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Sequential C–H activation enabled expedient delivery of polyfunctional arenes†

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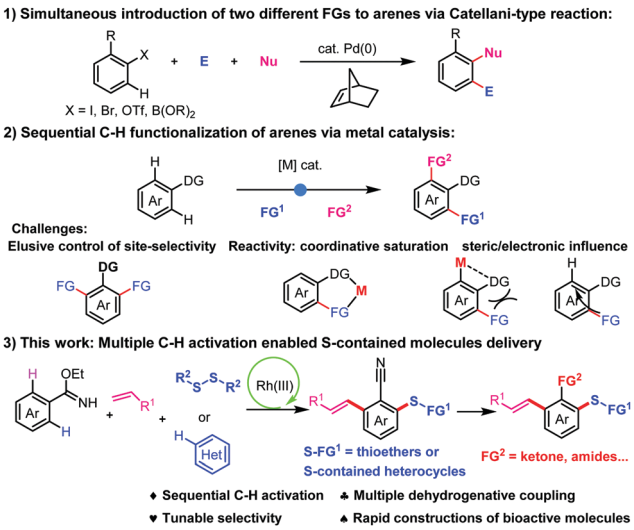
Modular construction of polyfunctional arenes from abundant feedstocks stands as an unremitting pursue in synthetic chemistry, accelerating the discovery of drugs and materials. Herein, using the multiple C–H activation strategy with versatile imidate esters, the expedient delivery of molecular libraries of densely functionalized sulfur-containing arenes was achieved, which enabled the concise construction of biologically active molecules, such as Bipenamol.

The exploration of the concise construction of synthetically valuable polyfunctional arenes holds a great synthetic promise and challenge.[1] Towards this end, the catalytic cascade reaction, using aryl halides or borons, such as the Catellani-type reaction, has emerged as one reliable strategy for a quick access to molecular complexiety.[2] In this context, sequential multiple C–H activation that features step-economy and provides a new retro-synthetic insight would be highly desirable for the direct introduction of multiple functionalities into molecules.

However, formidable challenges remain in the controllable multiple C–H activation[3] (Scheme 1): (1) elusive control of site-selectivity, which often leads to the formation of difunctionalization byproducts; (2) coordinative saturation derived from the intrinsic directing group and the first introduced functionality, leading to the deactivation of the catalyst; (3) steric and electronic influence, caused by the first C–H functionalization intermediate.

To enhance the overall synthetic practicality, the use of weak coordination would be also beneficial for the second C–H activation process, thus providing an arsenal for the modular construction of molecular libraries of multiple functionalized arenes.[4] With the above principle in mind, herein, using versatile imidate esters as the key directing groups and by the well-tuning of the catalytic systems, we developed a multiple C–H activation strategy-enabled modular access to poly-substituted arenes, enabling the multiple C–H activation of materials and



Scheme 1 Expedient delivery of polyfunctional arenes.

pharmaceuticals, and the concise construction of biologically active molecules, such as Bipenamol.

This initiative study commenced with selective C–H activation using a synthetic versatile imidate ester **1a**[5] and switchable C–H sulfenylation[6] was observed under Rh(III) catalysis[7] using Ag(I) or Cu(II) as the key additive, affording nitrile- or imidate ester-substituted thioethers **3a** or **4a** (see Table S1 in ESI† for details). Notably, the obtained 1,2-thiobenzonitriles[8] are key skeletons in pharmaceuticals, pesticides and advanced materials, while nitrile-directed C–H sulfenylation remains underdeveloped.[9] To our delight, Rh(III) exhibited an optimal result, and the use of Cu(II) salt or Ag(I) switched the selectivity for the generation of the imidate ester- or nitrile-substituted thioether product **3a** or **4a** (entries 1 and 2). The metal catalyst candidate investigation revealed that Ru(II) exhibited slightly lower yield (entry 3); however, Ir(III), Pd(II) and Ni(II) salts showed no efficiency in this transformation (entries 4–6). Control experiments indicated that the Rh(III) catalyst was indispensable (entry 7), and $AgNTf_2$

