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Synthesis of Substituted Naphtho[1,8-*bc*]thiopyrans by Sulfhydryl-Directed Rhodium-Catalyzed *peri*-Selective C−H Bond Activation and Cyclization of Naphthalene-1-thiols

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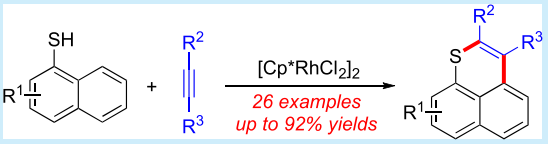
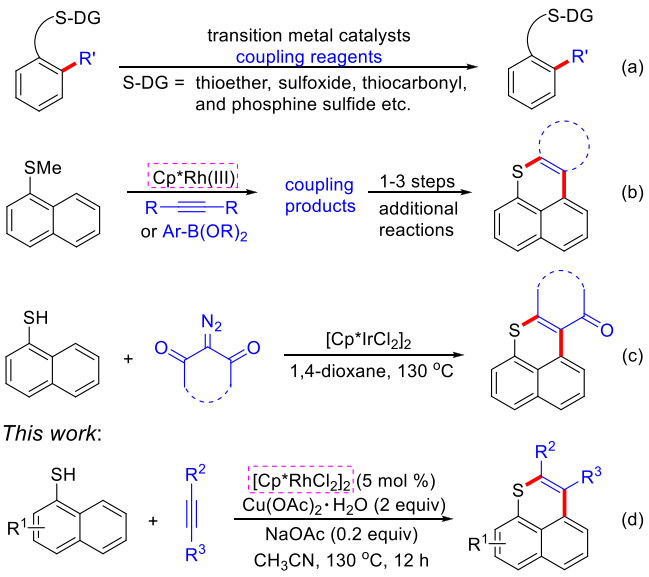
ABSTRACT: The sulfhydryl-directed *peri*-selective C−H bond activation and tandem cyclization of naphthalene-1-thiols with alkynes proceed efficiently. Most products of naphthothiopyrans with various substituents are achieved in good yields under rhodium catalysis. This protocol has some advantages over the traditional methods in synthesizing naphtho[1,8-*bc*]thiopyrans in terms of stable coupling substrates, simple operation, *peri*-selectivity, and atom and step economy.



In the past decades, C−H bond activation has developed rapidly, which efficiently constructs a variety of organic molecules without the need to convert C−H bonds into other functional groups.[1] Directing groups have a marked impact on these reactions, and they may affect the yields of reactions, control the reaction sites, or even determine whether the reactions can proceed efficiently.[2] Among various guiding groups, sulfur-containing groups are a common type of directing group, which can promote the construction of sulfur-containing compounds.[3] However, most of the currently reported sulfur-containing groups such as thioether,[4] sulfoxide,[5] thiocarbonyl,[6] and phosphine sulfide[7] directed C−H bond activations usually produce the sulfur-containing open chain products (Scheme 1a). In this case, directing groups of these reactions are introduced into the products as substituents, making it generally difficult to remove. Unlike these sulfur-containing directing groups, sulfhydryl can undergo further cyclization with corresponding coupling products through some elementary reactions such as reduction elimination and dehydration condensation when it is used as the directing group.[8] As a result, sulfhydryl can be employed as part of the products and facilitate the construction of sulfur-containing heterocyclic compounds. Although sulfhydryl is the simplest and widely existing sulfur-containing group,[9] the C−H bond activations aided by sulfhydryl are rarely reported. Therefore, the creation of sulfhydryl-directed C−H functionalization protocols involving diverse metals and multiple coupling parts is urgently needed.

Naphtho[1,8-*bc*]thiopyrans have received extensive attention due to their broad functional properties.[10] However, investigations on the synthetic methods of such motifs are rather limited.[11] Recently, the team of Miura reported the coupling reactions of alkynes or aryl boronates with 1-(methylthio)naphthalenes under rhodium catalysis. The coupling products can be converted into naphtho[1,8-*bc*]-thiopyrans through additional reactions in 1−3 steps (Scheme 1b).[12] Very recently, we have reported a sulfhydryl-directed *peri*-selective C−H activation and annulation of naphthalene-1-

