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C–H Functionalization

Weak *O*-Assistance Outcompeting Strong *N,N*-Bidentate Directing Groups in Copper-Catalyzed C–H Chalcogenation

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Abstract: A copper-mediated C–H chalcogenation of triazoles has been achieved by weak coordination. The user-friendly protocol showed high functional-group tolerance and ample substrate scope, yielding fully substituted 1,2,3-triazoles with complete positional site-selectivity. The C–H selenylation could likewise be achieved by means of copper catalysis. Our findings highlight for the first time that weak *O*-coordination can outcompete the strong *N*,*N*-bidentate coordination mode in C–H functionalization technology.

Fully functionalized 1,2,3-triazoles constitute a privileged structural motif in various applied areas, inter alia present in medicinal chemistry and material sciences as well as in pharmacophores of numerous bioactive compounds.[1] For instance, carboxylamidotriazole **I** (CAI) shows anticancer activity,[2a] the sulfur-containing triazole **II** is a potential herbicide with antifungal activity,[2b] and triazole **III** is a powerful ligand in asymmetric catalysis (Figure 1).[2c]

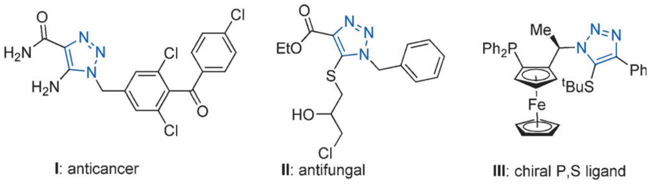

Figure 1. Important C5-functionalized triazoles **I**, **II**, and **III**.

The copper(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) is widely recognized as the most efficient tool to access 1,2,3-triazoles with high levels of chemo- and regiocontrol.[3] However, except a few rare examples,[4] this methodology continues to be severely restricted to terminal alkynes and thus fails short in providing a platform for the selective synthesis of fully functionalized 1,2,3-triazoles. Therefore, the nexus of CuAAC and C–H functionalization technology constitutes an attractive alternative to traditional CuAAC protocols.[5,6] Aryl chalcogenides are ubiquitous in material science and in bioactive organic compounds.[7] However, syntheses of sulfur- and selenium-containing compounds are often challenging, because the required chalgonide reagents inhibit effective catalysis by poisoning the active metal species. Recent progress was represented by the direct introduction of chalcogenides by means of C–H functionalization strategies[8] in order to overcome the limitations of traditional metal-catalyzed cross-coupling methods.[9] Therefore, we became attracted to developing a site-selective protocol for merging CuAAC click-chemistry with atom-economical C–H chalcogenation by late-stage diversification.[10] In this context, our group has developed, in the past few years, a new family of bidentate 1,2,3-triazole TAM auxiliaries for the selective *ortho*-C–H functionalization using inexpensive metal catalysts.[11] Hence, we disclosed iron-catalyzed C–H activations exploiting the strong bidentate binding motif.[11a] Within our program on copper-mediated C–H functionalizations,[12] we have now observed the C–H chalcogenation on 1,2,3-triazoles by weak[13] *O*-monodentate assistance, counterintuitively overriding a strong *N,N* bidentate[14] chelation assistance (Figure 2). Notable features of our findings include: i) the use of an inexpensive copper catalyst, ii) effective C–H sulfenylation and selenylation, iii) step-economical access to fully substituted triazoles, and iv) the unprecedented weak *O*-coordination outcompeting the *N,N*-bidentate directing group.

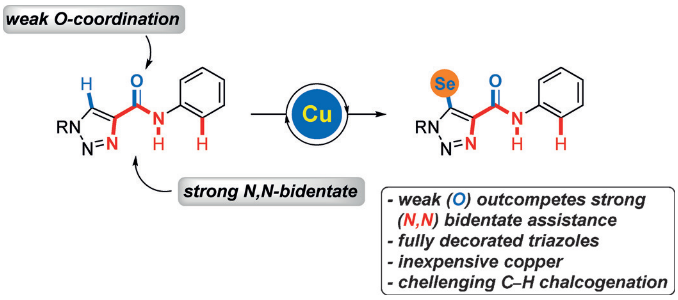

Figure 2. Weak (*O*) coordination overrides strong (*N,N*) bidentate motif.