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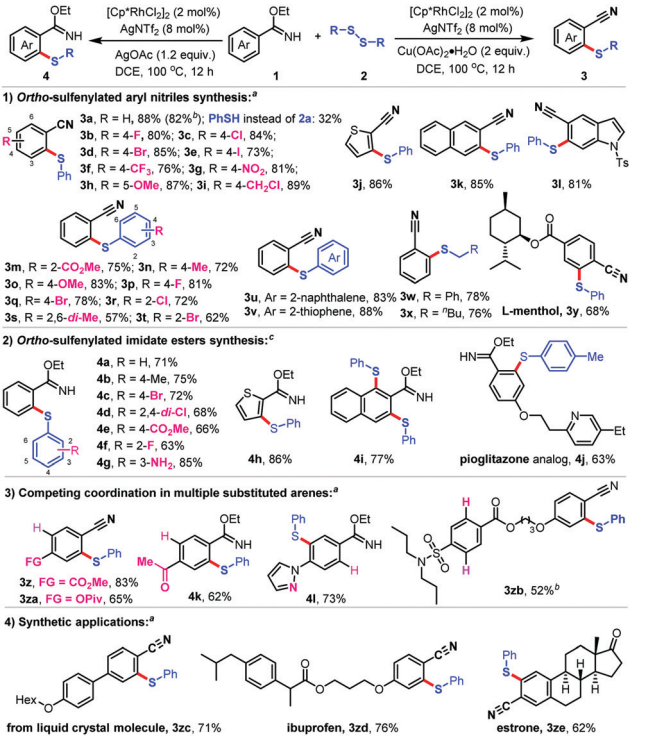
exhibited better performance than that of $AgSbF_6$ (entries 8 and 9). HOAc or PivOH performed sluggishly when they were used to replace sodium acetate (entry 10), while the Cu(II) salt was also essential for the generation of thioether **3a** (entry 12). Notably, thiol could also act as the sulfenylation reagent, albeit in a moderate yield (entry 13). 1,2-Dichloroethane was the optimal solvent, while the use of acetone or ^{t}BuOH led to a trace amount of the desired product (entry 14).

Under the optimal conditions, we explored the synthetic generality of this tunable C–H sulfenylation (Scheme 6). Great functional group tolerance was observed; halides including fluoro (**3b**), chloro (**3c**), bromo (**3d**), trifluoromethyl (**3f**) and even iodo (**3e**), were compatible, holding a great synthetic potential for the further decoration of thioether products *via* cross-couplings. Readily transformable groups, nitro (**3g**), benzyl chloride (**3i**) and methoxyl (**3h**), were also compatible. Heterocycles and fused rings were compatible in this regioselective C–H sulfenylation (**3j**, **3k**); notably, the site-selective C6–H sulfenylation of indole (**3l**) was obtained. For disulfides reagents, aromatic and aliphatic disulfides were amenable, in which ester (**3m**), methoxyl (**3o**), fluoro (**3p**), chloro (**3r**), bromo (**3q**) were well tolerated. Notably, no obvious steric effect was observed, and 2,6-disubstituted disulfides were viable sulfenylation partners (**3r**, **3s**, **3t**). Thiophene-(**3u**), naphthalene-(**3v**), benzyl-(**3w**) and pentyl (**3x**)-substituted disulfides could afford the desired products in good yields. The site-selective modification of the L-menthol derivative was also achieved (**3y**).

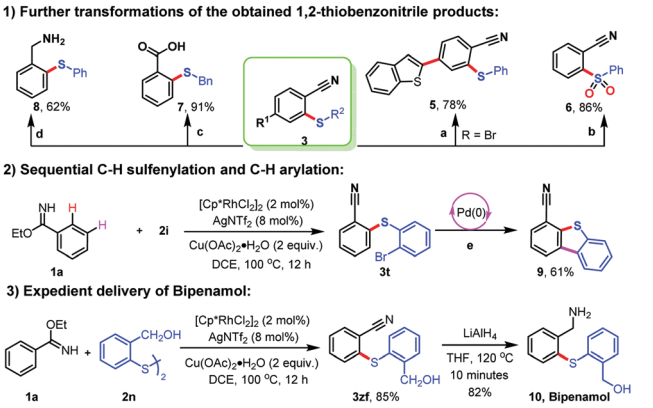
Intriguingly, the use of Ag(I) salt under Rh(III) catalysis switched the selectivity, affording thioether products **4**. Functional groups including fluoro (**4f**), chloro (**4d**), bromo (**4c**), ester (**4e**) and primary amine (**4g**) were well compatible. Heterocycle- and naphthalene-derived imidate esters (**4h**, **4i**) could afford the desired products with good efficiency. The site-selective modification of a pioglitazone analogue (**4j**) was also achieved (Scheme 2).

