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COMMUNICATION

Photo-induced Copper-Catalyzed C–H Chalcogenation of Azoles at Room Temperature

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Parthasarathy Gandeepan, Jiayu Mo and Lutz Ackermann*

Inexpensive copper catalysts enabled direct C–H chalcogenations at ambient temperature by means of photo-induced catalysis. The expedient copper catalysis set the stage for C–S and C–Se bond formation from readily accessible non-volatile elemental chalcogens. The photo-assisted copper catalysis manifold proved suitable for a wide range of substrates with good functional group tolerance and exhibited a high catalytic efficacy even at a reaction temperature of 25 °C.

Methods for the direct functionalization of C–H bonds by base metal catalysis are in high demand, due to their low toxicity, natural abundance, and cost effectiveness as compared to typically used precious transition metals.[1] Recently, significant advances have been accomplished in copper-catalyzed C–C and C–heteroatom bond formation via C–H activation.[2] While the use of cost-effective and environmentally-friendly copper catalysts is thus highly attractive, major disadvantages are represented by the requirement of stoichiometric quantities of copper, the need for strong silver(I) or peroxide oxidants, the limitation to specific ligands, and/or rather harsh reaction conditions with typical reaction temperatures of 100-140 °C.[3]

In recent years, photocatalysis has emerged as a powerful tool in organic synthesis.[4] Thus, enabling photoredox transformations were developed with transition metals, including iridium,[5] ruthenium,[6] gold,[7] nickel,[8] and copper.[9] Particularly, the possibility of merging photocatalysis with noble palladium, rhodium, and ruthenium catalyzed C–H functionalization has been highlighted,[10,11] albeit at elevated reaction temperatures of 100-120 °C. In sharp contrast, our group recently disclosed the photo-induced copper-catalyzed C–H arylation, proceeding at ambient temperature.[12]

Despite of notable progress in thiolation and selenation chemistry,[13,14] transition metal-catalyzed thermal transformations are largely restricted to rather harsh reaction conditions. In contrast, photo-mediated cross-couplings of thiols were recently achieved.[15] Hence, photo-induced copper-catalyzed cross-couplings of aryl iodides/bromides proved viable,[15a,d,g] while a nickel-catalyzed photoredox process was exploited for C–S forming cross-couplings in the presence of a precious iridium photo catalysts (PCs).[15b] In spite of these considerable advances, the necessity for prefunctionalized substrates in these cross-coupling approaches represents a considerable obstacle. Furthermore, synthetically useful selenides have as of yet proven elusive in photo-induced cross-couplings. Within our program on sustainable C–H activation by base-metal catalysis,[16] we herein report on first C–H chalcogenations at 25 °C by sustainable copper catalysis (Fig. 1). Notable features of our report include a) base metal-catalysis at room temperature, as well as b) copper-catalyzed C–H thiolations and selenations with c) non-volatile elemental chalcogens, being d) devoid of any expensive iridium or ruthenium catalyst.

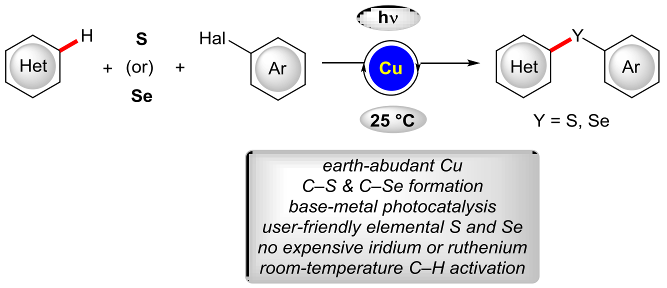

Fig. 1 Photo-induced copper-catalyzed C–H chalcogenation at 25 °C.

We initiated our studies by probing reaction conditions for the envisioned C–H thiolation of benzothiazole (**1a**) with 3-iodotoluene (**2a**), employing elemental sulphur (Table 1). Various ligands failed to improve the yield of desired product **3aa** (Table 1, entries 1-7). Furthermore, the catalytic efficiency was not significantly altered when the reaction was performed under an atmosphere of oxygen or nitrogen (entries 8 and 9). While different copper salts provided comparable results,

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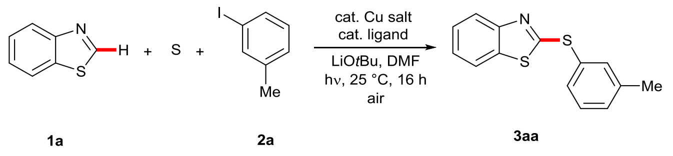
copper(I) thiophene-2-carboxylate (CuTc) displayed the best performance for the catalytic C–H thioarylation at room temperature. A reaction conducted in DMSO as the solvent proceeded less efficiently (entry 15), and other reaction media, including toluene, THF, Et_2O, 1,4-dioxane or CH_3CN, gave inferior results. Finally, control experiments verified that the C–H thioarylation did not occur in the absence of the copper complex or without irradiation (entries 17 and 18). The mass balance of the photo-induced C–H chalcogenation was accounted for by unreacted starting material **1a**.

