Organic LETTERS

Letter

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Ruthenium(II)-Catalyzed *ortho*-C−H Chalcogenation of Benzoic Acids via Weak O-Coordination: Synthesis of Chalcogenoxanthones

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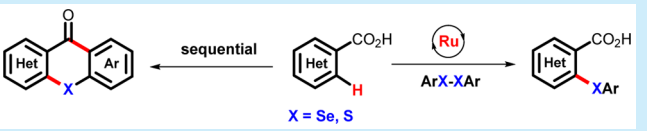
Supporting Information

ABSTRACT: A general protocol for direct chalcogenation of inert C−H bonds of (hetero)aromatic carboxylic acids is developed with a ruthenium(II) catalyst using readily available starting materials, offering densely substituted *ortho*-chalcogenyl aromatic acids in high yields (up to 96%). The strategy avoids the installation of an external directing group, use of metallic oxidants, and features operational simplicity with ample substrate scope. Synthetic application en route to biologically important chalcogenoxanthones is also demonstrated. This work represents the first example of ruthenium(II)-catalyzed direct C−H chalcogenation of benzoic acids.



Organochalcogenides, particularly molecules encompassing C−Se and C−S linkages, have received increasing attention owing to their prevalence in drug candidates and biological molecules with diverse functions (Figure 1).[1] They

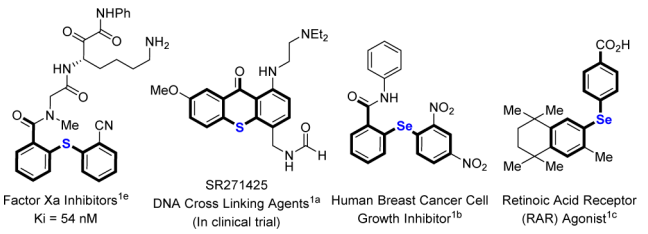
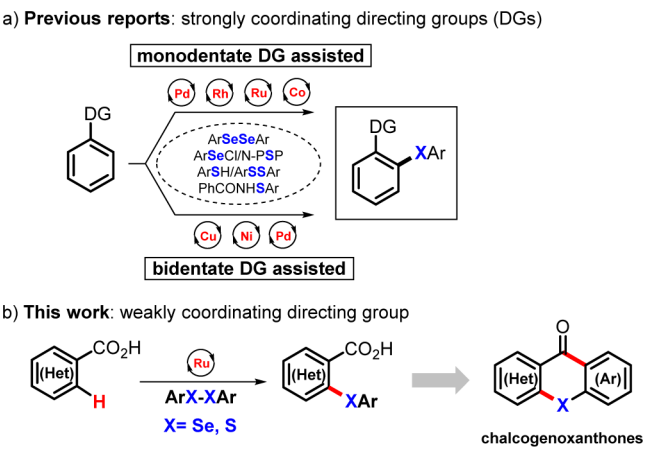


Figure 1. Examples of biologically active organochalcogenides.

have also found extensive applications in organic synthesis, catalysis, agrochemicals, and functional materials.[2] Consequently, construction of C−Se and C−S bonds in an efficient manner is of utmost importance and has remained in the focus of general interest.

Over the past decades, transition metal catalysis for the direct functionalization of otherwise unactivated C−H bonds has emerged as a powerful tool in organic synthesis, obviating the requirement of prefunctionalized substrates and narrow scope associated with traditional transformations.[3] However, compared with significant advancements perceived in various C−C and C−heteroatom bond-forming reactions, direct selenylation and sulfenylation of an inert aryl C−H bond are highly challenging, primarily because of the deactivation (catalyst poisoning) of the metal catalysts by strong coordination of selenium and sulfur species.[4] Nevertheless, regioselective C−H selenylation and sulfenylation of arenes have been accomplished with first-row and second-row transition metal catalysts under the assistance of strongly coordinating monodentate and bidentate auxiliaries (directing groups, Scheme 1a).[5,6] All these processes are very effective; however, in most of the cases, it is necessary to introduce the auxiliary prior to C−H bond activation and then

Scheme 1. Transition-Metal-Catalyzed Regioselective C−H Chalcogenation of Arenes



remove it at the end of the functionalization, leading to an increased number of synthetic manipulations. Many of these directing groups are synthetically less useful and are difficult to remove or modify. Furthermore, these catalytic protocols often require demanding reaction conditions or expensive additives, and very often, a single catalytic system is unsuitable to promote both selenylation and sulfenylation processes. Thus, development of efficient, step-economical, and environmentally benign catalytic protocol, amenable for the production of both C−Se as well as C−S bonds, is highly desirable.