Scheme 1. C−H Activations Aided by Sulfur-Containing Groups



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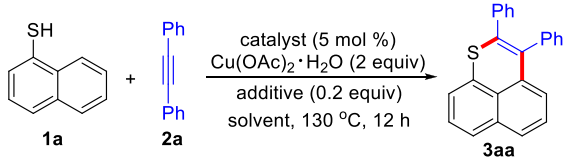
thiols using diazo compounds under iridium catalysis (Scheme 1c).[8] Although it is convenient and efficient, the possible dangers caused by the exothermic phenomenon when releasing nitrogen and low stability of diazo compounds might be difficult to avoid. With these background factors in mind and combined with previous reports in the *peri*-selective C−H activation of naphthalene,[13] we herein seek to build naphtho-[1,8-*bc*]thiopyrans through sulfhydryl-directed C−H activation and cyclization of 1-naphthylthiophenols with alkynes under rhodium catalysis (Scheme 1d). This method has some advantages over the traditional methods in stable coupling substrates, simple operation, *peri*-selectivity, and atom and step economy. To the best of our knowledge, we have initially reported the sulfhydryl-directed C−H functionalization under rhodium catalysis.

Initially, naphthalene-1-thiol (**1a**) reacted with 1,2-diphenylethyne (**2a**) accompanied by $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2\cdot H_2O$ in DMF at 130 °C under a nitrogen atmosphere for 12 h, and product 2,3-diphenylbenzo[*de*]thiochromene (**3aa**) was achieved in 46% yield (Table 1, entry 1). Regarding additives,

Table 1. Optimization Studies[a]



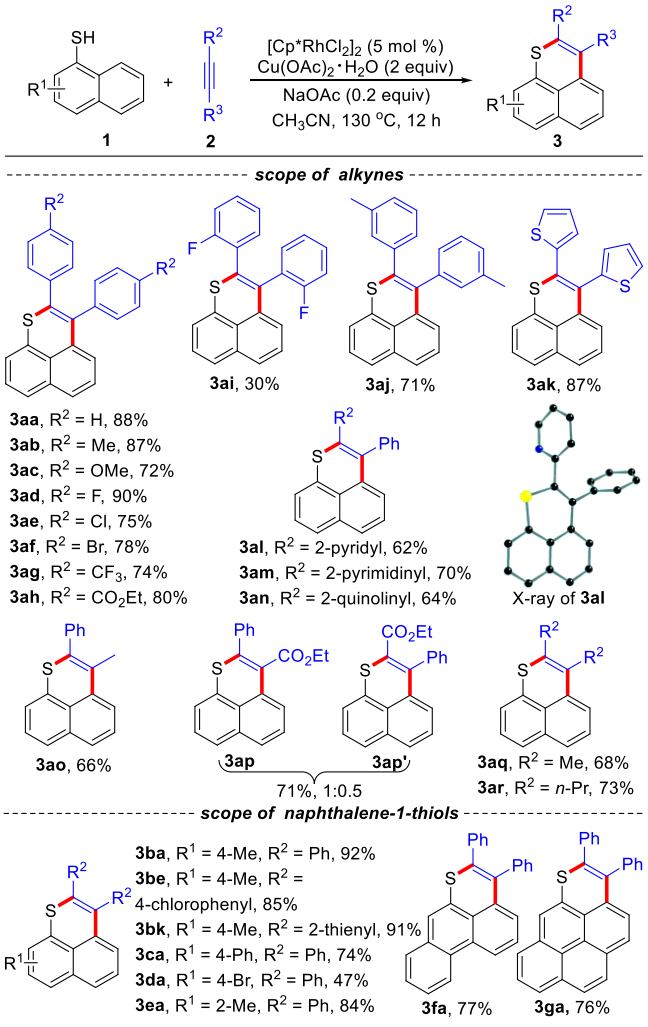
entry	catalyst	additive	solvent	yield[b] (%)
1	$[Cp^*RhCl_2]_2$		DMF	46
2	$[Cp^*RhCl_2]_2$	NaOAc	DMF	73
3	$[Cp^*RhCl_2]_2$	KOAc	DMF	69
4	$[Cp^*RhCl_2]_2$	CsOAc	DMF	47
5	$[Cp^*RhCl_2]_2$	HOAc	DMF	34
6	$[Cp^*RhCl_2]_2$	NaOAc	DMSO	15
7	$[Cp^*RhCl_2]_2$	NaOAc	1,4-dioxane	76
8	$[Cp^*RhCl_2]_2$	NaOAc	CH_3OH	20
9	**$[Cp^*RhCl_2]_2$**	**NaOAc**	**CH_3CN**	**88**
10	–	NaOAc	CH_3CN	0
11	$Cp^*Co(CO)I_2$	NaOAc	CH_3CN	0
12	$[Cp^*IrCl_2]_2$	NaOAc	CH_3CN	18
13	$[(p\text{-cymene})RuCl_2]_2$	NaOAc	CH_3CN	7

