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Utilization of sulfur function in directed catalytic C-H transformation: site-selective substitution on indole and naphthalene skeletons

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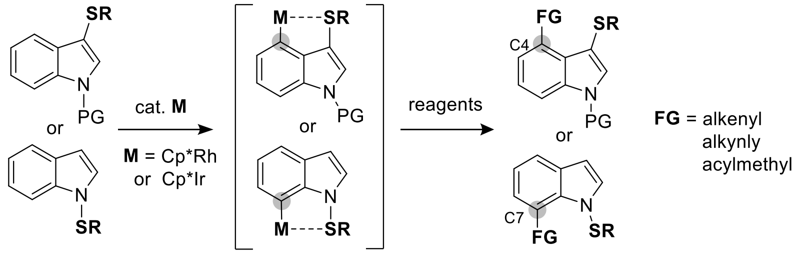
Abstract

Sulfur-containing functional groups, among various coordinating functions, have recently attracted attention as useful directing groups for the direct catalytic C-H transformation of aromatic and heteroaromatic compounds. Herein we briefly summarize our recent work on the site-selective substitution on indole and naphthalene skeletons using thioether directing groups under either Cp*Rh(III) or Cp*Ir(III) catalysis. The thioether groups can readily be removed and transformed to other functional groups. The reactions developed appear to be of importance in pharmaceutical and materials chemistry.

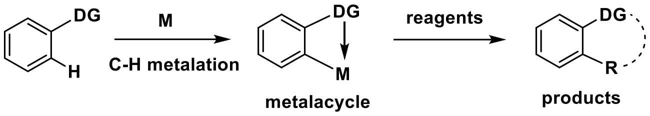
Graphical abstract



Keywords C-H transformation; Thioether; Indole; Rhodium; Iridium

Introduction

The directed catalytic C-H transformation of functionalized (hetero)arenes is currently recognized to be a potent strategy in organic synthesis as it realizes various regioselective (hetero)aromatic substitution reactions in atom- and step-economic manners (Scheme 1).[1] The ortho-substituted or annulated products together with the directing group are usually obtained.



Scheme 1. Schematic concept of directed catalytic C-H transformation.

We have been developing various aromatic C-H transformation reactions under transition metal catalysis.[2] In 2007, we disclosed that a Cp*Rh(III) (Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl) complex or its Ir(III) analog (M = Cp*Rh or Cp*Ir) can be effective catalyst for the oxidative C-H coupling of aromatic acids (DG = COOH) with alkenes and alkynes.[3] Since then, the Cp*-complexes have proved to be highly versatile catalysts for the C-H transformation reactions of various functionalized arenes through the efforts of many research groups including ours.[4]

Meanwhile, indoles and their derivatives are privileged heteroaromatic motifs because of substantial importance in pharmaceutical and materials chemistry.[5] The indole core has six different reaction sites, and thus, it has been a challenging scaffold to develop methods for selective aromatic C-H transformations (Figure 1).[6] The electron-rich C2 and C3 sites in the pyrrole moiety are inherently reactive and there have been many reports on the direct substitution of the sites. In contrast, the benzenoid moiety of indole is less reactive than the pyrrole moiety and the utilization of suitable directing groups has been the major strategy for achieving the substitution on the benzenoid ring.

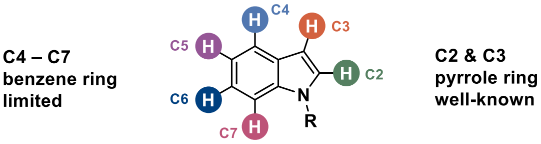
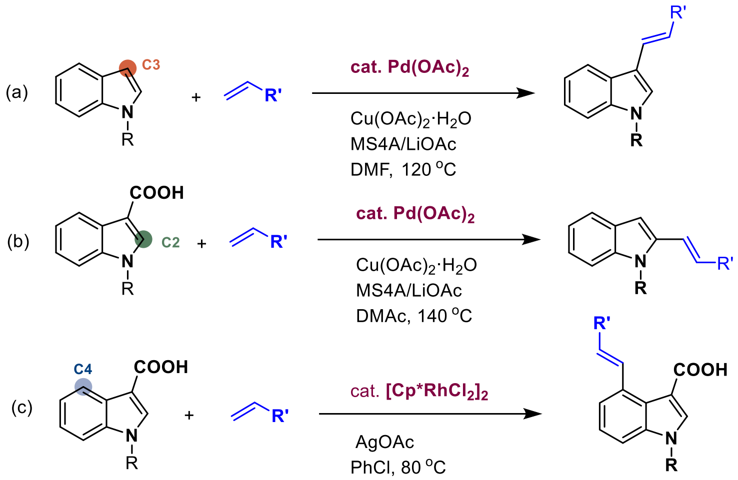


Figure 1. Reaction sites of indole.