Since the pioneering work of Murai and the advancement demonstrated by Ackermann et al., Ru catalysis has turned out to be a very effective technique for direct C_{sp^2}−H bond functionalization through the weak coordination of commonly employed and synthetically valuable functional groups such as ketones, acids, amides, etc.[7−9] In this context, direct C−H

Received: April 2, 2017

DOI: 10.1021/acs.orglett.7b00996
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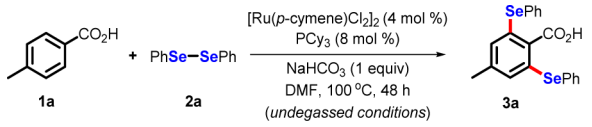
functionalization of aromatic carboxylic acid is advantageous as they are readily available, shelf-stable, have relatively benign toxicological profile, and can also be easily transformed into a broad range of functional groups. Recently, Gooßen, Weix, Ackermann, and Larrosa independently unfolded Ru-catalyzed *ortho*-C−H arylation of benzoic acid using electrophilic aryl halides.[10] We envisioned that Ru catalysis could promote chalcogenation of the *ortho*-C−H bond of aromatic carboxylic acids with an electrophilic chalcogenating source (Scheme 1b). Herein, we report the first example of Ru-catalyzed direct *ortho*-C−H selenylation and sulfenylation of (hetero)aromatic acids via weak coordination under mild conditions using readily available diselenides and disulfides, respectively. The protocol also further extended to access biologically important selenoxanthone and thioxanthone derivatives in high yields.

We commenced our investigation by evaluating the reaction of commercially available *p*-toluic acid **1a** with diphenyl diselenide **2a** as the selenium source (Table 1; a detailed summary is given in the Supporting Information). Readily available and bench-stable $[Ru(p\text{-cymene})Cl_2]_2$ was selected as a choice of catalyst. Gratifyingly, when the mixture of **1a** and **2a** was exposed to Ru(II) catalyst (4 mol %) in the presence of $NaHCO_3$ base in DMF at 100 °C, the C−H selenylation reaction proceeded smoothly, delivering *ortho*-diselenylated product **3a** in 83% isolated yield (Table 1, entry 1). Control experiments revealed that the reaction was unfruitful in the absence of either $[Ru(p\text{-cymene})Cl_2]_2$ or $NaHCO_3$, demonstrating indispensable roles of catalyst and base (entries 2 and 3). When the PCy_3 (8 mol %) was introduced into the reaction conditions, the catalytic selenylation reaction became cleaner and the desired product was isolated in 96% yield (entry 4). It is worth noting that the reaction was setup under open air conditions, and thus, the actual ligand for this reaction is tricyclohexylphosphine oxide (Cy_3PO), which was generated through aerial oxidation of PCy_3. In fact, when preformed Cy_3PO was used as a ligand, product **3a** was isolated in comparable yields (entry 5). Screening of other bases (entries 6−9) and solvents (entries 10−13) gave inferior results. The catalytic activity also strongly depended on the reaction temperature; the yield reduced significantly upon lowering (80 °C) as well as increasing (120 °C) the reaction temperature (entries 14 and 15). The reaction was very sluggish under nitrogen atmosphere, and product **3a** was isolated only in 48% yield with the recovery of both starting materials (entry 16).