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (5 mol %), $Cu(OAc)_2\cdot H_2O$ (2 equiv), additive (0.2 equiv), solvent (1.5 mL), 130 °C, 12 h, under N_2. [b]Isolated yields.

NaOAc gave the highest yield (73%) (entries 2−5). Then, several solvents including DMSO, 1,4-dioxane, CH_3OH, and CH_3CN were tested, and CH_3CN proved to be the most appropriate solvent for this conversion (entries 2, 6−9). No product was obtained or the yields of **3aa** were not higher than 18% when no $[Cp^*RhCl_2]_2$ or other catalysts were used (entries 10−13).

Under the optimized conditions, the scope and generality of substrates were investigated (Scheme 2). Initially, the universality of alkynes was studied. When some symmetric diarylacetylenes with various substituents at different phenyl positions were treated with naphthalene-1-thiol (**1a**), low to good yields (30−90%) of naphtho[1,8-*bc*]thiopyrans (**3aa**−**3aj**) were achieved. Meanwhile, heterocyclic alkyne 1,2-di(thiophen-2-yl)ethyne (**2k**) participated in this conversion, affording **3ak** in 87% yield. When **1a** was treated with

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2\cdot H_2O$ (2 equiv), NaOAc (0.2 equiv), CH_3CN (1.5 mL), 130 °C, 12 h, under N_2, isolated yield.

unsymmetrical heterocyclic aromatic alkynes 2-(phenylethynyl)pyridine (**2l**), 2-(phenylethynyl)pyrimidine (**2m**), and 2-(phenylethynyl)quinoline (**2n**) respectively, three regioisomeric products (**3al**−**3an**) with heterocycle adjacent to the S atom were obtained in 62−70% yields. This may have resulted from the complexation between the N atom of alkynes and rhodium in the coordination and migratory insertion process. The reaction involving alkyl aryl alkyne 1-phenyl-1-propyne (**1o**) proceeded smoothly and provided a single product **3ao** in 66% yield. This is due to the high regioselective insertion of alkynes with the phenyl-substituted carbon atom close to the heteroatom.[14] **3al** was verified by the analysis of single-crystal X-ray diffraction (CCDC 2019641). Products **3am**, **3an**, and **3ao** exclude another isomer through their $^1H-^1H$ NOESY spectra. However, a mixture (1:0.5) of products **3ap** and **3ap′** was obtained with a total yield of 71% when naphthalene-1-thiol (**1a**) reacted with another unsymmetrical alkyne ethyl 3-phenylpropiolate (**2p**). When the reaction conditions such as oxidants, additives, solvents, and reaction temperature are changed, the selectivity of the mixture was not significantly improved (**3ap**:**3ap′** ≈ 1:0.5, 0−69% yields). In addition, some

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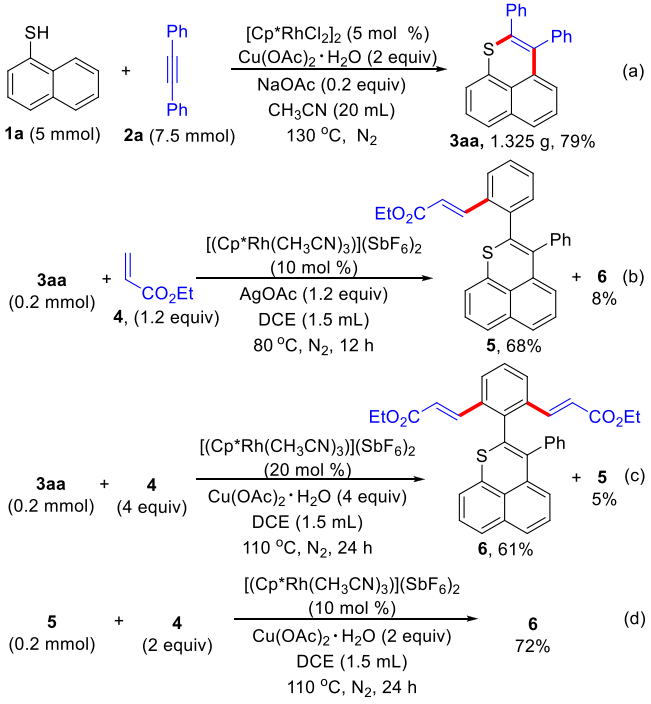
reactions involving open-chain alkynes can occur smoothly, and the target compounds can be obtained in 68−73% yields. Unfortunately, the reaction between ethynylbenzene and **1a** failed to afford any naphthothiopyrans.

