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Direct α-Chalcogenation of Aliphatic Carboxylic Acid Equivalents

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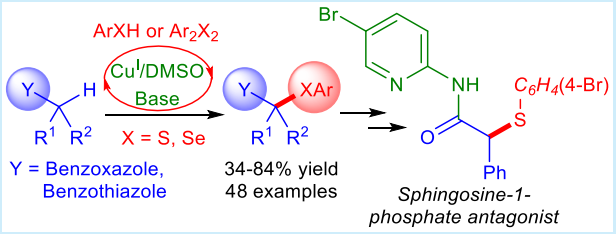
Supporting Information

ABSTRACT: A novel approach to α-chalcogenation of aliphatic carboxylic acids has been developed by means of transforming them as the corresponding benzazoles. The catalyst system, consisting of Cu^{I}, DMSO, and a base, operates through a unique mechanism to access a range of practically significant thio- and selenoethers that are otherwise challenging to achieve. The applicative potentials have been exemplified by utilizing the resultant chalcogenated compounds as the precursor for the synthesis of biologically pertinent molecules and synthetic intermediates.

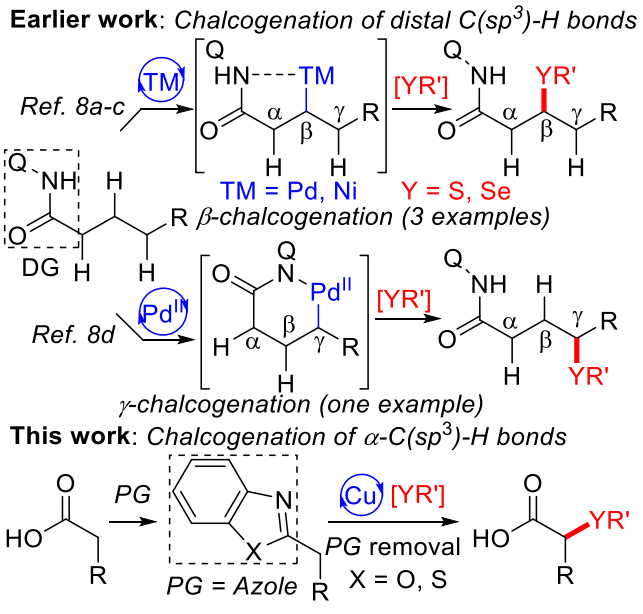


The selective functionalization of a specific C−H bond plays a central role to access targeted molecular scaffolds in modern organic synthesis.[1] Despite the many successes, the catalytic functionalization of relatively inert C−H bonds of alkanes appears to be an arduous challenge to synthetic chemists.[2] In general, these C−H functionalizations rely on the directed strategy in which a chelating directing group of the substrate assists to hold the transition metal catalyst close to the cleavable C−H bond.[2a−e] Essentially, the C−H bond positioned at an appropriate distance (typically at the β-, γ-, or even δ-position) with respect to the directing group is activated via the formation of thermodynamically favored five- or six-membered metallacycle intermediates, by using primarily palladium catalysts[3] and others.[4] Nevertheless, the proximal α-functionalization of common substrates, e.g., carboxylic acids, amides, imines, etc., via a directed strategy was not achieved presumably due to the requirement of a strained four-membered metallacycle intermediate.[5] In this paper, we describe a novel approach that enables the direct α-functionalization of aliphatic carboxylic acid equivalents.

Chalcogenated acetic acids, in particular, α-thiolated acetic acid derivatives, are prevalent in a myriad of biological systems, approved drugs, and functional materials.[6] Thus, their synthesis via the regiospecific installation of a thio-based substituent (C−S) at an unactivated C−H bond of aliphatic carboxylic acid equivalents is a noteworthy transformation of fundamental importance, but there are several hitches, including the reported catalyst retarding effect of sulfur compounds.[7] To date, a number of methods have appeared to access β- and γ-thiolated carboxylic acids via the classical directed strategy.[8] However, the direct synthesis of α-thiolated carboxylic acid equivalents has remained elusive.