Table 1. Optimization of Catalytic Selenylation Reaction[a]

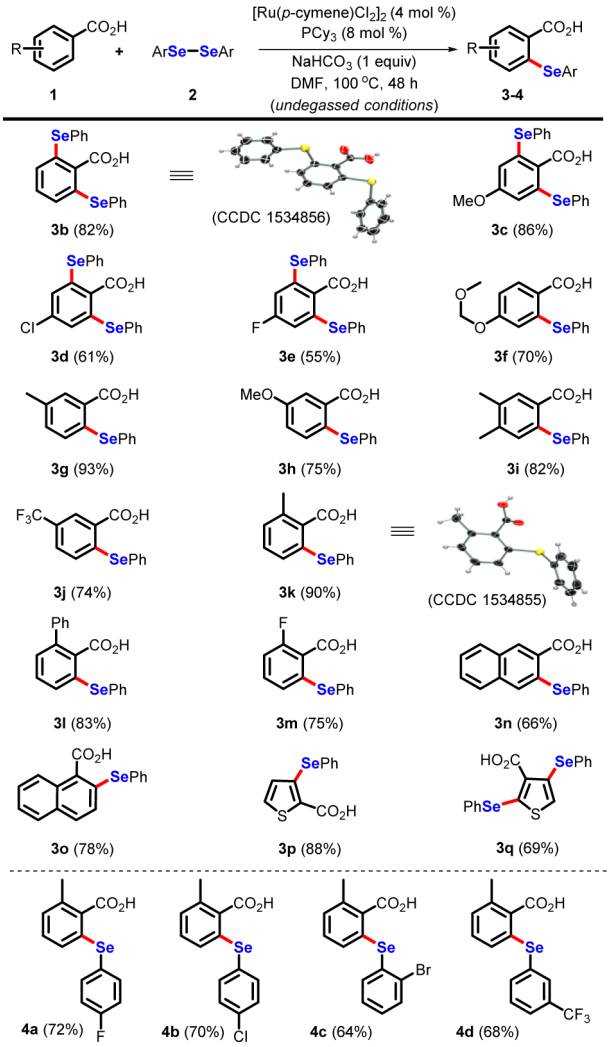


1a 2a 3a

entry	deviation from standard conditions	yield[b] (%)
1	without PCy_3	83
2	without Ru(II) catalyst and PCy_3	0
3	without $NaHCO_3$ and PCy_3	0
4	**none**	**96**
5	Cy_3PO instead of PCy_3	94
6	K_2CO_3 instead of $NaHCO_3$	40
7	Na_2CO_3 instead of $NaHCO_3$	90
8	$KHCO_3$ instead of $NaHCO_3$	56
9	K_3PO_4 instead of $NaHCO_3$	80
10	1,4-dioxane instead of DMF	27
11	TFT instead of DMF	20
12	toluene instead of DMF	trace
13	DMAc instead of DMF	0
14	at 80 °C	55
15	at 120 °C	75
16	under N_2	48[c]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (4 mol %), PCy_3 (8 mol %), base (1 equiv), solvent (1.5 mL), 48 h. [b]Isolated yields. [c]35% of **1a** was recovered.

Scheme 2. Scope of *ortho*-C−H Selenylation with Respect to Aromatic Carboxylic Acids and Diaryl Diselenides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (4 mol %), PCy_3 (8 mol %), $NaHCO_3$ (1 equiv), DMF (1.5 mL), 48 h. Yields of isolated products are given.

With the optimal reaction conditions in hand, the scope of this novel transformation was investigated (Scheme 2). The reaction is quite general for a wide range of substituted aromatic carboxylic acids. Benzoic acids bearing electron-donating as well as electron-withdrawing groups at the *para*-position smoothly reacted to furnish diselenylated products **3a**−**e** in good yields (Scheme 2). Compound **3b** was crystallized, and X-ray analysis unambiguously confirmed the structure of the product and the regioselectivity pattern. Surprisingly, in the case of MOM-protected *para*-salicylic acid, diselenylated product was not formed, and instead, only monoselenylated product **3f** was