Moreover, this protocol was applied to various substituted naphthalene-1-thiols (**1b**−**1e**). As expected, moderate to high yields can be expected successfully for naphtho[1,8-*bc*]-thiopyran derivatives. Among them, electron-rich naphthalene-1-thiols reacted nicely with alkynes and afforded products (**3ba**−**3ca**, **3ea**) in 74−92% yields. However, product **3da** was obtained in moderate yield (47%), when 4-bromonaphthalene-1-thiol (**1d**) bearing an electron-withdrawing group was tested. Much to our delight, the reactions between **2a** and phenanthrene-9-thiol (**1f**) or pyrene-1-thiol (**1g**) could proceed smoothly with products of **3fa** and **3ga** in 77% and 76% yields, respectively. However, no corresponding product was obtained when 4-methylbenzenethiol reacted with **2a**. This may be because the four-membered rhodacycle intermediate formed by the reaction of 4-methylbenzenethiol and the rhodium catalyst is unstable, which is not conducive to the occurrence of C−H activation.

Next, the synthetic potential was explored. Initially, the gram-scale reaction achieved **3aa** in 79% yield (Scheme 3a).

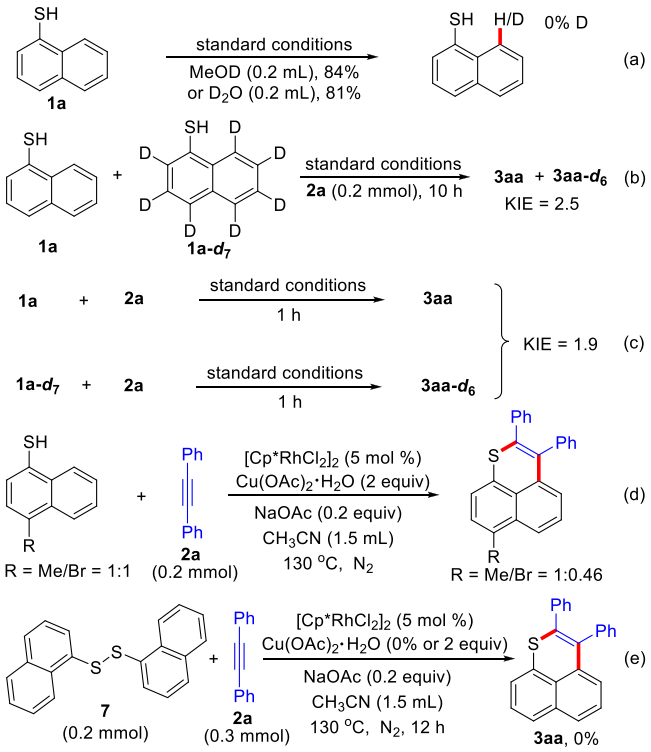
Scheme 3. Synthetic Applications of 3aa



Then, sulfur-directed C−H olefination reactions of **3aa** happened smoothly, and the olefination product ethyl (*E*)-3-(2-(3-phenylbenzo[*de*]thiochromen-2-yl)phenyl)acrylate (**5**) was mainly obtained in 68% yield (Scheme 3b). In addition, an 8% yield of the diolefination product **6** (diethyl 3,3′-(2-(3-phenylbenzo[*de*]thiochromen-2-yl)-1,3-phenylene)(2*E*,2′*E*)-diacrylate) was formed in the reaction. By changing the oxidant to $Cu(OAc)_2{\cdot}H_2O$ and adjusting the ratio of reactants, reaction temperature, and time, the diolefination product **6** could be mainly achieved in 61% yield (Scheme 3c). In addition, compound **5** can be converted to **6** with a yield of 72% under rhodium catalysis (Scheme 3d). These examples demonstrate the value of this protocol in the construction of naphtho[1,8-*bc*]thiopyrans.