To accomplish the title transformation, we have conceived another approach. We envisioned that if aliphatic carboxylic acids were converted into the corresponding 2-alkylazoles, the α-position with respect to the heterocycle in the 2-alkyl chain would be rather activated by the azole, thereby facilitating the required chalcogenation process. This was further supported by our recent finding of a C−H methoxylation process under palladium catalysis.[9] We herein report a novel α-chalcogenation strategy (ArS−C and ArSe−C) of 2-alkylbenzazoles, as synthons of aliphatic carboxylic acids, by means of a copper-based catalyst system (Scheme 1).

Scheme 1. C(sp³)−H Chalcogenations of Aliphatic Carboxylic Acid Equivalents



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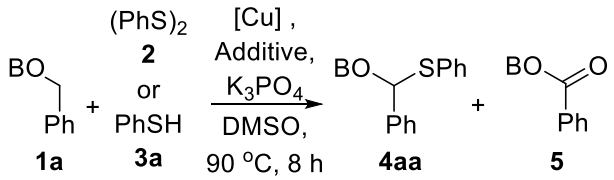
We commenced our investigation by studying the reaction between 2-benzylbenzoxazole (**1a**) and diphenyldisulfide (**2**) in the presence of $CuBr_2$ and K_3PO_4 under aerial conditions (Table 1 and Table S1, Supporting Information). However,

Table 1. Optimization of the Reaction Condition[a]



entry	S source	[Cu]	additive	**4aa** (%)	**5** (%)
1	**2**	$CuBr_2$	air	0	80
2	**2**	$CuBr_2$	–	38	25
3	**3**	$CuBr_2$	–	49	16
4	**3**	CuI	–	79	8
5[b]	**3**	CuI	picolinic acid	80	<5
6[c]	**3**	CuI	–	84	0
7[d]	**3**	CuI	–	0	14
8[e]	**3**	–	–	7	0

[a]Reaction conditions: **1a** (0.5 mmol), **2** or **3a** (1.1 mmol), Cu salt (20 mol %), K_3PO_4 (1.0 mmol), DMSO (6 mL), N_2 atmosphere, 90 °C, 8 h. [b]With 20 mol % 2-picolinic acid, 12 h. [c]With 10 mol % CuI. [d]Without K_3PO_4. [e]For 24 h. BO = benzoxazole.

ketone **5** was the sole product due to a known copper-catalyzed benzylic oxygenation process (entry 1).[10] To circumvent this problem and inspired by the report of Lei et al. that DMSO can be utilized as a mild and selective oxidant for Cu^I species, we carried out the thiolation under inert conditions that provided **4aa** in an isolable quantity (entry 2).[11] Because thiols are known to dimerize into the corresponding disulfide upon heating in DMSO, we used thiophenol (**3**) directly and found that **4aa** was formed in a slightly improved yield (entry 3).[12] Replacing $CuBr_2$ with CuI resulted in significant enhancement of the product yield (entry 4). The use of 2-picolinic acid among the other N-,O-ligands provided comparable yields with regard to the ligand-free reaction (entry 5). Gratifyingly, the yield was further improved by reducing the copper loading up to 10 mol % (entry 6). Any additional modification of the reaction parameters gave an inferior result in terms of the yield of **4aa** (see Table S1).

Control experiments revealed that the thiolation does not proceed in the absence of any base (entry 7). Without CuI, the reaction becomes sluggish, giving **4aa** only in traces even after a prolonged period (entry 8). These findings point out that CuI together with a base, e.g., K_3PO_4, in DMSO constitutes conceivably the most essential component of the catalyst system.