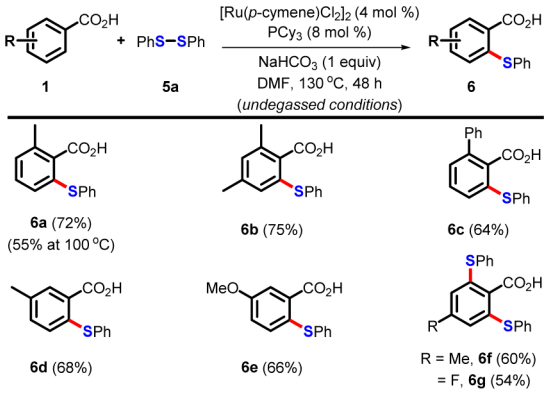
DOI: 10.1021/acs.orglett.7b00996
Org. Lett. XXXX, XXX, XXX−XXX

isolated in 70% yield. *meta*-Substituted benzoic acids selectively produced monoselenylated products **3g–j** in excellent yields (74–93%) at the less hindered side due to the steric constraints. The reaction is also efficient with sterically hindered *ortho*-substituted benzoic acid, and expected monoselenylation products **3k–m** were obtained in 75–90% yields. The structure of **3k** was also explicitly confirmed by X-ray analysis. Bicyclic 1- and 2-naphthoic acids (**1o**,**n**) also provided the monoselenylated products in 78 and 66% yields, respectively. The methodology was successfully applied to heteroaryl carboxylic acid such as thiophene-2-carboxylic acid, and the desired monoselenylated product **3p** was isolated in 88% yield. When thiophene-3-carboxylic acid was considered, the corresponding diselenylated product **3q** was obtained in 69% yield.

The reaction efficiency of different diselenides was also evaluated. Several functionalized diaryl diselenides efficiently participated in the reaction, rendering corresponding selenylated products **4a–d** in good yields (64–72%, Scheme 2). It is worth noting that the reaction tolerates different halogen substituents (**4a–c** and **4d**), which are handy synthetic tools for further functionalization to complex molecules.

The viability of this approach for direct C–Se bond formation encouraged us to explore the feasibility of a C–S bond-forming process. Accordingly, the reaction of *ortho*-toluic acid **1k** and diphenyl disulfide **5a** was examined under the optimized conditions established for the selenylation process (Scheme 3).

Scheme 3. Scope of C–H Sulfenylation Process[a]

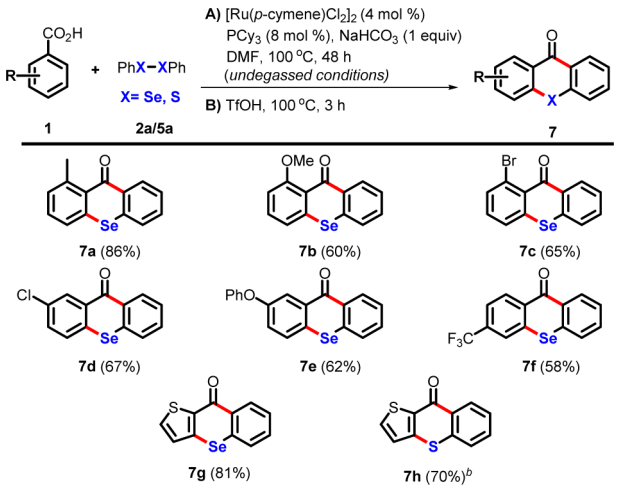


[a]Reaction conditions: **1** (0.2 mmol), **5a** (0.4 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (4 mol %), PCy_3 (8 mol %), $NaHCO_3$ (1 equiv), DMF (1.5 mL), 48 h. Yields of isolated products are given.

Pleasingly, the same catalytic system is also effective for the sulfenylation reaction, and the desired monosulfenylated product **6a** was isolated in 55% yield. When the reaction was performed at 130 °C, the yield was increased significantly, offering **6a** in 72% isolated yield. Similar to selenylation reaction, a variety of *ortho*- and *meta*-substituted benzoic acids promptly participated in the sulfenylation reaction to produce monosulfenylated product in 64–75% yields. As expected, *para*-substituted benzoic acids **1f**,**g** delivered disulfenylated products **6f**,**g** in good yields.