Furthermore, several mechanistic experiments have been conducted. First, 81−84% yields of **1a** were recovered in the hydrogen−deuterium exchange experiments, showing no H/D exchange (Scheme 4a). It should disclose that the C-8 position

Scheme 4. Mechanism Research Experiments



C−H bond cleavage of naphthalene-1-thiol might follow an irreversible process. Second, the deuterium competition reaction (Scheme 4b) and two parallel independent reactions (Scheme 4c) of substrates **1a** and **1a**-d_7 were carried out, manifesting k_H/k_D values of 2.5 and 1.9, respectively. Both results indicate that the rate-determining step might involve the *peri*-selective C−H bond cleavage of naphthalene-1-thiol. Third, the ^{1}H NMR spectrum of the intermolecular competition experiment between 4-methylnaphthalene-1-thiol (**1b**) and 4-bromonaphthalene-1-thiol (**1d**) shows a ratio of products **3ba** and **3da** of 1:0.46, suggesting that this protocol might favor the electron-rich naphthalene-1-thiols (Scheme 4d). Finally, 1,2-di(naphthalen-1-yl)disulfane (**7**) was used as a substrate to react with **2a** under standard conditions or in the absence of $Cu(OAc)_2{\cdot}H_2O$, and no **3aa** was produced in both reactions (Scheme 4e). This experiment ruled out the possibility that naphthalene-1-thiols were first oxidized to disulfides and then participated in the cyclization reactions.

Based on the above results and referring literatures[8,15] a possible mechanism is thereby proposed (Scheme 5). At the beginning, the conversion of $[Cp^*RhCl_2]_2$ to $Cp^*Rh(OAc)_2$ might occur under treatment of $^-$OAc, and then the active catalyst $Cp^*Rh(OAc)_2$ might participate in the process of *peri*-selective C−H bond activation of **1a** to yield the intermediate **A**.[16] Further, the coordination of diphenylacetylene (**2a**) with intermediate **A** generates complex **B**. Migratory insertion of diphenylacetylene into Rh−C bond affords intermediate **C**. Subsequently, the final product 2,3-diphenylbenzo[*de*]-

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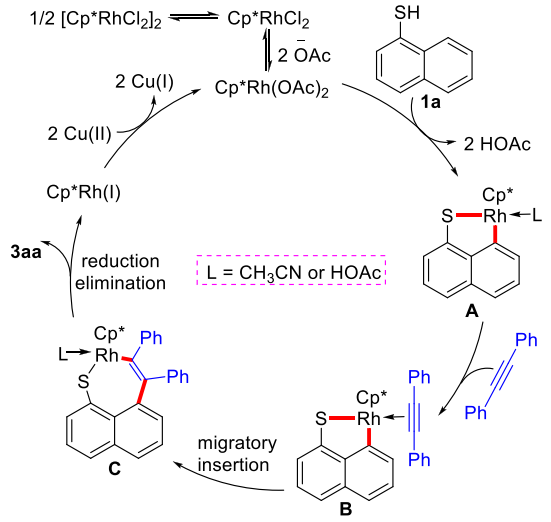
Scheme 5. Proposed Mechanistic Pathway



thiochromene (**3aa**) and Rh(I) species would be thus obtained by reductive elimination of **C**. The catalytic cycle would be completed through the oxidation of Rh(I) to regenerate the $Cp^*Rh(OAc)_2$ species with the aid of a copper oxidant.

To summarize, a new method has been proposed for the convenient and efficient preparation of substituted naphtho-[1,8-*bc*]thiopyrans via the sulfhydryl-directed *peri*-selective C−H bond activation of diverse naphthalene-1-thiols with alkynes under the catalysis of rhodium. Also, the regioselective products can be synthesized in good yields with multiple substituents. In particular, several synthetic applications as well as the mechanistic investigation have been conducted. The detailed mechanism and extensive applications of this approach will be studied for the construction of organic optoelectronic materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02703.

Full experimental procedures, characterization and NMR spectra of products (PDF)

Accession Codes

CCDC 2019641 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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