We previously reported that 1-substituted indoles undergo Fujiwara-Moritani-type oxidative alkenylation at the most electron-rich C3 position under Pd(II) catalysis, whereas the C2 position is alkenylated using the C3-carboxylic directing function along with spontaneous decarboxylation under the similar reaction conditions (Scheme 2a,b).[7] Interestingly, the indole-3-carboxylic acids are selectively alkenylated at the

C4 position under Cp*Rh(III) catalysis with the directing group intact (Scheme 2c).[8] These results suggest that the site selectivity depends on not only the directing group, but also the catalytic species, which is probably due to the stability and reactivity of the possible metalacyclic intermediates formed through C-H bond activation.



Scheme 2. Examples of oxidative alkenylation of indoles at C2, C3, and C4 positions.

Recently, sulfur-containing functional groups such as thioether, sulfoxide, sulfone, thioketone, and thioamide, besides common oxygen- and nitrogen-containing groups, have attracted attention as removable and transformable directing groups.[9] In the context of our work of S-containing function-directed Cp*Rh(III)/Cp*Ir(III) catalysis,[10] we envisioned that thioethers could act as useful directing groups for the C-H functionalization of indoles: The C3 and N1 alkylthiolated indoles, which are readily prepared by electrophilic alkylthiolation, would undergo selective substitution at the C4 and C7 positions, respectively, via relatively stable 5-membered metalacycle intermediates rather than the corresponding 4-membered intermediates (Figure 2a,b).[11] Indeed, we could develop the regioselective alkenylation, alkynylation, and acylmethylation reactions. Additionally, we applied this concept to the selective peri-substitutions of naphthalene as the structurally relevant aromatic carbocycle (Figure 2c). These C-H transformation reactions are briefly summarized in this article.

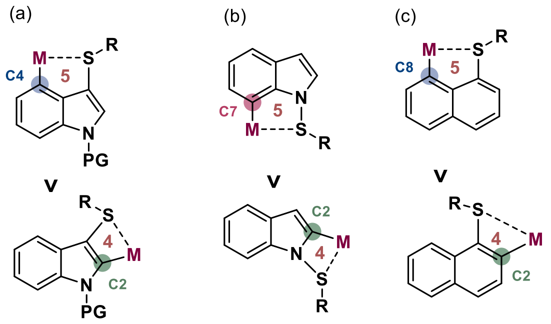
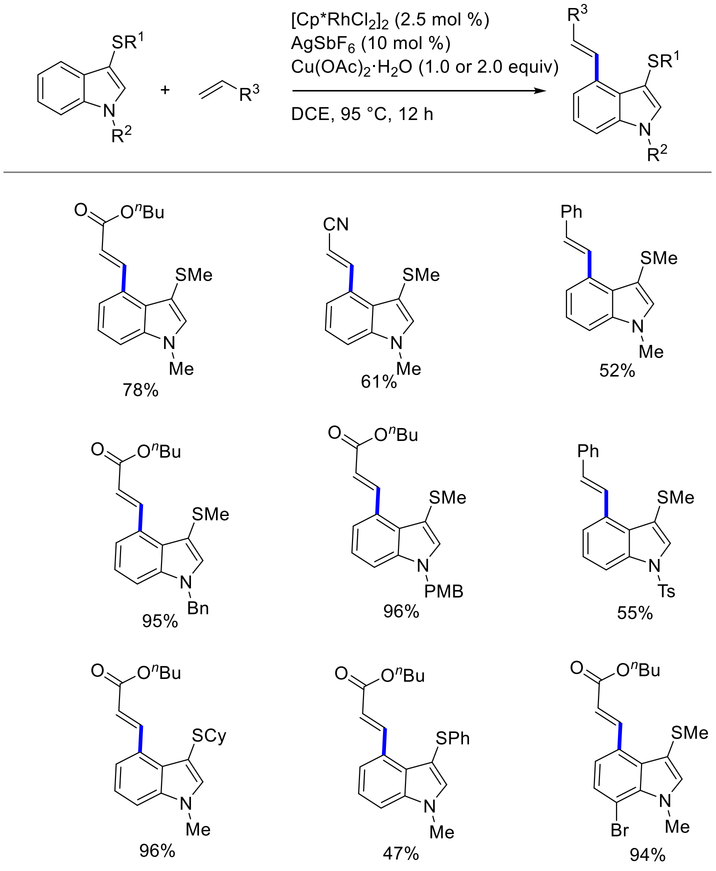


