

Site-Specific Oxidative C–H Chalcogenation of (Hetero)Aryl-Fused Cyclic Amines Enabled by Nanocobalt Oxides

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Supporting Information

ABSTRACT: By employing reusable nanocobalt oxides as the catalysts, a site-specific oxidative C-H chalcogenation of (hetero)aryl-fused cyclic amines with various thiols and diselenides is presented for the first time. The reaction proceeds selectively at the sites of the (hetero)aryl rings para to the N atom, and enables access to a wide array of chalcogenyl N-heteroarenes. The merits of the transformation involve high step- and atom-efficiency, excellent substrate and functional compatibility, operational simplicity, and the use of a naturally abundant Co/O_2 system. The present work has



offered a fundamental basis for the selective synthesis of functional N-heteroarenes from readily available feedstocks.

-heteroarenes with a chalcogenyl group *para* to the N atom represent a class of important compounds, as they are frequently found to exhibit diverse biological and therapeutic activities. Selected examples, such as antiviral (compound A, Figure 1),^{1a} potent inhibitors of the G4 ligand



and telomerase (compound B),^{1b} kinase (SGX-523),^{1c,d} and PED4 (compound \mathbf{C}),^{1e} are shown in Figure 1. Moreover, such compounds serve as useful building blocks for various synthetic purposes.^{1e,2} Owing to their interesting functions, considerable attention has been directed toward the development of efficient methods to access the related scaffolds during the past decade. Representative methods mainly involve the following: (1) cross-coupling of chalcogenyl reagents with prefunctionalized substrates (e.g., heteroaryl halides, amines, diazonium salts and boronic acids);³ (2) direct C-H chalcogenation of heteroarenes assisted by directing groups; (3) oxidative C-H chalcogenation of electron-rich (hetero)- coupling agents and/or directing groups, the use of noble metal catalysts with difficult reusability, and limited substrate scope and selectivity. As such, the development of new approaches, enabling direct and site-specific C-H chalcogenation of readily available substrates in the presence of naturally abundant catalyst systems, would be highly desirable.

Enlightened by our recent work on the functionalization and construction of N-heterocycles,^{7,8} we here wished to develop a new C-H chalcogenation that is para to the N atom of the Nheterocycles. As illustrated in Scheme 1, the reaction of



tetrahydroquinoline⁹ (THQ) 1a and *p*-toluenethiol 2a is selected as a prototypical example. In consideration of that fact, and under catalytic oxidative conditions, the preferential single electron oxidation (SEO) of the N atom in 1a could result in aryl radicals^{7a,c,8a} at position-6 and 8 due to the conjugate effect-induced charge distribution, and the α -radical (position-2);^{8c,d} the reaction would possibly generate three chalcogenyl N-heteroarenes (**3aa**, **3aa**-**A** and **3aa**-**B**), and one noncoupling quinoline (1a').^{9,10} To achieve selective synthesis of **3aa**, there should be a compatible catalyst system to ensure that the

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arenes (e.g., benzenes,^{5a-c} anilines,^{5d} indoles,^{5e-j} and benzo-thiazoles^{5k}); and radical coupling.⁶ Despite the significant

utility of these transformations, some key issues still remain to

be addressed, such as the need for preinstallation of specific

coupling of **1a** at position-6 with **2a** is fast enough, thus suppressing the formation of undesired byproducts.

To test the feasibility of the above idea, we initially performed the reaction of 1a and 2a at 120 °C for 18 h by employing different homogeneous catalysts (i.e., copper and iron salts, Ru, Pd and Ir complexes). However, the reaction generated quinoline 1a' as the major product, whereas the desired product 3aa was detected in poor yields (see Table S3 in the Supporting Information (SI)). Then, we turned our attention to heterogeneous catalysis, as it is sharply different from homogeneous catalysis. In general, heterogeneous catalysts could exhibit lower dehydrogenation efficiency toward THQs due to the reaction occurring on the solid surface and limited catalytically active sites.¹¹ Thus, the use of a suitable heterogeneous catalyst would be beneficial for the coupling step and would offer a solution to address the issue of chemoselectivity. Recently, we have reported a reductive β alkylation of the quinolines by utilizing the newly designed multispherical cavity carbon-embedded nanocobalt oxides (CoO_/MSCC).^{7b} Herein, by employing the same catalysts (see XPS and morphology in Figures S2, S3 and S5 in SI), we described, for the first time, a site-specific oxidative C-H chalcogenation of aryl-fused cyclic amines with readily available thiols and diselenides. The present work has demonstrated the first application of the $CoO_x/MSCC$ catalyst in a dehydrogenative coupling reaction.