The site-specific C–H activation of multiple-functionalized arenes provide a valuable insight into novel drug discovery, thus accelerating the new drug discovery.[10] Competing coordination studies (Scheme 3) reveal that the imidate ester showed directing priority towards ester (**3z**), ketone (**4j**) and phenol ester (**3za**), while pyrazole overrode imidate ester (**4k**) in this site-selective C–H sulfenylation. The regio-selective modification of a probenecid analogue took place exclusively (**3zb**) with the C–H bonds proximal to sulfonamide and ester remained intact. This procedure also enabled the modification of a biaryl nitrile-type liquid crystal molecule (**3zc**), while ibuprofen (**3zd**) and estrone (**3ze**) could be decorated with nitrile and thioether functionalities.

The transformable products could serve as a versatile platform for the construction of functionalized sulfur molecular libraries (Scheme 3). For instance, the benzo[*b*]thiophene skeleton could be introduced *via* the cross-coupling of halides to afford **5**, a potential liquid crystal molecule. The oxidation of the thioether product led to sulfone **6**, and the hydrolysis of nitrile afforded carboxylic acid **7**, while benzyl amine **8** was obtained through the reduction of nitrile. Functionalized dibenzo[*b*,*d*]thiophene **9** could be accessed *via* a sequential C–H thiolation, followed by intramolecular C–H arylation.



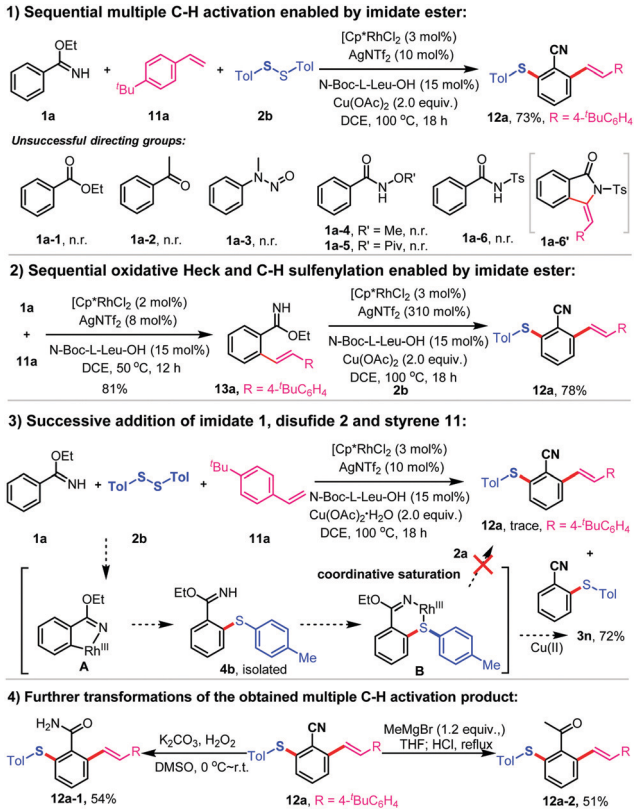
Scheme 2 Site-selective C–H sulfenylation. [a]Conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2 mol%), $AgNTf_2$ (8 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv.), DCE (1 mL), 100 °C, 12 h. [b]$Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv.) and BQ (0.5 equiv.) were used instead of $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv.). [c]With AgOAc (1.2 equiv.) instead of $Cu(OAc)_2{\cdot}H_2O$.



Scheme 3 Synthetic application. Conditions: (a) **3d** (0.1 mmol), $Pd(PPh_3)_4$ (5 mol%), 1,4-dioxane (0.1 M), $NaHCO_3$ (aq.), benzo[*b*]thiophen-2-ylboronic acid (1.1 equiv.), r.t. to reflux, 1 h; (b) **3a** (0.1 mmol), *m*CPBA (1.5 equiv.), EtOAc (0.2 M), 0 °C, 12 h; (c) **3w** (0.1 mmol), NaOH (1.5 M, 30 equiv.), ethylene glycol (0.04 M), 130 °C, overnight; HCl (2 M, 40 equiv.); (d) **3a** (0.1 mmol), $LiAlH_4$ (4 equiv.), Et_2O (0.2 M), 0 °C, 1 h; 4 M NaOH (aq.); (e) **3t** (0.3 mmol), $PdCl_2(PPh_3)_2$ (2 mol%), KOPiv (2.0 equiv.), DMA, 140 °C, 12 h.