Figure 2. Possible metalacyclic intermediates using thioether directing groups.

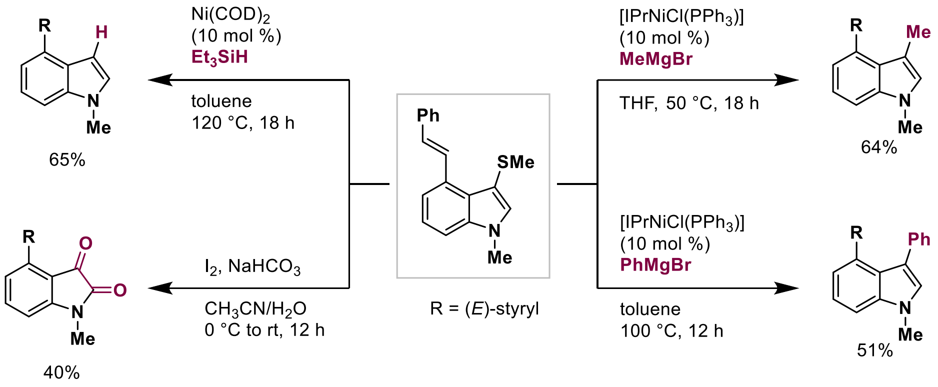
Alkenylation

1-Methyl-3-(methylthio)indole was found to react with butyl acrylate selectively at the C4 position in the presence of a Cp*Rh catalyst using $Cu(OAc)_2$ as the terminal oxidant (Scheme 3).[12] Acrylonitrile and styrene could be used as the alkene coupling partners. The N-substituent could be replaced by Bn, PMB, and Ts groups. The thioether function could be CyS and PhS in place of MeS. The 7-bromo group was intact during the coupling event, and it may be used as further derivatizations.



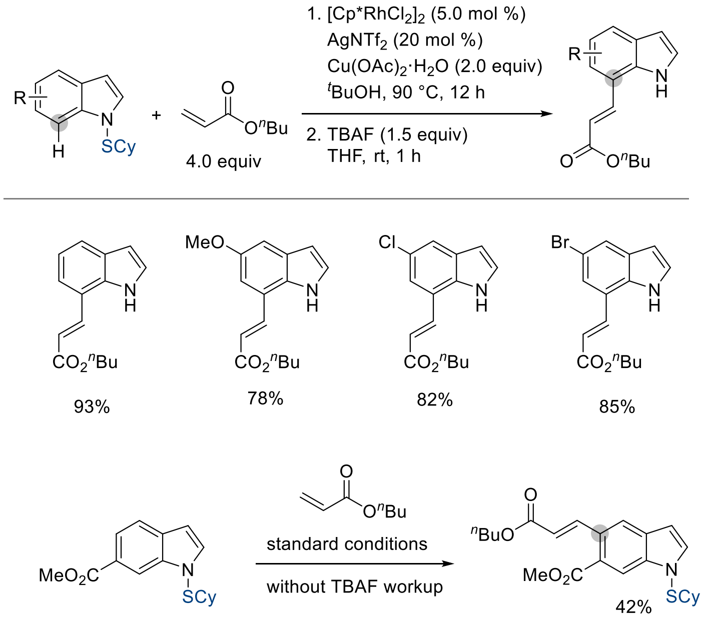
Scheme 3. C4 alkenylation of 3-alkylthioindoles.