Table 1 Optimization of copper-catalyzed C–H thioarylation at room temperature[a]

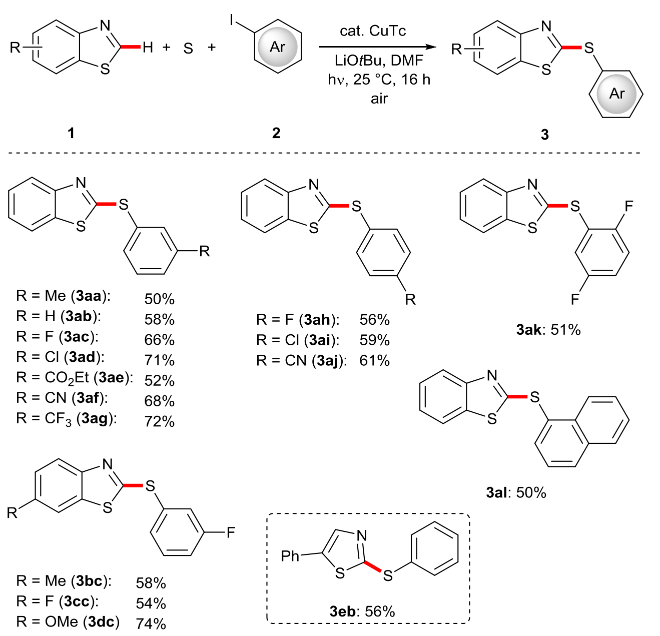


Entry	Cu Salt	Ligand	Solvent	Yield (%)
1	CuI	1,10-Phen	DMF	26
2	CuI	bpy	DMF	30
3	CuI	DMEDA	DMF	28
4	CuI	TMEDA	DMF	35
5	CuI	L-Proline	DMF	28
6	CuI	$Me_2NCH_2CO_2H$	DMF	26
7	CuI	--	DMF	44
8	CuI	--	DMF	47[b]
9	CuI	--	DMF	42[c]
10	CuCl	--	DMF	41
11	CuBr	--	DMF	43
12	CuOAc	--	DMF	19
13	**CuTc**	**--**	**DMF**	**50**
14	$Cu(OAc)_2$	--	DMF	35
15	CuTc	--	DMSO	40
16	CuTc	--	PhMe	6
17	CuTc	--	DMF	0[d]
18	--	--	DMF	0
19	CuTc	--	DMF	5[e]
20	CuTc	--	DMF	0[f]

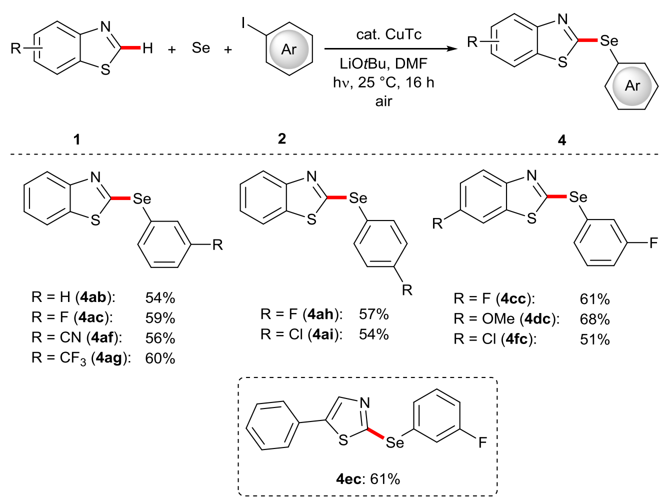
[a] Reaction conditions: **1a** (0.40 mmol), **2a** (1.20 mmol), S (0.80 mmol), Cu salt (20 mol %), ligand (30 mol %), 254 nm, LiOtBu (1.20 mmol), DMF (2.0 mL), under air, yield of isolated product. [b] Under O_2. [c] Under N_2. [d] Reaction performed in the dark. [e] 22 W CFL. [f] 5 W blue LED. Phen = phenanthroline, bpy = 2,2'-bipyridine, DMEDA = N,N'-dimethylethylenediamine, TMEDA = *N,N,N',N'*-tetramethylethylenediamine, CuTc = copper(I) thiophene-2-carboxylate.