Next, via application of the optimized reaction condition, a series of 2-alkyl- and 2-benzylbenzazoles with varied substitution patterns were consistently converted into the corresponding α-thiolated derivatives in synthetically useful yields (Scheme 2). Furthermore, a diverse range of functional groups, including fluoro, chloro, methyl, methoxy, bromo, nitro, amine, pyridyl, etc., were tolerant to the reaction condition. Notably, the competitive thiolation at the cross-coupling sensitive C(aryl)−Br and C(aryl)−Cl bonds was entirely repressed. For 2-benzylbenzazoles, the thiolation occurred regiospecifically at the $C(sp^3)$−H bonds adjacent to the azole rings without any concomitant thiolation at the aromatic rings. In general, monothiolated compounds were formed as the single product with few cases of bis-thiolated compounds. The extent of mono- and bis-thiolation depends upon the steric crowding of the two coupling partners (e.g., **4aa** vs **4na** or **4pa** vs **4xa**). However, alkylthio substituents could not be installed under the optimized condition.

With the success of thiolations, we subsequently applied this approach to analogous selenylation reactions (Scheme 3). It soon turned out that the Cu-based system was equally effective for the phenylselenylation of 2-benzylazoles with diphenyldiselenide even at ambient temperature (25 °C). The new selenylated compounds are believed to function as important intermediates in the synthesis of complex structures.

To gain insight into the mechanism, several experiments were carried out (see the Supporting Information). The presence of a radical quencher, e.g., 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) (1.5 equiv each), completely suppressed product formation, suggesting the involvement of radical species.[13]

We speculated that 2-alkylbenzazoles might act as an electron donor that transfers a single electron to the copper catalyst in a manner similar to that of aryl ketones as described by Lei et al.[11] To validate this assumption, EPR experiments were conducted (see the Supporting Information). When the reaction between **1a** and CuI in DMSO was monitored by EPR, a the intensity of the signal at $g = 2.166$ for Cu^{II} increased steadily with time. However, no signal for Cu^{II} was observed when the reaction was performed in the presence of K_3PO_4. These results suggest that Cu^{II} generated *in situ*, via the oxidation of CuI by DMSO, was rapidly reduced to Cu^I through single-electron transfer (SET) from **1a** in the presence of K_3PO_4. Next, we carried out the reaction of **1a** with $CuBr_2$ in DMF in the absence and presence of K_3PO_4. The EPR of the reaction without K_3PO_4 revealed that the initial signal for Cu^{II} remained unchanged while that of Cu^{II} entirely disappeared over time for the reaction with K_3PO_4. Moreover, the reactive DMSO radical was also detected by a low-temperature EPR experiment (see the Supporting Information).[14] These experiments not only confirmed our postulation but also evidenced that DMSO had served as the oxidant for the Cu^I to Cu^{II} transition in this reaction.[11]

When benzylic substrates holding conjugated functions, e.g., amides, ester, carboxylic acid, imine, phenyl, etc., were subjected to thiolation, either very little or no desired thiolated products were obtained (see the Supporting Information). We speculate that the carbo-radicals formed in the case of 2-alkylazoles are rather stabilized by the azole ring. Furthermore, a stabilized thio radical, e.g., arylthio radicals, might be required for a successful thiolation, because the attempted thiolations by employing either a free alkylthiol or dialkyldisulfide led to the formation of undesired thiolated compounds presumably via the $C(sp^3)$−H bond oxidation in the alkylthio substituent (Scheme 4).

On the basis of these studies, we propose a mechanistic pathway outlined in Scheme 5. In a catalytic cycle, the Cu^I catalyst is initially oxidized by DMSO to give a Cu^{II} species, which upon a base-mediated SET from 2-alkylazole **1** regenerates the Cu^I species.[15] The carbo-radical thus produced from **1** reacts readily with the *in situ*-formed disulfide to furnish α-thiolated product **4**. We believe that a similar mechanism is also operational for the selenylation reaction.