Some transformation reactions of a C4-styrylated product are shown in Scheme 4. The MeS function could be reductively and oxidatively removed, and also replaced by Me and Ph groups using the corresponding Grignard reagents.[13]



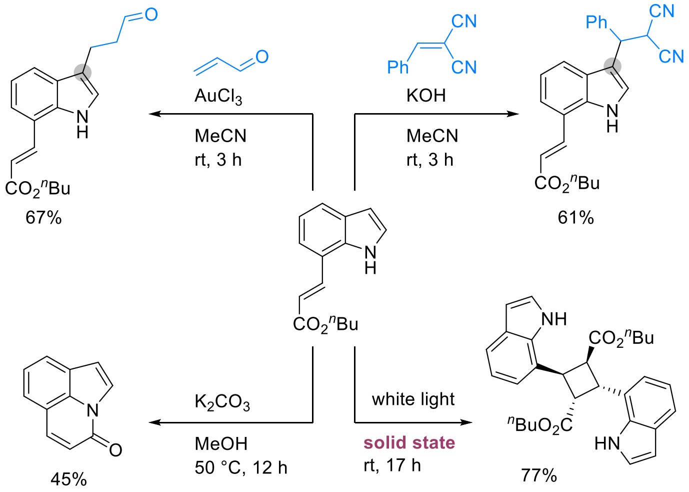
Scheme 4. Transformation of 1-methyl-4-styryl-3-thiomethyl-indole.

The C7 alkenylation with acrylate esters was accomplished effectively by using the N-SCy directing function (Scheme 5),[14] while using MeS was less effective and PhS did not work (not shown). The CyS group could be easily removed by treatment with TBAF after the oxidative coupling and the reaction products were obtained as the NH-free compounds. Various substituents on the C5 position were tolerable. The C6 methyl ester substituent on the indole core exceptionally induced the C5 alkenylation, probably due to steric reasons.



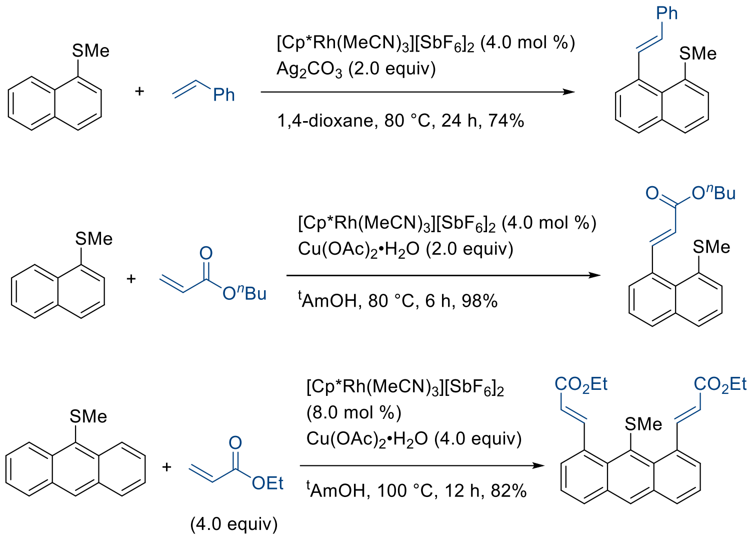
Scheme 5. Reaction of 1-cyclohexylthioindoles with butyl acrylate.

Some transformation reactions of an indolylacrylate product are shown in Scheme 6.[14] The free C3 position could be substituted with suitable alkenes under acidic or basic conditions. It could be cyclized under basic conditions to give a tricyclic compound. It was of quite interest to observe that the product was dimerized stereospecifically to give a cyclobutane derivative upon irradiation of white light to the solid state.



Scheme 6. Transformation of butyl 2-(7-indolyl)acrylate.

