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Palladium-Catalysed Direct Thiolation and Selenation of Aryl C–H Bonds Assisted by Directing Groups

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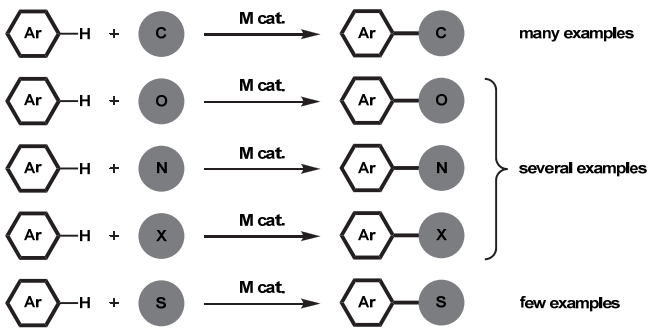
Masayuki Iwasaki*[a] and Yasushi Nishihara*[a]

Direct chalcogenation of aryl C–H bonds have attracted much attetion because arylcharcogen compounds represent useful building blocks in bioactive molecules and functional organic materials. Very recently, chelate-assisted intermolecular direct thiolation and selenation has been developed by using various transition-metal catalysts, such as palladium, rhodium, nickel, copper, and ruthenium. In addition, an appropreate choice of directing groups could control the reaction sites. This highlight review focuses on recent advances in catalytic C–H chalcogenation.

Introduction

Transition-metal-catalysed and chelate-assisted direct functionalization of aryl C–H bonds has been dramatically developed in these two decades, most of which involves carbon–carbon bond formation (Scheme 1).[1] Recently, C–H oxygenation, amination, and halogenation reactions have been also achieved by several research groups. However, intermolecular catalytic direct carbon–sulfur bond formation has yet to be disclosed.[2]



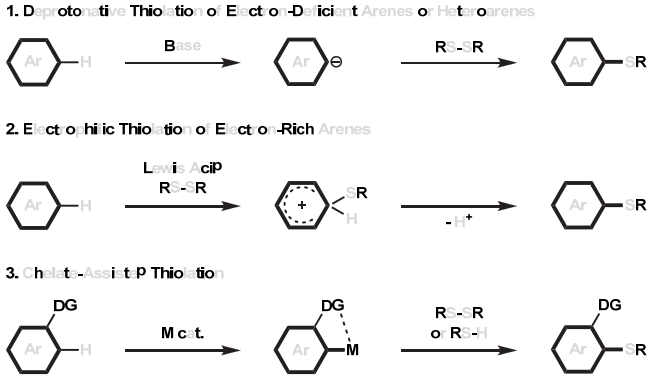
Scheme 1 Transition-metal-catalysed chelate-assisted direct functionalization of C–H bonds.

Until recently, C–H thiolation has been limited to deprotonative thiolation with strong bases[3] and electrophilic thiolation of electron-rich arenes (Scheme 2).[4,5] Although these classical methods constructed carbon–sulfur bonds efficiently, the reactions suffered from narrow scope and poor tolerance of functionalities. Consequently, third C–H thiolation using the chelate auxiliaries would be desirable for general synthetic method of organosulfur compounds. Nevertheless, there is no report on catalytic chelate-assisted C–H thiolation probably because organosulfur compounds had been believed to be a catalyst poison.[6] Even in 2010, Sanford described, "*Palladium-catalyzed ligand-directed formation of carbon–sulfur bonds remains relatively rare, and most examples involve intramolecular reactions to generate the C–S linkage.*" in her review.[7] Very recently, this area has been greatly and rapidly developed by several research groups. In this review, recent advances in catalytic direct thiolation and selenation of inert C–H bonds with directing groups are overviewed.[8]

[a] *Research Institute for Interdisciplinary Science, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan. E-mail: iwasa-m@okayama-u.ac.jp; ynishiha@okayama-u.ac.jp*

Masayuki Iwasaki was born in Okayama, Japan, in 1982. He received his B.S. and Ph.D. degrees in 2006 and 2010, respectively, from Kyoto University under the supervision of Professors Koichiro Oshima, Seijiro Matsubara, and Hideki Yorimitsu. During his doctoral program, he studied for one year as a visiting student in the group of Professor Valery V. Fokin at The Scripps Research Institute. In 2010, He became an Assistant Professor at Okayama University working with Professor Yasushi Nishihara. He spent one month as a visiting scholar in the group of Professor Corey R. J. Stephenson at the University of Michigan in 2015. His research interests include the development of new synthetic reactions by transition-metal catalysts.