We next explored the scope of the photo-assisted C–H thioarylation of heteroarenes **1** by probing diversely substituted aryl iodides **2** (Scheme 1). Thus, the optimized copper catalyst performed well with good functional group tolerance to deliver the desired C–H thioarylation products **3**. Moreover, a thiazole also provided the desired C–H thiolation product **3eb**.

The catalytic system was not restricted to the C–H thiolation manifold. Indeed, C–H selenations with elemental selenium at room temperature were also viable under otherwise identical reaction conditions (Scheme 2). Thus, a variety of 2-arylselanylbenzothiazoles **4** were obtained within the three-component C–H activation regime. The robustness of the photo-induced copper-catalyzed C–H activation was further reflected by the C–H chalcogenation of benzothiazole **1a** with both elemental sulphur and selenium and aryl bromides **5** at ambient temperature (Scheme 3). It is particularly noteworthy that challenging heteroaryl bromides derived from quinoline and isoquinoline were effectively transformed into the desired 2-thionylbenzothiazoles **3** and 2-selanylbenzothiazoles **4** with high levels of chemo and positional selectivities.



Scheme 1 Photo-induced copper-catalyzed C–H thioarylation at 25 °C.



Scheme 2 Photo-induced copper-catalyzed C–H selenation at 25 °C.

In consideration of the unique versatility of the photo-induced copper catalysis, we became attracted by rationalizing its mode of action. To this end, intermolecular competition experiments revealed electron-deficient aryl iodides **2** to be

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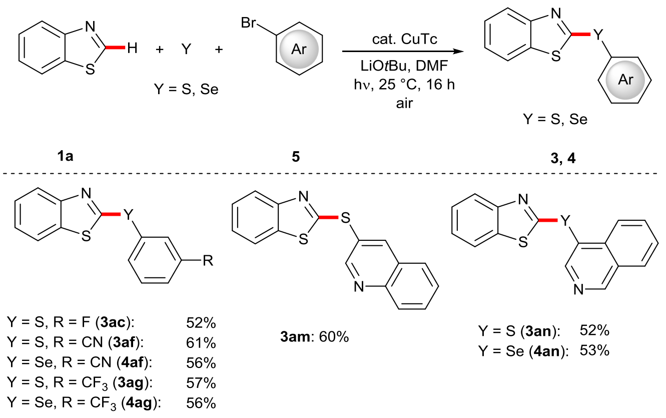
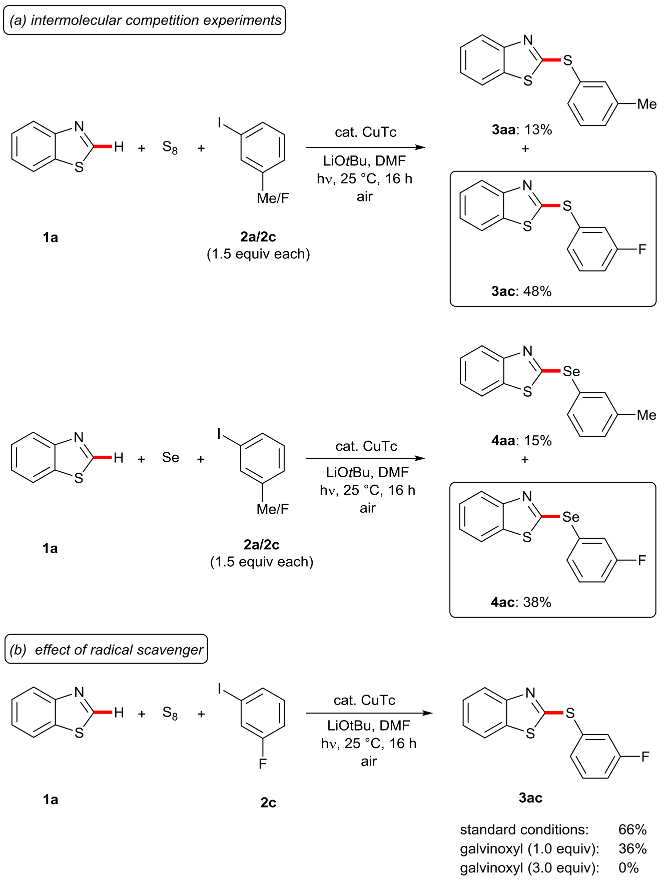
preferentially converted (Scheme 4a). Further, we probed a SET-type reaction regime by the use of the typical radical scavenger galvinoxyl (Scheme 4b), which resulted in a significant inhibition of the catalytic efficacy.