Significantly, bipenamol **10** could be concisely obtained from commercially available thiosalicylic acid *via* the *ortho* C–H sulfenylation of the imidate ester, followed by a reduction with $LiAlH_4$, with a total 72% yield in two steps.

The switchable C–H sulfenylation stimulated us to investigate multiple C–H activation, leading to polyfunctional arenes,



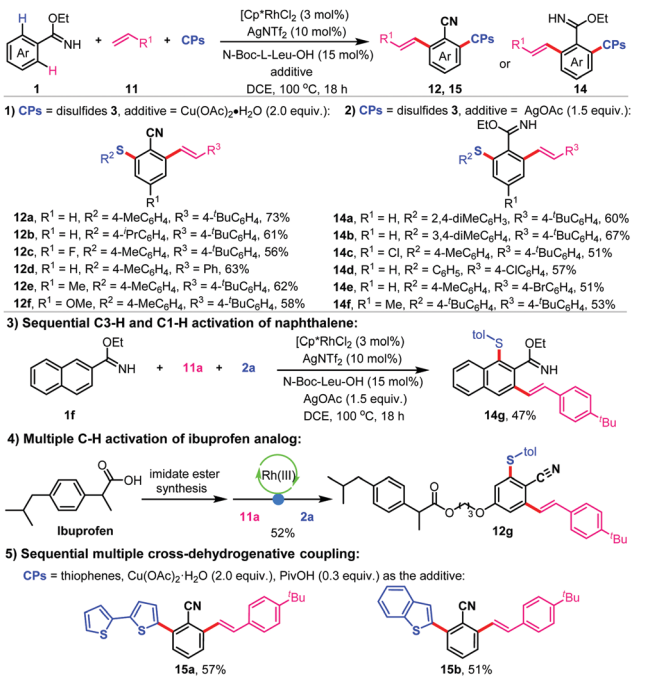
Scheme 4 Primary investigation for sequential C–H activation.

which were promising while challenging skeletons. Extensive investigation revealed that with the assistance of MPAA (mono-*N*-protected amino acid) under this Rh(III) catalysis using the imidate, multiple C–H activation was achieved (Scheme 4-1),[11] while ketone, ester, *N*-nitroso anilines or amides performed sluggishly. For N–Ts amide **1a-6**, only oxidative olefination product **1a-6′** was obtained, which exhibited no efficiency for further C–H sulfenylation (see ESI† for details). Notably, dehydrogenative olefination enabled by imidates was obtained under the Rh(III)/MPAA catalysis, affording **13a**, followed by a C–H sulfenylation under Rh(III) catalysis (Scheme 4-2). Control experiments indicated that the successive addition of imidate esters **1**, disulfides **2**, and olefin **3** into this multiple C–H activation under Rh(III) catalysis led to no desired products (Scheme 4-3). Moreover, the isolated **4** showed no reactivity in the subsequent dehydrogenative olefination under Rh(III) catalysis. It was speculated that this sequential C–H activation might proceed *via* an imidate ester-enabled C–H activation to afford rhodacycle **A**, which assisted the generation of C–H sulfenylated product **3b** by the addition of electrophilic disulfide **2**. Further interaction of thioether and intrinsic imidate ester group led to the coordinative saturation of Rh(III),[12] and thus, led to no catalytic reactivity of Rh(III) species **B**. Finally, 1,2-thiobenzonitriles product **3n** was obtained, with the treatment of base to the intermediate **3b** or **B**.