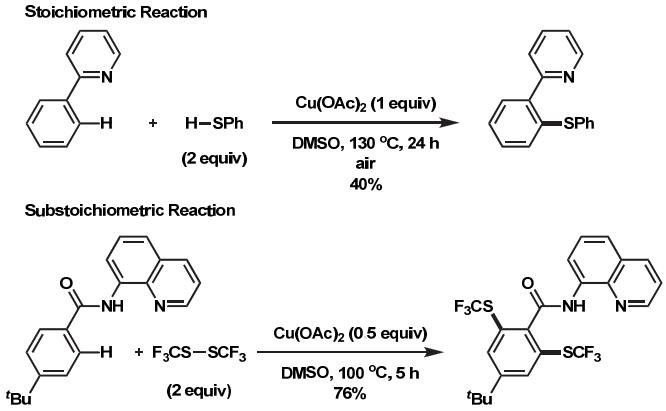
Yasushi Nishihara was born in Hiroshima, Japan in 1968. He earned a B.S. degree from Hiroshima University in 1992. He studied at the University of Notre Dame and University of Iowa, USA under the supervision of Professors Thomas P. Fehlner and Richard F Jordan, respectively. He received his Ph.D. (1997) from the Graduate University for Advanced Studies (SOKENDAI) under the supervision of Professor Tamotsu Takahashi. He became an Assistant Professor at the Tokyo Institute of Technology in 1996, working with Professors Tamejiro Hiyama and Kohtaro Osakada; he moved to Okayama University as an associate professor in 2004 and was promoted to full Professor in 2010. He was awarded the Chemical Society of Japan Presentation Award 2008 for Industries (2008), Incentive Award in Synthetic Organic Chemistry, Japan (2009), and Incentive Culture Award in Okayama Prefecture, Japan (2010). His current research interests are organic synthesis mediated and/or catalysed by organometallic compounds and their application in functional materials such as organic transistors and photovoltaics.



Scheme 2 Approaches to C–H thiolation of arenes.

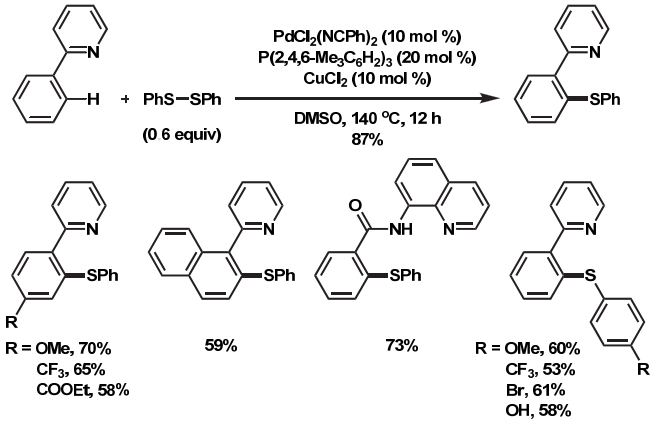
Direct Thiolation of Aryl C–H Bonds with Disulfides

As a pioneering work, Yu and co-workers reported copper-mediated direct thiolation of 2-phenylpyridine in 2006 (Scheme 3, top).[9] The authors proposed that the reaction was initiated by a single electron transfer from arenes to copper(II), generating carbon radical intermediate. Although several related studies have been achieved,[10] a catalytic direct thiolation has been still challenging. In 2012, Daugulis and co-workers reported the direct thiolation of amide derivatives bearing an *N*,*N*′-bidentate directing group (Scheme 3, bottom).[11] In the studies, they achieved a catalytic direct thiolation in some limited substrates.