Finally, the synthetic practicality of the new approach was established by a gram-scale synthesis (from 1.26 g, 6 mmol of

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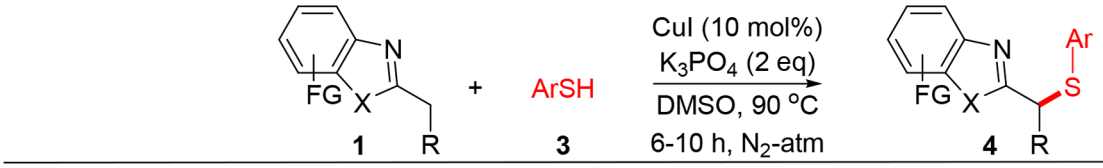
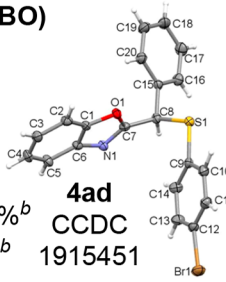
Scheme 2. Copper-Catalyzed Thiolation of 2-Alkylbenzoxazoles and Benzothiazoles[a]



A. with regard to Benzoxazoles (BO)

4aa, Ar = Ph, 84%
4ab, Ar = 4-FC_6H_4, 61%
4ac, Ar = 4-ClC_6H_4, 55%
4ad, Ar = 4-BrC_6H_4, 64%
4ae, Ar = 4-$NO_2C_6H_4$, 51%[b]
4af, Ar = 2-MeC_6H_4, 61%[b]



4ad
CCDC 1915451

4ba, Ar = 2-ClC_6H_4, 70%
4ca, Ar = 2-MeC_6H_4, 75%
4da, Ar = 4-$NO_2C_6H_4$, 68%[c]
4eg, Ar = 3-MeC_6H_4, 78%
4fg, Ar = 4-$MeOC_6H_4$, 70%
4gg, Ar = 4-BrC_6H_4, 80%

4ha, 64%

4ih, R = *n*Hex 48%[d,e]
4jh, R = Bn, 80%[b,e]

4kg, 64%[b,e]

4lh, 61%[b,e]

4mg, 46%[b,e]

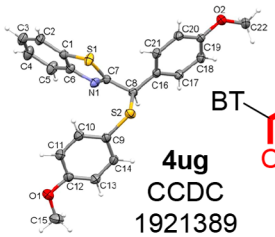
B. with regard to Benzothiazoles (BT)

4na, 64%[b,e]

4oh, 57%[b,e]

4pa, Ar = Ph, 77%[b,e]
4pb, Ar = 4-FC_6H_4, 80%[b,e]
4pc, Ar = 4-ClC_6H_4, 82%[d,e]
4pd, Ar = 4-BrC_6H_4, 78%[d,e]
4pg, Ar = 4-$OMeC_6H_4$, 80%[e]
4pi, Ar = 2-Pyridyl, 41%[b]
4pj, Ar = 1-Naphthyl, 69%

4qa, Ar = 2-ClC_6H_4, 64%[d,e]
4ra, Ar = 4-BrC_6H_4, 72%[d,e]
4sa, Ar = 4-$NO_2C_6H_4$, 57%[f]
4ta, Ar = 3-MeC_6H_4, 71%[e]



4ug
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4ug, 65%[e]

4sk, 75%[c]

4vh, R = Me, 73%[e,g]
4wh, R = *n*Bu, 48%[e]

4xa, 69%[d,e]

4ya, 34%[g]

Beyond Scope
Y = BO, BT
0%

[a]Reaction conditions: **1** (0.5 mmol), **3** (1.1 mmol), CuI (10 mol %), K_3PO_4 (1.0 mmol), DMSO (3 mL), N_2 atmosphere, 90 °C, 6−10 h. [b]Twelve hours. [c]Two hours. [d]Fourteen hours. [e]With 20% CuI and 20% picolinic acid. [f]Three hours. [g]Twenty-four hours. BT = benzothiazole.

Scheme 3. Scope of C(sp^3)−H Phenylselenylation[a]

6a, R = Ph, 69%
6b, R = 2-Me-C_6H_4, 73%
6c, R = 3-Me-C_6H_4, 64%
6d, R = 4-NO_2-C_6H_4, 57%[b]
6e, R = 4-Br-C_6H_4, 66%
6f, R = Me, 0%