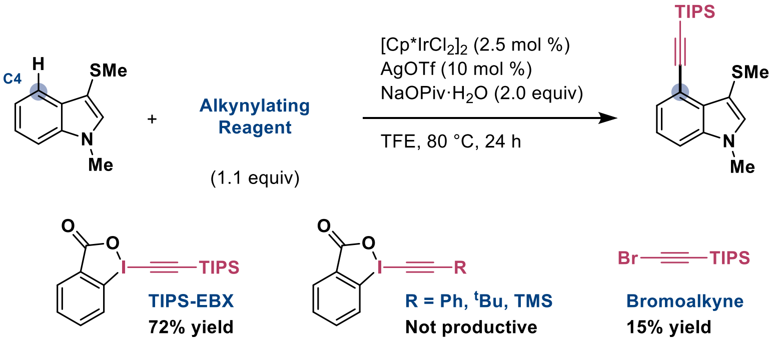
1-Methylthionaphthalene underwent oxidative alkenylation at the peri(C8)-position with styrene and acrylate esters as anticipated. 9-Methylthioanthracene was doubly alkenylated at the C1 and C8 positions (Scheme 7).[15]



Scheme 7. Alkenylation of 1-methylthionaphthalene and 9-methylthioanthracene.

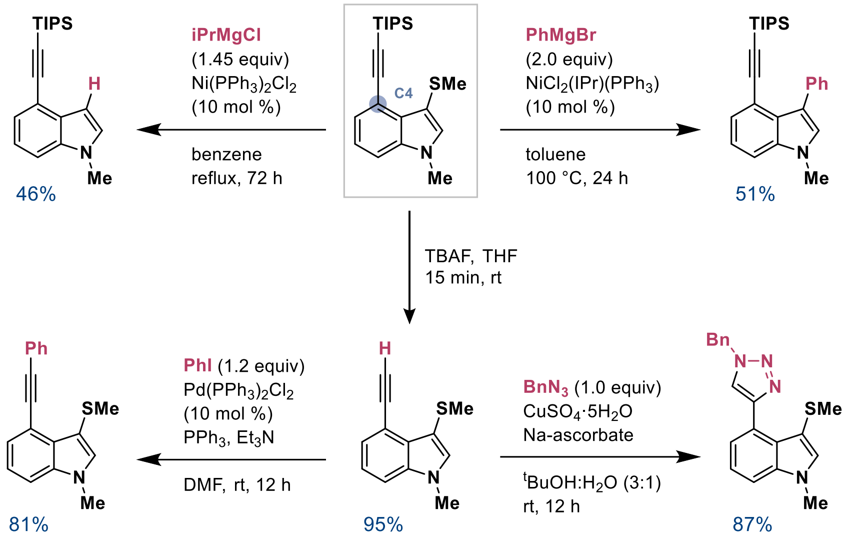
Alkynylation

The reaction of 1-methyl-3-(methylthio)indole effectively proceeded at the C4 position with TIPS-EBX[16] as the alkynylating reagent in the presence of a Cp*Ir catalyst.[17] Other EBX reagents and bromoalkynes did not work or were less effective (Scheme 8). The related Cp*Rh catalysts did not work for this reaction.



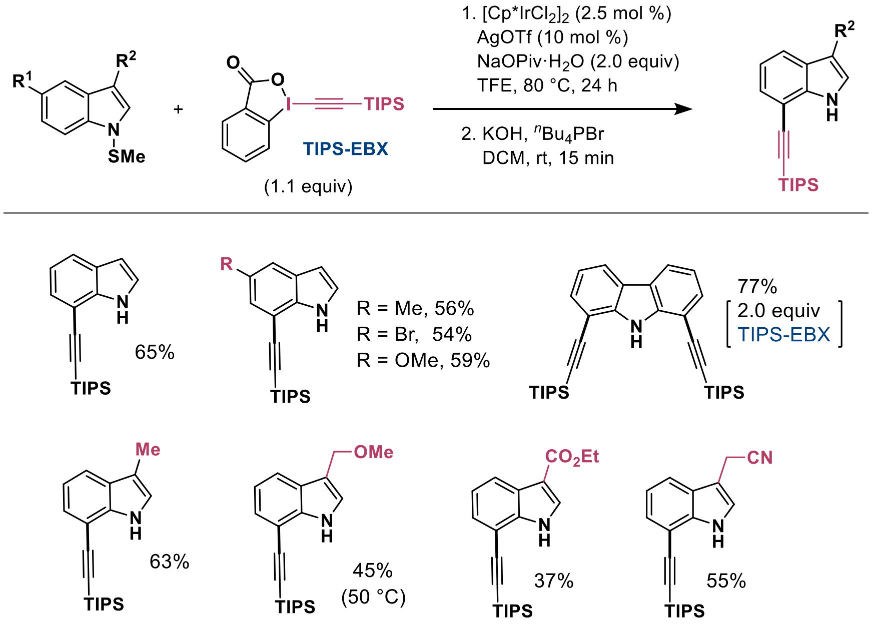
Scheme 8. Alkynylation of 1-methyl-3-methylthioindole.