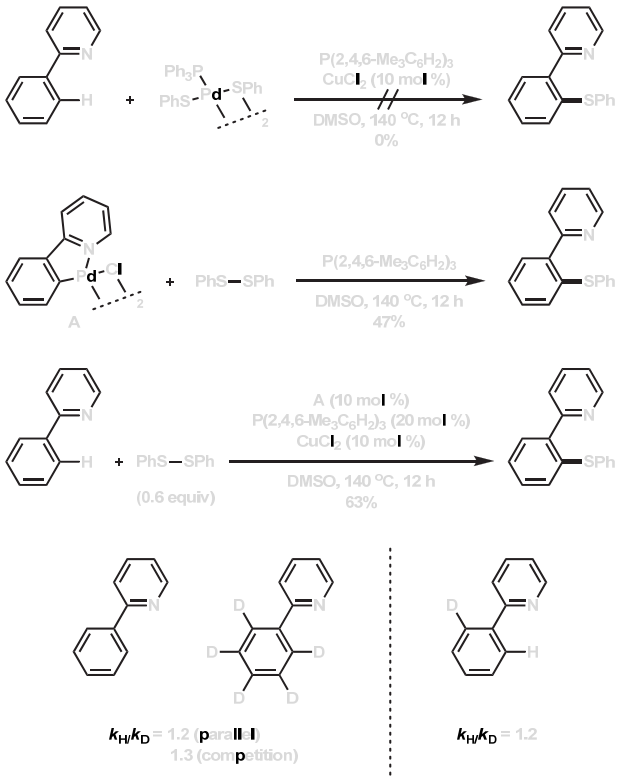
Scheme 3 Copper-mediated direct thiolation.

Our group has also studied the novel carbon–sulfur bond formation reactions.[12] During the course of our research, we developed the palladium-catalysed direct thiolation of aryl C–H bonds with disulfides or thiols.[13] In the presence of a catalytic amount of the palladium complex, a mixture of 2-phenylpyridine and diphenyl disulfide was heated to provide the desired product (Scheme 4). Notably, in our catalytic system, a half equivalent of disulfide was enough to complete the reaction. Namely, the in-situ formed thiol was oxidized to disulfide. Indeed, the addition of the copper catalyst improved the product yield, which might accelerate oxidation of thiol.[14] Moreover, a choice of DMSO (dimethyl sulfoxide) as solvent was crucial. DMSO might act as a terminal oxidant, and the resulted dimethyl sulfide was detected after the reaction.[15] Furthermore, various substrates were applicable to the present reaction. The reactions of both electron-rich and –poor substrates proceeded smoothly to yield the corresponding products in good yields. When 2-(1-naphthyl)pyridine was used, site-selective thiolation occurred at the *ortho*-position of the directing group. Benzamide derivatives with a removable directing group also underwent the desired direct thiolation. With respect to disulfides, a variety of functional groups tolerated the reaction, such as methoxy, trifluoromethyl, bromo, and even unprotected hydroxy groups.



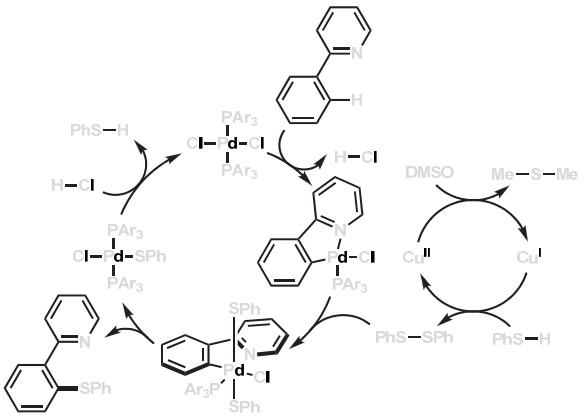
Scheme 4 Palladium-catalysed direct thiolation.