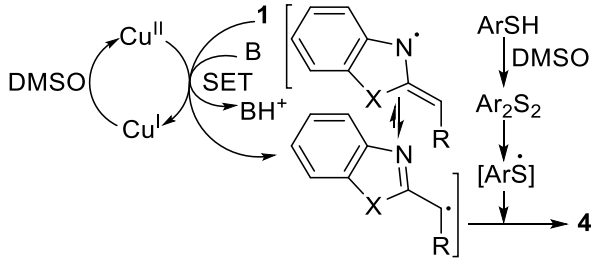
6g, 70%[c]

6h, R = Me, 68%
6i, R = Cl, 68%[c]

6j, R = 2-Me-C_6H_4, 70%
6k, R = 2-Cl-C_6H_4, 61%
6l, R = 4-NO_2-C_6H_4, 52%[b]

[a]Reaction conditions: **1** (0.5 mmol), Ph_2Se_2 (0.65 mmol), CuI (10 mol %), K_3PO_4 (1 mmol), DMSO (3 mL), N_2 atmosphere, 25 °C, 6 h. [b]Two hours. [c]Ten hours.

Scheme 4. Plausible Mechanistic Pathway



1a) of **4ad** (1.45 g, 61%). Subsequently, **4ad** was transformed into α-thilolated carboxylic acid **7**, which was further converted into a bioactive sphingosine 1-phosphate antagonist **8** that is capable of preventing glaucoma, dry eye, and angiogenesis-related diseases.[9,16] Additional applications were demonstrated via the conversion to a sulfone **9** and a ketal **10** giving access to important benzothiazole derivatives, which can be successively transformed into a ketone or an aldehyde by a literature method.[17]

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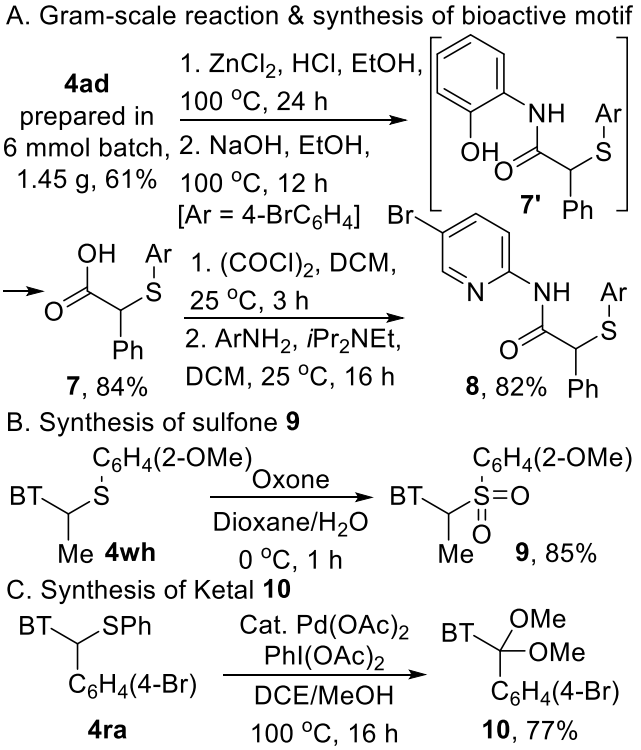
Scheme 5. Transformations of α-Thiolated Compounds



In summary, we have successfully demonstrated the regiospecific α-chalcogenation of aliphatic carboxylic acids via converting them into the corresponding 2-alkylbenzazoles by using a copper-based system. In this transformation, DMSO played crucial roles as both a 2-fold oxidant and a solvent. The practicality of the chalcogenation approach has been illustrated in numerous ways: (1) gram-scale synthesis and subsequent transformations to access the α-chalcogenated carboxylic acid and a bioactive molecule and (2) further transformation of the resulting thiolated compounds via the synthesis of sulfone and ketal derivatives. To the best of our knowledge, the new approach establishes the first example of the direct α-arylchalcogenation of aliphatic carboxylic acid synthons. The unique reactivity of benzazoles toward functionalizing at the C−H bonds adjacent to the ring opens up new possibilities of analogous C−C and C−heteroatom bond forming reactions and is presently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02424.

Optimization table, experimental procedures, mechanistic studies, and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1915451 and 1921389 contain 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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