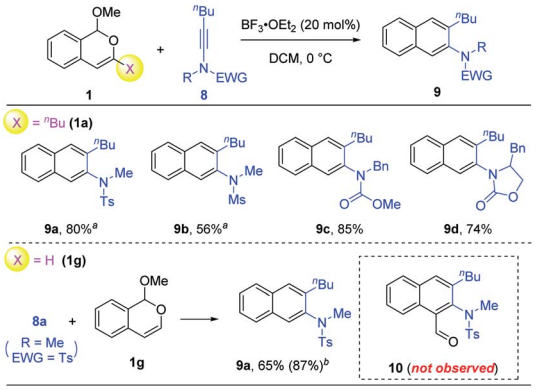
Finally, we were curious about the reactivity of ynamides in such benzannulations.[10] To our delight, in the presence of 20 mol% of $BF_3\cdot OEt_2$, the reaction between isochromene **1a** and different ynamides **8** successfully afforded the desired 2-naphthylamine products **9** with excellent regioselectivity and good efficiency (Scheme 5). Different electron-withdrawing groups on the ynamides were all compatible with this protocol. However, to our surprise, the use of 3-unsubstituted isochromene **1g** did



Scheme 3 Scope for the synthesis of 2-hydroxy-1-naphthaldehydes **4**. Reaction scale: **1** (0.5 mmol), **2** (0.6 mmol), DCM (5 mL), 12 h, and isolated yield. [a] Run for 16 h. [b] Run for 19 h.



Scheme 4 Scope for the synthesis of 2-naphthyl thioethers. Reaction scale: **1** (0.3 mmol), **5** (0.36 mmol), 12 h, and isolated yield. [a] Run for 37 h. [b] Run for 19 h. The unreacted alkyne accounted for the major mass balance.

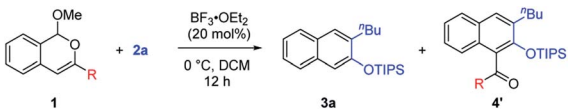


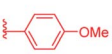
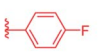
Scheme 5 Scope of ynamides. Reaction scale: **1** (0.5 mmol), **8** (0.6 mmol), DCM (5 mL), 12 h, and isolated yield. [a] Run for 30 h. [b] Yield in parentheses is obtained with $BF_3 \cdot OEt_2$ (2.0 equiv.), 2,4,6-collidine (1.0 equiv.), 0 °C, and DCM.

not lead to the expected naphthaldehyde **10** at all. Instead, the same product **9a** was obtained as the only product, even if two equivalents of $BF_3 \cdot OEt_2$ were used together with collidine as the additive (conditions in Scheme 3). This result is in dramatic contrast to the cases of siloxy alkynes and thioalkynes.

Next, further studies were performed to help understand the unusual selectivity divergence observed with siloxy alkynes and thioalkynes. It is obvious that the substituent at the 3-position of the isochromene substrates has a crucial impact on the product distribution. To further probe the possible steric and electronic effects, we incorporated various other substituents, such as different aryl groups and the bulky ^{t}Bu group (Table 3). We found that these reactions afforded products **3a** and **4′** with variable ratios. With the ^{t}Bu group, almost the same product distribution as the ^{n}Bu group was observed, exclusively forming **3a** (Table 3, entry 2). However, aryl substitution reversed this ratio, giving product **4′** as the major product (entries 3–5). More importantly, the preference toward **4′** is more pronounced with electron-deficient aryl groups. *p*-Fluorophenyl substitution led to almost only **4′**. These results suggested that the product distribution appeared to be more related to the electronic effect than the steric effect.

Table 3 Influence of the 3-substituents in isochromenes[a]

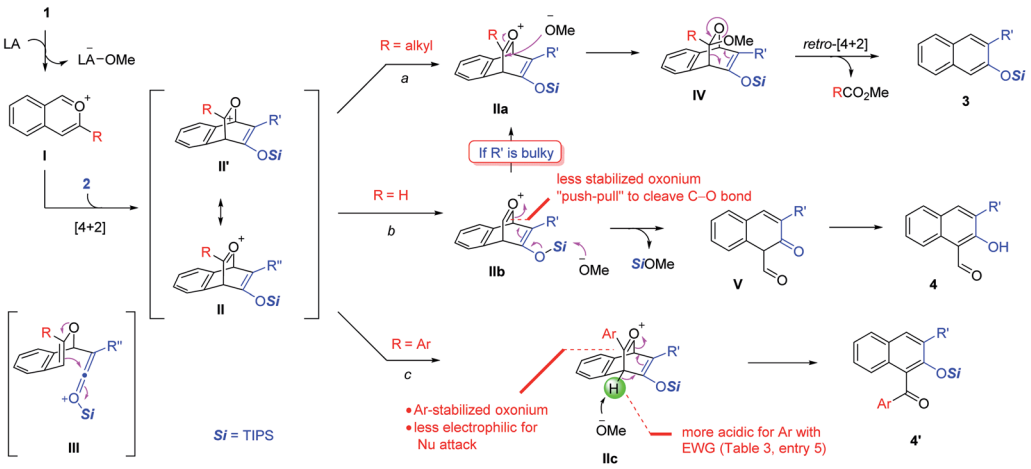


entry	R	yield of **3a**	yield of **4′**	**3a/4′**
1	^{n}Bu	85%	0	>20:1
2	^{t}Bu	67%	0	>20:1
3		28%	40%	1:1.4
4	Ph	8%	70%	1:8.8
5		0	72%	<1:20
6[b]	H	0	64% (**4a**)	<1:20

[a] Reaction scale: **1** (0.05 mmol), **2a** (0.06 mmol), and 12 h. Yield is based on the analysis of the NMR yield of the crude mixture using CH_2Br_2 as an internal standard. [b] Run with 10 mol% of $BF_3 \cdot OEt_2$.