To determine an efficient reaction system, we chose the cross-coupling of 1a and 2a as a benchmark reaction to evaluate different reaction parameters. As shown in Table 1, the reaction charged with an O₂ balloon was performed at 120 °C for 18 h with $CoO_x/MSCC$ as the catalysts. Among various halogenated salts tested (entries 1–6), NaI was shown to be the best choice and afforded **3aa** in 95% yield with excellent

Table 1. Optimization of Reaction Conditions^a

1a	N + Ja Si	<u>cat. / additiv</u> solvent, O ₂ H		S 3aa ^N + 1a'
entry	catalyst	additive	solvent	yields of 3aa/1a ′ ^b
1	CoO _x /MSCC	LiBr	DMSO	35/58
2	$CoO_x/MSCC$	LiCl	DMSO	18/67
3	$CoO_x/MSCC$	LiI	DMSO	92/2
4	$CoO_x/MSCC$	NaI	DMSO	95/2
5	$CoO_x/MSCC$	CuI	DMSO	48/51
6	$CoO_x/MSCC$	ZnI_2	DMSO	45/5
7	$CoO_x/MSCC$	-	DMSO	trace/95
8	-	NaI	DMSO	-/-
9	MSCC	NaI	DMSO	-/trace
10	$Co(OAc)_2$	NaI	DMSO	trace/-
11	$CoO_x/MSCC$	NaI	p-xylene	trace/65
12	$CoO_x/MSCC$	NaI	H_2O	-/-
13	$CoO_x/MSCC$	NaI	Cy-hexanol	71/trace
14	$CoO_x/MSCC$	NaI	DMF	88/8
15	$CoO_x/MSCC$	NaI	DMSO	(85/10, trace/45) ^c
16	$CoO_x/MSCC$	NaI	DMSO	$48/37^{d}$
17	CoO _x /MSCC	NaI	DMSO	-/- ^e

^{*a*}Unless otherwise stated, the reaction was performed with 1a (0.25 mmol), 2a (0.25 mmol), cat. (3 mol %, 15 mg), additives (0.25 mmol) in solvent (1 mL) at 120 °C for 18 h using O₂ balloon. ^{*b*}GC yield (%). 'Yields are with respect to the temperatures at 100 and 80 °C, respectively. ^{*d*}NaI (0.125 mmol). ^{*c*}N₂.

selectivity. However, the absence of catalyst or NaI additive was unable to afford the product (entries 7–8), and the use of catalyst support MSCC and catalyst precursor $Co(OAc)_2$ led to poor results (entries 9–10). Further, the screening of other solvents indicated that they were inferior to DMSO (entries 11–14). Finally, the decrease of temperature (entry 15) or additive loading (entry 16) led to diminished yields, and performing the reaction under an N₂ atmosphere failed to produce the desired product (entry 17). Thus, the optimal conditions (standard conditions) are as shown in entry 4 of Table 1.

With the optimal reaction conditions established, we sought to explore the scope of diverse thiols **2** with THQ **1a**. As shown in Scheme 2, all the reactions proceeded smoothly and

Scheme 2. Variation of Thiols



Scheme 3. Variation of (Hetero)Aryl-Fused Cyclic Amines



furnished the 6-sulfurated quinolines in good to excellent yields upon isolation (3ab-3ag). Various functional groups, regardless of electron-donating and electron-withdrawing $(-OMe, -NH_2, -Cl, -Br, -CO_2Me)$ ones, were well tolerated, and electron-rich thiols (3aa-3ad) gave relatively higher yields than those of electron-deficient ones (3ae-3ag). Interestingly, heteroaryl thiols (3ah-3ai) also served as effective coupling partners, affording the corresponding asymmetric heteroaryl thioethers in moderate to excellent yields (3ah-3ai). In addition to (hetero)aryl thiols, aliphatic

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one 2k also underwent smooth oxidative coupling to give the desired product 3ak in moderate yield (3aj).

Next, we turned our attention to the variation of both coupling partners. First, different substituted tetrahydroquinolines 1 (THQs: 1b-1g) in combination with thiols 2 (2b-2c) were tested. Gratifyingly, all the reactions afforded the desired products (3bb-3eb, 3fc-3gc) in moderate yields. Further, indolines (1h-1i) and the analogue (1j) also underwent smooth oxidative dehydrogenative coupling reactions and produced 5-sulfurated indole derivatives (3hb, 3ib and 3ja). In comparison, 3-methylindole 1i gave much higher yield than the other two substrates (1h and 1i), which is due to the partial formation of 3-sulfurated indoles when the reactions employ 3nonsubstituted indolines. Interestingly, (hetero)aryl-fused THQs (1k-1l) were proven to be highly effective coupling partners to react with thiols, generating the desired product in excellent isolated yields (3kc, 3kg and 3lb). Importantly, the successful synthesis of compound 3lb has demonstrated the potential of the developed chemistry in further preparation of novel 1,10-phenanthrolines, a class of valuable ligands that can be applied in catalysis and organometallic chemistry.