The utility of this protocol was further expanded through the development of a straightforward synthetic route to chalcogenoxanthones, an emerging scaffold for drug discovery and diagnosis.[11] Thus, crude product obtained from the Ru(II)-catalyzed selenylation or sulfenylation process was subjected to an intramolecular cyclization by being treated with triflic acid at 100 °C, affording derivatives of selenoxanthones (**7a–g**) and thioxanthone (**7h**) in high yields (up to 86%, Scheme 4). This sequential protocol is compatible with various functional groups including heterocycles.

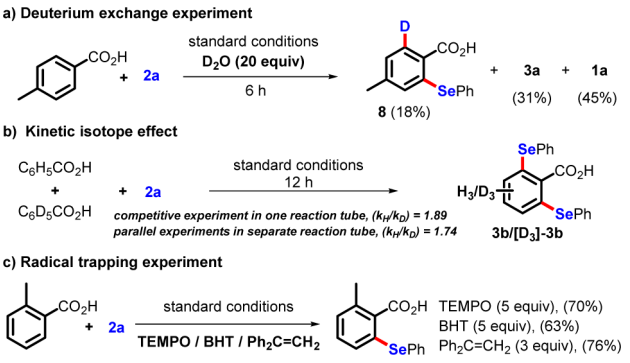
Scheme 4. Sequential Synthesis of Chalcogenoxanthones[a]



[a]Reaction conditions: (A) **1** (0.2 mmol), **2a**/**5a** (0.4 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (4 mol %), PCy_3 (8 mol %), $NaHCO_3$ (1 equiv), DMF (1.5 mL), 48 h; (B) TfOH (0.5 mL), 3 h. [b]Reaction was performed at 130 °C with condition A. Yields of isolated products are given.

To probe the reaction mechanism, various controlled experiments were performed (Scheme 5). When the catalytic

Scheme 5. Control Experiments



selenylation reaction was executed in the presence of D_2O under the standard reaction conditions, deuterium-incorporated monoselenylation product **8** was isolated in 18% yield, corroborating that the initial C–H ruthenation process is reversible (Scheme 5a). The kinetic isotope effect revealed k_H/k_D = 1.89 and 1.74 (from intermolecular competition experiment and independent parallel experiment, respectively), indicating that the C–H bond breaking may be involved in the rate-determining step (Scheme 5b). Furthermore, the catalytic C–H chalcogenation protocol was unaffected in the presence of radical scavengers such as TEMPO, BHT, and 1,1-diphenylethylene (Scheme 5c), and these results refute the involvement of radical species in the reaction pathway. In-depth mechanistic investigations are underway to fully elucidate the reaction pathway.

In conclusion, we have developed the first ruthenium-catalyzed direct selenylation and sulfenylation of C–H bonds of aromatic caroboxylic acids, offering densely substituted organochalcogenides in high yields. The reaction proceeded with *ortho*-selectivity under air, and no metallic oxidants or

DOI: 10.1021/acs.orglett.7b00996
Org. Lett. XXXX, XXX, XXX–XXX

cocatalysts are required. The synthesis of chalcogenoxanthones, a highly important framework in biological and material sciences, was also accomplished. The inexpensive nature and ready availability of the reaction components, operational simplicity, use of bench-stable Ru(II) catalyst, broader substrates scope, and ease of selective postsynthetic transformation of a carboxylic unit bode well for its rapid adoption.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00996.

Complete experimental details, characterization data for the prepared compounds (PDF)
X-ray data for **3b** (CIF)
X-ray data for **3k** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge CSIR New Delhi for the financial support (02(0212)/14/EMR-II). A.M. and G.S.G. acknowledge UGC for JRF; H.S. and S.D. acknowledge IIT-Madras for HTRA. We also thank the Department of Chemistry, IIT-Madras, for instrumental facilities.

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DOI: 10.1021/acs.orglett.7b00996
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