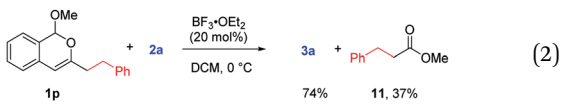
Possible mechanisms are depicted in Scheme 6 using a siloxy alkyne as an example. The reaction begins with Lewis acid activation on the acetal motif to form the isobenzopyrylium intermediate **I**. The subsequent cycloaddition with the alkyne triple bond forms the key bicyclic oxonium intermediate **II**, which has a resonance form **II′**. This step might also be stepwise by forming one C–C bond first *via* ketenium **III**. In either case, the regioselectivity is precisely controlled by matching the polarity of the two partners, which explains the exclusive formation of only one regioisomer in all the cases. Depending on the R substituent, oxonium **II** can proceed *via* three possible pathways. In path a (R = alkyl), the methoxide attacks the oxonium carbon to form intermediate **IV**, which then undergoes retro-[4 + 2] cycloaddition with concomitant rearomatization to form naphthalene **3**, together with the release of ester RCO_2Me. However, if the oxonium carbon is unsubstituted (R = H), this intermediate is relatively unstable due to less stabilization of the positive charge (also viewed as a secondary cation in **II′**, *versus* tertiary carbocation if R ≠ H). Thus, the silyl enol ether motif tends to push the electron toward this unstable oxonium (a "push–pull" scenario) to cleave the bridging C–O bond. This step, likely assisted by the methoxide attack on the silyl unit, leads to 1,3-dicarbonyl intermediate **V**. The subsequent tautomerization/aromatization leads to the observed 2-hydroxy-1-naphthaldehyde **4**.[6b] As an exception, if the siloxy alkyne is bulky (*e.g.*, R′ = ^{t}Bu or TBS), the reaction preferentially gives product **3** (Scheme 3, **4l–m**). We believe that the increased steric repulsion by bulky R′ significantly disfavors the approach of methoxide to the neighboring silyl group in **IIb**. Instead, the methoxide prefers to add to the oxonium carbon, which allows path a to operate and forms **3** as the major product. Another exceptional case is the use of ynamides, which exclusively give products **3** even if R = H. Although actual rationalization would require more sophisticated mechanistic study, we currently reason that the enamide unit in the **IIb** analogue might not be electron-rich enough to exert sufficient driving force to cleave the C–O bond. This can also be viewed from the standpoint of the limited stabilization of the resulting iminium ion next to an electron-withdrawing group if this C–O bond is cleaved. Consequently, the methoxide prefers to attack the oxonium carbon to favor path a. Finally, with 3-aryl-substituted isochromenes (R = Ar), we believe that the oxonium intermediate **IIc** is well stabilized by aryl resonance. Thus, the effective delocalization of the positive charge makes this oxonium carbon less electrophilic for nucleophilic attack by methoxide. Instead, the methoxide serves as a base to deprotonate the bridgehead hydrogen, which triggers rearomatization and C–O cleavage to form product **4′**. The more electron-deficient aryl group makes this bridgehead hydrogen more acidic, thus further favoring this pathway, which explains the trend in entries 3–5, Table 3.

To further substantiate the above rationale, we carried out some control experiments. First of all, to confirm the fate of the leaving part in the isochromene substrates when β-naphthols **3**

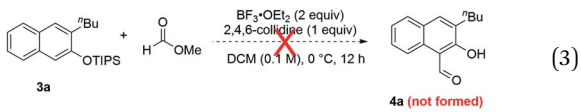


Scheme 6 Proposed mechanism.

were formed, we used a large homobenzyl group in isochromene **1p** (eqn (2)). After its reaction with **2a**, we were able to isolate ester **11**, which is consistent with path a of the proposed mechanism. Next, we also suspected that products **3** and **4** might interconvert to each other depending on the reaction conditions. To probe this possibility, a mixture of **3a** and methyl formate was treated with $BF_3{\cdot}OEt_2$ and 2,4,6-collidine, the standard conditions toward products **4** (eqn (3)). However, product **4a** was not observed at all, indicating that **3** is not an intermediate toward **4**. Similarly, subjecting **4a** and MeOH (or MeONa) to $BF_3{\cdot}OEt_2$ did not lead to the deformylation product β-naphthol **3a′**, suggesting that **4** is unlikely an intermediate in the formation of **3** (eqn (4)). These observations are consistent with the proposed mechanism, in which the product distribution is kinetically controlled by the barrier in each case and these paths are likely irreversible, but not thermodynamically controlled by product stability.



(2)



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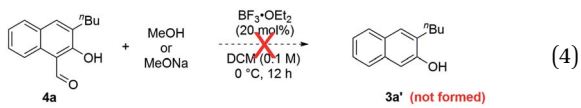

(4)

In summary, we have developed a modular strategy for the rapid synthesis of valuable β-functionalized electron-rich naphthalenes, specifically, β-naphthol, β-naphthylamine, and β-naphthyl thioether derivatives. It also represents the first systematic study of the benzannulations of versatile isobenzopyryliums with general electron-rich alkynes. With suitable choice of the isochromene substrates and the Lewis acid catalysts, different types of electron-rich alkynes, such as siloxy alkynes, ynamides, and thioalkynes, participated in the intermolecular cycloaddition reactions under mild conditions with high efficiency and complete regioselectivity. Moreover, depending on the substitution pattern of the isochromene substrates, unusual divergence toward different naphthalene products was observed, thus allowing further diversification of the naphthalene products. Control experiments provided preliminary insights into the intriguing mechanism. Further detailed investigations toward a better understanding are ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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