In order to gain mechanistic insights into the palladium-catalysed direct thiolation, we investigated some control experiments (Scheme 5). Instead of diphenyl disulphide (0.6 equiv), the reaction with benzenethiol (1.2 equiv) was conducted under the identical conditions. As a result, the desired product was obtained in a comparable yield. We next explored the stoichiometric reactions. While the reaction of 2-phenylpyridine with the palladium complex prepared from $Pd(PPh_3)_4$ and diphenyl disulfide gave no product, the desired product was obtained from the reaction of diphenyl disulfide with five-membered palladacycle intermediate **A**. In addition, the prepared palladacycle **A** worked as a catalyst for the representative reaction. These results suggest that the reaction involves the five-membered palladacycle as the key intermediate. Moreover, kinetic isotope experiments with deuterated 2-phenylpyriudines revealed that C–H bond cleavage did not involve a rate-determining step. Significant primary kinetic isotope effects were not observed in parallel experiments (k_H/k_D = 1.2) as well as intermolecular (k_H/k_D = 1.3) and intramolecular competitions (k_H/k_D = 1.2).



Scheme 5 Control experiments.

On the basis of the above results, although the present mechanistic consideration is premature, we are tended to assume the reaction mechanism for the catalytic direct thiolation (Scheme 6). An initial palladation of 2-phenylpyridine generates the five-membered palladacycle intermediate. The following oxidative addition of diphenyl disulfide provides high-valent palladium(IV) species.[16] The productive reductive elimination yields the corresponding sulfide and thiolatopalladium complex. The initial palladium species is regenerated by ligand exchange to afford benzenethiol. The formed benzenethiol is oxidized by DMSO with the aid of the copper catalyst, furnishing diphenyl disulphide as the substrate.[14,15]

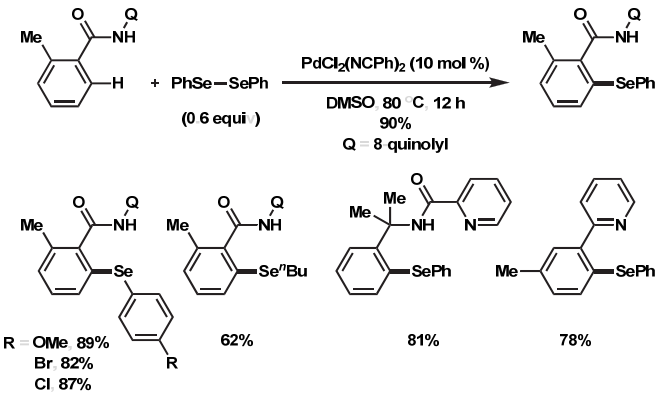


Scheme 6 A plausible reaction mechanism.

At the same time that we reported, the similar rhodium-catalysed direct thiolation has been independently developed by Zou, Li, and co-workers.[17] In addition, several research groups also disclosed a direct thiolation by using palladium,[18] rhodium,[19] copper,[20] nickel,[21] and cobalt catalysts.[22]

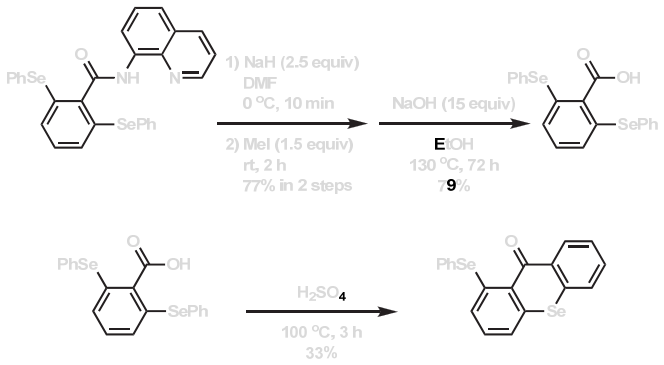
Direct Selenation of Aryl C–H Bonds with Diselenides