The MeS group in the C4 alkynylated product could be removed or replaced by phenyl group. The TIPS group was smoothly removed by treatment with TBAF and the terminal alkyne moiety formed underwent Sonogashira coupling and Click 1,3-dipolar addition (Scheme 9).



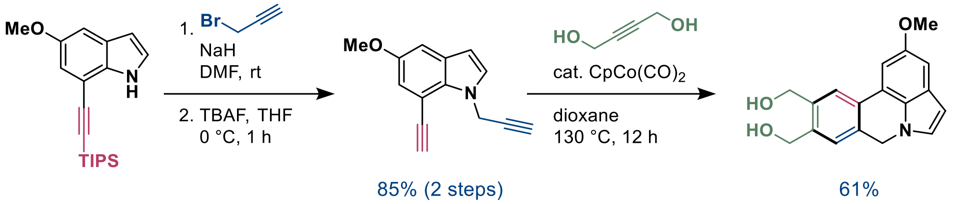
Scheme 9. Transformation of a 4-alkynylated indole.

The C7 alkynylation of N-SMe indoles was also successfully accomplished with TIPS-EBX under the Ir-catalysis (Scheme 10).[17] Part of the SMe group was eliminated under the rection conditions and the NH free products were exclusively obtained by a basic treatment after the alkynylation. Various C5 and C3 substituents were tolerable. The N-SMe carbazole underwent double alkynylation at the C1 and C8 positions as anticipated.



Scheme 10. C7 alkynylation of 1-methylthioindoles.

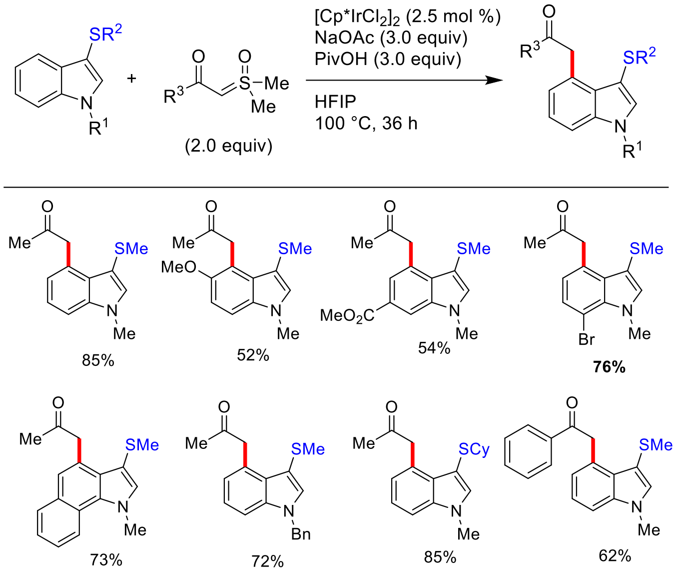
The C7 alkynylated indole with C-5 methoxy substituent could be transformed to a natural product-like 4-ring system through base assisted N-propargylation, desilylation, and catalytic [2+2+2] cyclization with 2-butyn-1,4-diol (Scheme 11).[18]



Scheme 11. Synthesis of an alkaloid-like multi-ring compound.

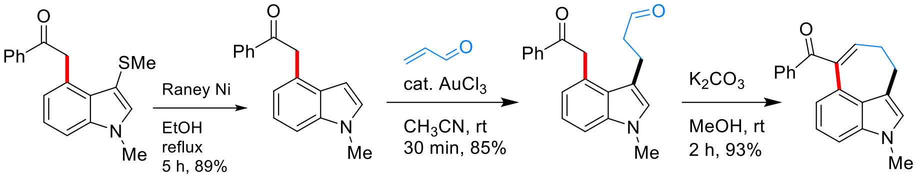
Acylmethylation

The C4 acylmethylation of 3-alkylthioindoles occurred effectively with α-carbonyl sulfoxionium ylides[19] under Cp*Ir catalysis.[20] This kind of reaction is considered to involve carbenoid species.[19] A number of electron-donating and electron-withdrawing C5, C6, and C7 substituents were tolerable (Scheme 12).