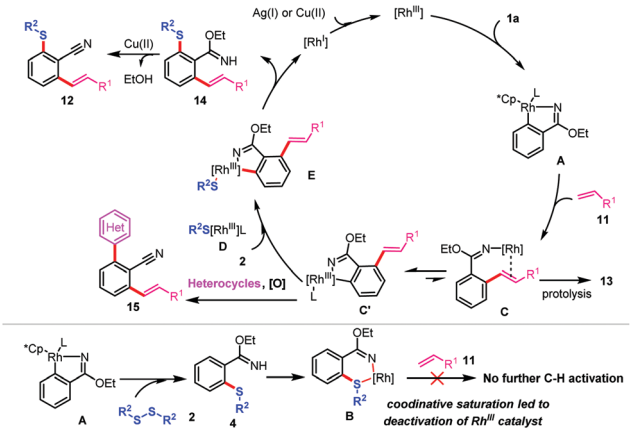
The obtained multiple-functionalized arenes could be further converted to the corresponding ketone- or amide-substituted thioethers, expediting the divergent construction of polyfunctional arenes (Schemes 4-4).

This sequential C–H activation could also be switched with Ag(I) or Cu(II) salt as the key additive, affording polyfunctional arenes **12** or **14** (Scheme 5). Further assessment of substrates indicated that an array of aryl imidate esters with methyl (**12e**, **14f**), methoxyl (**12f**), fluoro (**12c**) and chloro (**14c**) substituents could be compatible. Disulfides (**12a**, **12b**) including poly-substituted (**14b**), and even steric hindered aryl disulfides (**14a**) were viable coupling partners. Olefins (**12d**) including halide-substituted styrenes (**14d**, **14e**) were suitable substrates. Significantly, sequential C3–H olefination and C1–H sulfenylation of naphthalene were achieved with great site-selectivity, affording 1,2,3-functionalized naphthalene **14g**, which is a synthetically valuable skeleton while difficult to access. The ibuprofen analogue could also undergo this sequential C–H activation (**12g**).

The dual cross-dehydrogenative coupling (CDC) strategy provided an expedient arena for the rapid construction of molecular complexity.[13] We thus conducted further attempts for the sequential introduction of olefin and heterocycles *via* multiple C–H activation. To our delight, with the assistance of PivOH under Rh(III) catalysis, two C–C bonds were constructed through sequential aryl C–H/alkenyl C–H bond and aryl C–H/heteroaryl C–H bond activation, affording multifunctional arenes **15**, in which thiophene and benzothiophene could act as suitable partners (Scheme 5-5). Notably, biaryl nitriles are widely used liquid crystal materials, considering the readily modifiable obtained products, this procedure might find their further utilization in pharmaceuticals, agrochemicals and materials science.



Scheme 5 Sequential multiple C–H activation. Conditions: **1** (0.3 mmol), **11** (0.45 mmol), **CPs** (0.45 mmol), $[Cp^*RhCl_2]_2$ (3 mol%), $AgNTf_2$ (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv.), DCE (1 mL), 100 °C, 18 h.



Scheme 6 Proposed mechanism.

Inspired by the related precedent literature and the experimental observations, a tentative mechanism was proposed (Scheme 6). First, with the assistance of MPAA,[6,14] the C–H activation of **1a** takes place to give rhodacycle species **A**. A subsequent oxidative Heck reaction leads to intermediate **C** or **C′** *via* second C–H activation, which facilitates further reaction with sulfide species **D** generated from disulfide **2**, affording key intermediate **E**. Finally, the desired multiple C–H activation products **12** or **14** are obtained *via* C–S bond formation, and the re-oxidation of the released Rh(I) species by Ag(I) or Cu(II) oxidant. With key intermediate **C**, the dual cross-dehydrogenative coupling of the imidate ester with arene and terminal olefins can also proceed with the assistance of PivOH and the oxidant, affording multiple-functionalized products **15**.

Notably, when disulfides **2** were subjected into the reaction prior to terminal olefins **11**, C–H sulfenylation occurred affording **4**. However, the coordinative saturation of the imidate and thioether group to Rh(III) led to the deactivation of the Rh(III) catalyst, and thus, no second C–H activation proceeded.

In summary, by the judicious choice of versatile imidate esters as the key directing groups and through well tuning of the catalytic systems, sequential C–H activation was developed, leading to polyfunctional arenes. This transformation enabled the multiple C–H modification of pharmaceuticals and advanced material analogues, and the concise construction of biologically active molecules. Further endeavor towards the expedient delivery of functionalized pharmaceuticals and materials *via* sequential C–H activation is underway.

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Conflicts of interest

There are no conflicts to declare.

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