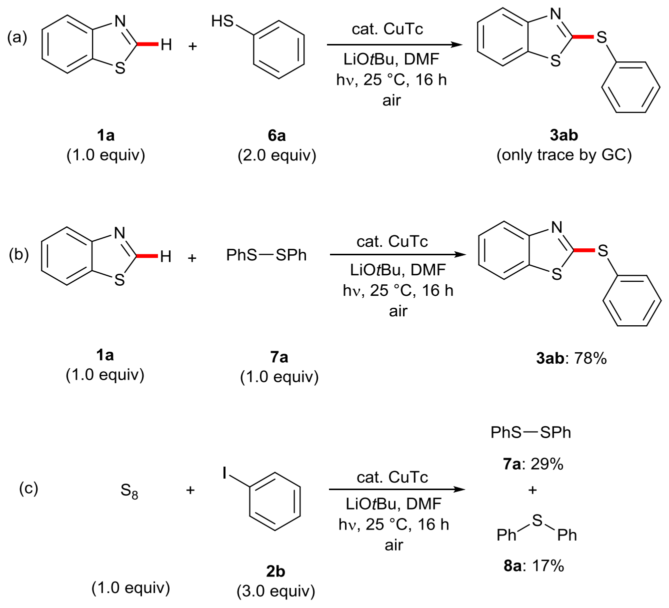


Scheme 3 Photo-induced C–H chalcogenation with aryl bromides **5**.



Scheme 4 Key mechanistic studies.

To further elucidate the nature of the thiolating reagent, we performed a series of additional experiments (Scheme 5). Under otherwise identical reaction conditions, the use of the thiophenol PhSH (**6a**) in place of the aryl electrophile and elemental sulphur did not provide the desired product **3ab** (Scheme 5a).[17] However, the reaction of substrate **1a** with diphenyl disulfide (**7a**) afforded product **3ab** in high yield.[18] Finally, we treated iodobenzene **2b** with elemental sulphur, delivering diphenyl disulfide (**7a**) and diphenyl sulfide (**8a**). These results provided strong evidence for the *in-situ* formation of diaryl disulfides as the key intermediates.



Scheme 5 Probing a reaction intermediate.

In summary, we have developed the unprecedented photo-induced copper-catalyzed C–H chalcogenation at room temperature. The C–H functionalization of azoles[19] with (hetero)aryl electrophiles and elemental sulphur/selenium enabled C–H arylchalcogenations of aromatic heterocycles with ample scope. The characteristic features of these transformations include an operationally-simple copper catalysis, user-friendly elemental chalcogens, sustainable base-metal catalysis, and ambient reaction temperature under aerobic reaction conditions.

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19 Under otherwise identical reaction conditions, the use of benzimidazoles led thus far to less satisfactory results.

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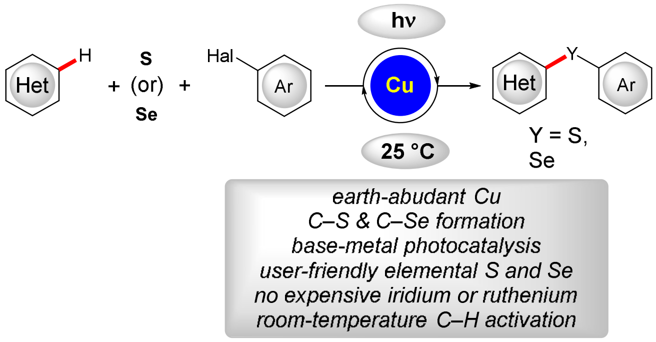
TOC:

Photo-induced copper-catalyzed C–H chalcogenation at 25 °C

Parthasarathy Gandeepan, Jiayu Mo, Lutz Ackermann*



Copper-catalyzed C−H chalcogenations of heteroarenes were achieved at room temperature of 25 °C by photo-induced catalysis within a three-component C–S and C–Se forming regime.