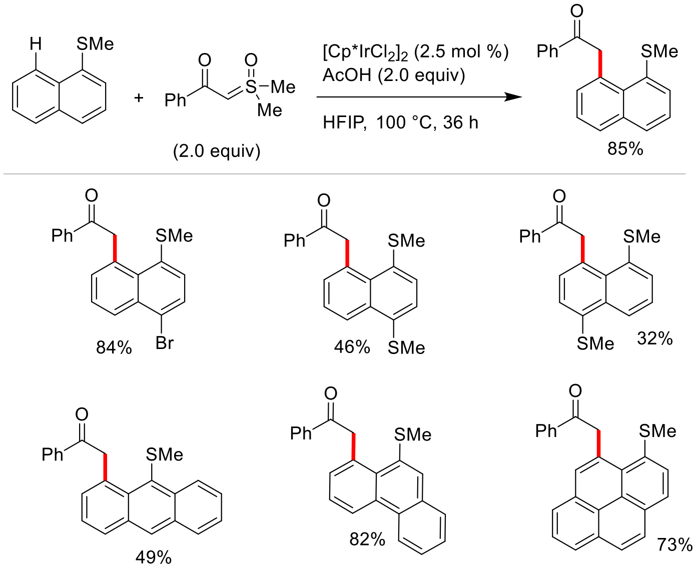
Scheme 12. C4 acylmethylation of 3-alkylthioindoles.

A benzoylmethylated product was efficiently transformed to a natural product-like 5,6,7-three ring system by reductive desulfurization, catalytic alkylation with acrolein,[21] and aldol cyclization (Scheme 13).



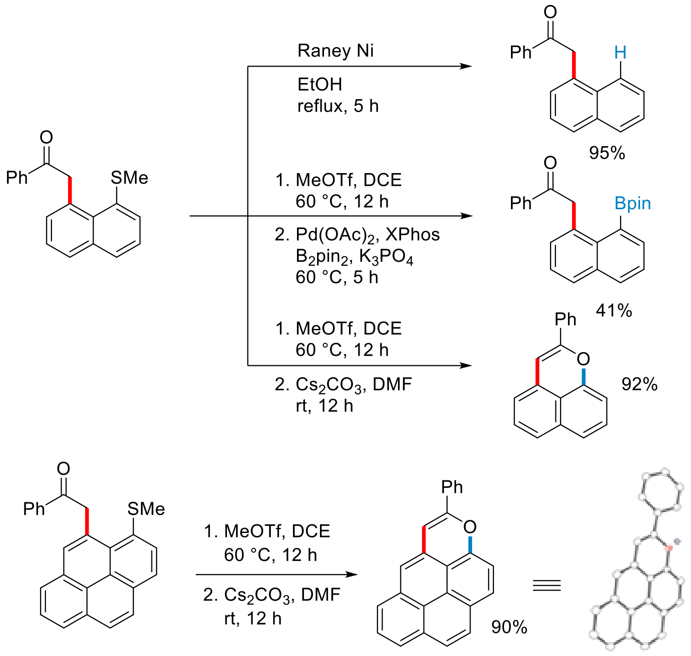
Scheme 13. Construction of a natural product-like 5,6,7-three ring system.

While the optimization studies of C7 acylmethylation of indole core have not been finished, the reaction of 1-methylthionaphtalene at the C8 position was found to proceed effectively under Cp*Ir catalysis (Scheme 14).[22] The C4 bromo function was intact and it can be used for further derivatizations. The 1,4- and 1,5-dimethylthionaphthalenes underwent only mono acylmethylation even with 2 equiv of the ylide, while the reason is unclear. On the other hand, not only naphthalene, but also anthracene, phenanthrene, and pyrene skeletons were the suitable scaffolds for the reaction.



Scheme 14. Benzoylmethylation of 1-methylthionaphtalene and related substrates.