The successful results of the direct thiolation led us to examine the related direct selenation of 2-methyl-*N*-(8-quinolyl)benzamide with diphenyl diselenide (Scheme 7).[23] After the optimization of reaction conditions, the palladium-catalysed direct selenation proved to proceed under milder conditions than the aforementioned direct thiolation. Even without the phosphine ligand and the copper catalyst, the desired product was obtained at lower reaction temperature, which might result in the higher reactivity of diselenides. The structure of the product was unambiguously determined by X-ray crystallography.[24] As well as the direct thiolation, the selenation reaction in DMSO required only a half amount of diselenide toward the substrate. Not only diphenyl diselenide but also benzeneselenol could be used as the selenation reagents. In addition to diaryl diselenides, dialkyl diselenides were amenable to the reaction, providing the corresponding products in good yields. From the screening the directing groups, *N*-benzylpicolinamide and 2-arylpyridine were also applicable to the reaction. It is of note that selective selenation occurred at the less hindered position when *meta*-substituted substrate was employed. The similar control experiments and kinetic isotope experiments supported that the reaction proceeded through C–H bond cleavage of the substrate, oxidative addition of diselenide, and C–Se bond-forming reductive elimination.



Scheme 7 Palladium-catalysed direct selenation.

The removal of the directing 8-quinolylamino group was successfully demonstrated as shown in Scheme 8. The protection of the selenated amide with a methyl group followed by base-mediated solvolysis provided the corresponding benzoic acid in a good yield, which represents an important synthetic intermediate. Acid-catalysed intramolecular cyclization afforded selenoxantone, which could be transformed to a selenoxanthylium dye.[25]

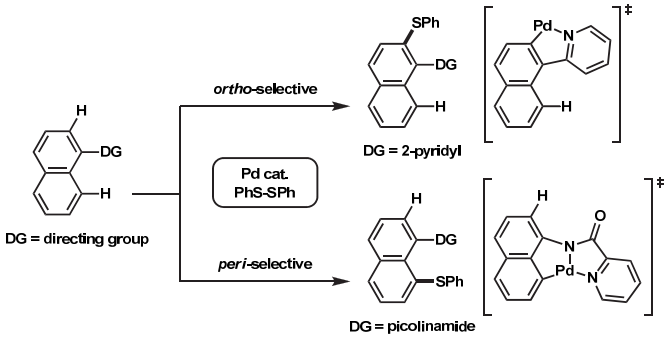


Scheme 8 Removal of the directing group and synthesis of selenoxantone.

Since we have first reported chelate-assisted catalytic direct selenation, the related reactions catalysed by palladium,[18b] rhodium,[19b,26] nickel,[21c] ruthenium,[27] and copper[28] have been disclosed by other research groups.

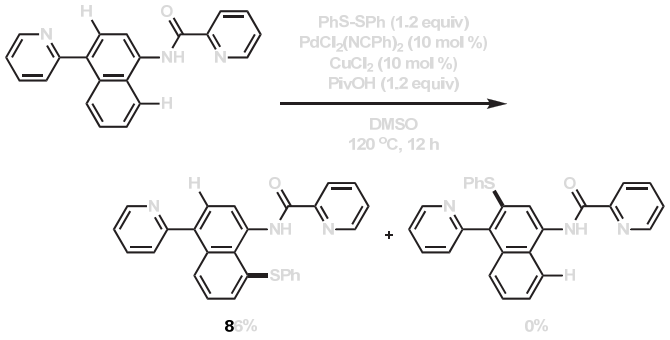
Site-Selective Direct Thiolation and Selenation of Naphthylamine Derivatives

As described above, *ortho*-selective thiolation and selenation were achieved by transition-metal catalysts. During our continuous investigation of directing groups, we found that site-selectivity of the direct thiolation of naphthalene derivatives can be controlled by choosing the appropriate directing group. Direct thiolation of 2-(1-naphthyl)pyridine proceeded exclusively at the *ortho*-position of the directing 2-pyridyl group (Scheme 9, top). On the other hand, when a picolinamide group was employed instead of a 2-pyridyl group, *peri*-selective direct thiolation proceeded to give a corresponding product with a perfect selectivity (Scheme 9, bottom).[29,30] Under the modified reaction conditions, the reaction of 1-naphthylpicolinamide with diphenyl disulfide yielded the desired *peri*-thiolated product. The addition of pivalic acid (1.2 equiv) along with $CuCl_2$ (10 mol %) was found to be effective, which might accelerate the C–H bond cleavage through concerted metalation/deprotonation pathway.[31] The present method provided various 8-sulfenyl-1-aminonaphthalenes in good yields. Additionally, a pyrene derivative also underwent the *peri*-selective direct thiolation, giving the thiolated PAH. The structure of the product was unambiguously confirmed by X-ray diffraction analysis.[32] The site-selectivity of the reaction might be determined by the sole formation of the relatively stable five-membered palladacycle intermediate although a highly strained four-membered palladacycle that leads to the formation of *ortho*-thiolated product would be unfavourable. As expected, the corresponding *peri*-selective direct selenation has been accomplished by using diselenides. Selenation of 1-naphthylpicolinamide was complete with even 5 mol % of the palladium complex.