To further demonstrate the synthetic diversity, we explored the selenylation version of the developed chemistry. Thus, the coupling of various aryl-fused cyclic amines (1) with the diselenides (4) was tested. As expected, the aryl rings of substrates 1 were selectively functionalized at the sites *para* to the N atom, affording the selenylated N-heteroarenes 5 in moderate to excellent yields upon isolation (Scheme 4).





Similar to the results described in Scheme 3, the (hetero)arylfused THQs gave much higher yields (5kc and 5la) than other THQs (5aa-5ae), which is attributed to the (hetero)arylfused THQs favoring the formation of more stable intermediates.

Subsequently, we tested the stability and reusability of the catalyst. As shown in Figure S6 in SI, the catalyst was recycled and reused for six consecutive times in the model reaction. The catalytic activity was very well maintained. After six runs, only a slight decrease of cobalt content from 3.14% to 3.07% was found by ICP–OES. Meanwhile, only a slight increase of pore width was determined (Figure S4), which counts for the retention of the catalytic efficiency. Moreover, TEM images of the used CoO_x/MSCC show that the catalysts remain its morphology even after six runs (Figure S5 in SI).

To gain mechanistic insight into the reaction, a timeconcentration profile of different components of the model reaction under the standard conditions is depicted in Figure 2. Thiol 2a was rapidly consumed and converted into disulfide



Figure 2. Representative time course of the reaction.

2a' within 1 h, and 2a' is also efficiently captured by THQ to form 6-*p*-tolylthio THQ 3aa'. Finally, 3aa' underwent slow oxidative dehydroaromatization to generate the cross-coupling product 3aa within 18 h. The results indicate that the disulfide (2a') and 6-*p*-tolylthio THQ 3aa' are the key reaction intermediates, and the in situ formation of disulfide 2a' occurs prior to the cross-coupling of 1a and 2a' to 3aa'. Further, we conducted some control experiments (Scheme 5); treating 1a





under the standard conditions failed to generate 6-iodoquinoline 1a-1 and 6-iodotetrahydroquinoline 1a-2 during the entire reaction (eq 1). Moreover, compounds 1a-1 and 1a-2 (eq 2) as well as 1a' (eq 3) were unable to react with 2a and yielded product 3aa, indicating that these three compounds serving as the reaction intermediates can be ruled out. Further, the addition of excess TEMPO into the model reaction significantly suppressed the product formation, and the TEMPO trapping of one molecule of thiol 2a was observed by GC-MS analysis (eq 4), showing that, at least, the reaction involves a thiol radical intermediate.

On the basis of the above-observed findings and the reported mechanisms, ^{7c,12,13} the plausible reaction pathways are proposed in Scheme 6. Initially, species **A** is formed via the capture of molecular O_2 by the active CoO_x sites of the catalyst followed by single electron oxidation (SEO)^{8a} of thiol **2** and proton transfer. Then, the interaction of **A** with another molecule of thiol **2** would generate arylsulfenyl radical **B** and disulfide **2'** following regeneration of the catalyst (Scheme S5, eq 5).¹³ Further, the homolytic or heterolytic cleavage of

Scheme 6. Possible Reaction Pathways



disulfide 2' (radical B or cation D) can be transformed in combination with I⁻ into the RSI under the oxidative conditions. For product formation, two pathways are proposed. In path a, an electrophilic sulfuration is suggested via successive delocalization of 1a to zwitterionic form (1a-1), interaction of RSI with 1a-1 to form ammonium salt 3aa-1, and the tautomerization of 3aa-1 to intermediate 3aa'. In path b, the addition of B (arising from 2') to the aryl ring of 1a followed by SEO of the adduct **3aa-2** by RSI or $[Co^nO_r]/O_2$ also rationalize the formation 3aa'. Finally, the oxidative dehydroaromatization of 3aa' would yield product 3aa. Similarly, the reactions employing diselenides 4 would produce the selenylation products 5. Due to the unique charge distribution of electron-rich aniline systems and the influence of steric effect at position-8 of THQ 1a, the fast capture of 1a at position-6 by disulfide 2' (Figure 2) counts for the high chemo- and regioselectivity of the developed reaction.

In conclusion, by employing nanocobalt oxides as the catalysts, we have demonstrated a site-specific oxidative C–H chalcogenation of aryl-fused cyclic amines with various thiols and diselenides, which enables access to a wide array of chalcogenyl *N*-heteroarenes in a step- and atom-economic fashion. The developed synthetic protocol proceeds with the merits of broad substrate scope, operational simplicity, good functional group tolerance, the use of reusable and earth-abundant cobalt catalyst, and molecular O_2 as the oxidant. The present work has offered a fundamental basis for the preparation of functionalized N-heteroarenes from readily available feedstocks.

ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data (PDF)

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Notes

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