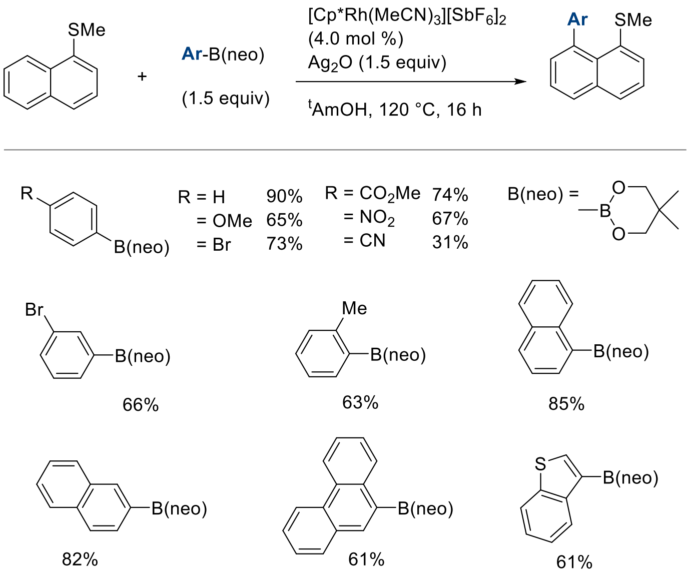
The methylthio group of 8-benzoylmethyl-1-methylthionaphthalene was easily removed (Scheme 15). The group was converted to Bpin as a versatile transformable function by treatment with MeOTf followed by the reaction with B_2Pin_2 under palladium catalysis.[23] Removal of thiomethyl function and nucleophilic cyclization were accomplished by treatment with MeOTf, and then, a base such as Cs_2CO_3.[24]



Scheme 15. Transformation of benzoylmethylated products.

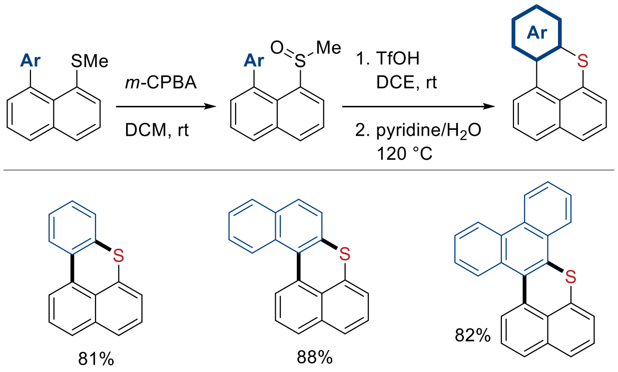
Arylation

The C8 arylation of 1-methylthionaphthalene could effectively take place using arylboron reagents under Cp*Rh(III) catalysis in the presence of an oxidant such as silver oxide (Scheme 16),[25] while the optimization studies for the arylation on alkylthioindoles still remain to be performed. As the aryl sources, neopenthyl glycolato arylborons were found to be suitable.[26] The mother arylboronic acids and relevant pinacolato arylboron species were less effective (not shown). Various aryl groups having electron-donating and electron-withdrawing substituents and multi-ring aryls could be introduced to the C8 position.



Scheme 16. Arylation of 1-methylthionaphthalene.

After the arylation, oxidation of the sulfur function with *m*-CPBA to sulfoxides followed by Pummerer-type cyclization led to the corresponding π-extended benzo[*k*,*l*]thioxantenes of interest in materials chemistry (Scheme 17).[27]



Scheme 17. Synthesis of π-extended benzo[*k*,*l*]thioxantenes.

Concluding remarks

We have shown that alkylthio ether functions effectively act as directing groups for the regioselective functionalization reactions on indole and naphthalene skeletons using Cp*Rh(III) and Cp*Ir(III) catalysts. The C4 and C7 decorations of indoles including alkenylation, alkynylation, and acylmethylation were accomplished using C3- and C7-alkylthiolated indole substrates, respectively. The alkylthio function could be removed or transformed to other functional groups with relative ease. This strategy was also logically applied to the peri(C8) functionalization of 1-methylthionaphtahlenes. These reactions appear to be of substantial importance in medicinal and materials chemistry.

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