Scheme 9 Site-selective direct thiolation.

We clearly disclosed that the directing groups employed could determine the reaction sites under similar palladium-catalysed conditions; a 2-pyridyl group promoted the *ortho*-selective direct thiolation while a picolinamide group attained the *peri*-selectivity. The reaction of naphthalene bearing 2-pyridyl and picolinamide groups resulted in the predominant formation of the *peri*-thiolated product in 86% yield (Scheme 10). It was proved that the *N*,*N*'-bidentate directing group coordinated to a palladium centre more effectively than a monodentate directing group.



Scheme 10 Competition experiment.

More recently, nickel-catalysed direct thiolation of aliphatic C–H bonds was simultaneously reported by independent three research groups.[33] In addition, trifluoromethylthiolation of aliphatic C–H bonds was also achieved under palladium catalysis.[34] They all used an *N*,*N*'-bidentate auxiliary as the directing group.

Conclusions

In summary, transition-metal-catalysed direct thiolation and selenation of C–H bonds have been rapidly developed by several research groups including us over these days. Until now, the direct charcogenation of aryl, alkenyl, and alkyl C–H bonds were successfully achieved by the combination of transition-metal catalysts and the suitable directing groups. Although catalytic C–H charcogenation seems to be well matured, the reaction still has some limitations. For example, unnecessary directing group has to be installed to the substrates. In addition, C–H telluration has yet to be disclosed despite its potential utility in the research areas of bioactive molecules as well as functional organic materials.[35] Further

development of direct carbon–charcogen bond-forming reactions may provide practical synthetic method of highly important organocharcogen compounds.

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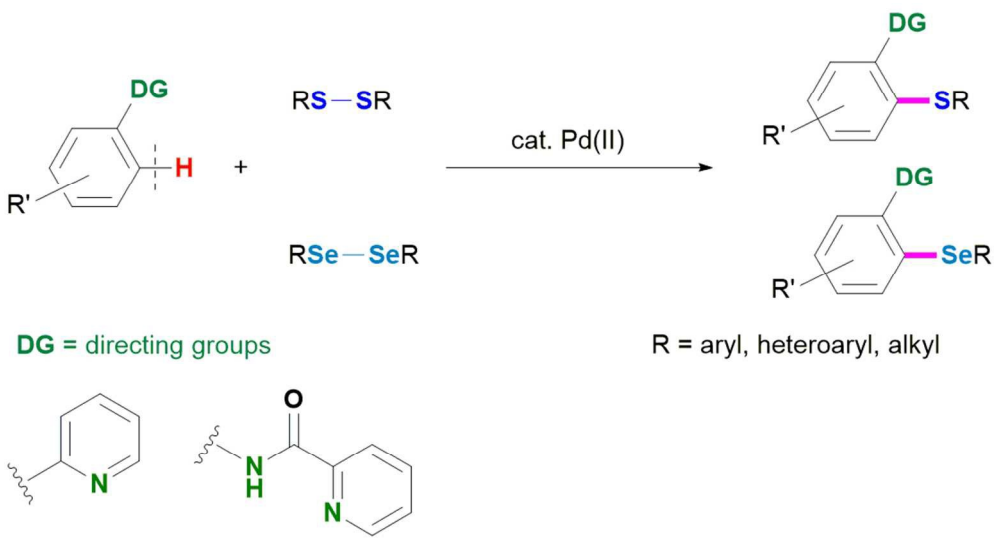

DG = directing groups

R = aryl, heteroaryl, alkyl

94x51mm (300 x 300 DPI)