At the outset of our studies, we probed the C–H selenylation of *N*-(triazolyl)-anilide **1a** in the presence of $Cu(OAc)_2$ and Ph_2Se_2 (Table 1, entry 1). Interestingly, the C–H selenylation of substrate **1a** exclusively proceeded at the C5 position of the triazole moiety through the weakly coordinating *O*-bonding

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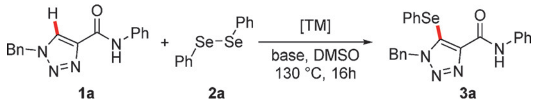
Table 1. Optimization of C–H chalcogenation by weak coordination.[a]

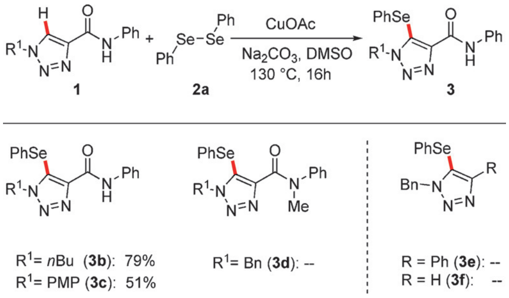


Entry	[TM]	Base	Yield [%]
1	$Cu(OAc)_2$	K_2CO_3	39
2	–	K_2CO_3	–
3	CuOAc	K_2CO_3	50
4	CuOAc	Li_2CO_3	52
5	CuOAc	Cs_2CO_3	47
6	CuOAc	Na_2CO_3	59
7[b]	**CuOAc**	**Na_2CO_3**	**81**
8[b]	CuTc	Na_2CO_3	70
9[b]	CuCl	Na_2CO_3	58
10[b]	CuI	Na_2CO_3	–
11	$Pd(OAc)_2$ (5 mol %)	Na_2CO_3	–

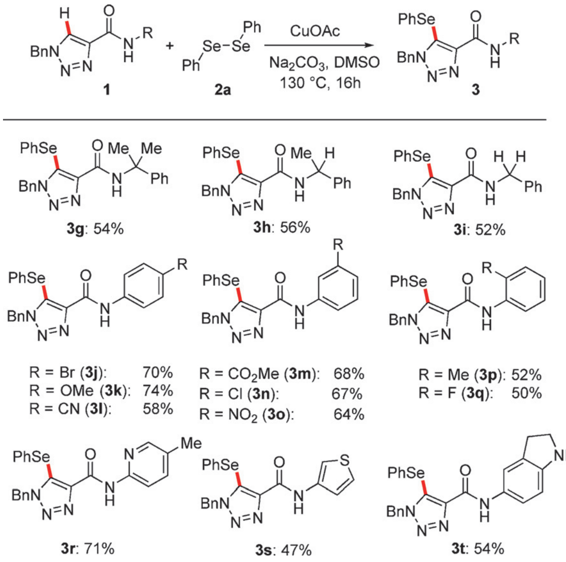
[a] General reaction conditions: **1a** (0.2 mmol), Ph_2Se_2 (0.4 mmol), [Cu] (0.1 mmol), base (0.2 mmol), DMSO (0.2 M), air, 130 °C, 16 h. [b] DMSO (0.2 M).

motif. Among a variety of copper salts, CuOAc gave optimal results, particularly with Na_2CO_3 as the base, affording product **3a** in 59 % yield (entries 1–6). The performance of the C–H selenylation could further be improved by increasing the concentration (entry 7). Other copper(I) salts provided less satisfactory results (entries 8 and 9), and CuI failed to convert substrate **1** (entry 10). It is also worth noting that $Pd(OAc)_2$ was found to be entirely ineffective for the C–H functionalization under otherwise identical reaction conditions (entry 11), highlighting the challenging nature of the C–H selenylation approach.

With the optimized C–H selenylation being established, its versatility was probed with differently substituted triazoles **1** (Scheme 1). Although secondary amides **1b** and **1c** efficiently delivered the desired products **3b** and **3c**, respectively, tertiary amide **1d** failed short in providing the desired product **3d**, as did aryl- or monosubstituted triazoles **1e** and **1f**, respectively. These findings provided strong support for the chelation assistance regime.



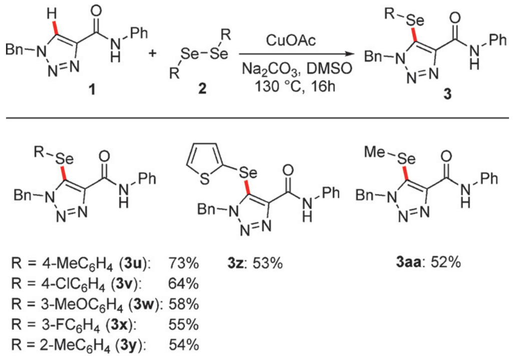
Scheme 1. C–H selenylation by weak coordination.



Scheme 2. Scope of C–H selenylation with triazoles **1**.

The optimized protocol proved to be widely applicable to the C–H selenylation of various triazole-functionalized anilides **1** (Scheme 2). The robust nature of the C–H selenylation was reflected by the tolerance of sterically hindered substrates as well as synthetically useful electrophilic functional groups, such as cyano, ester, and nitro substituents. Likewise, aryl bromides (**1j**) and chlorides (**1n**) were fully accepted without any sign of cross-coupling byproducts. The C–H selenylation strategy further proved amenable to heterocyclic substrates, including pyridine, indoline, and thiophene derivatives **1r**–**1t**.

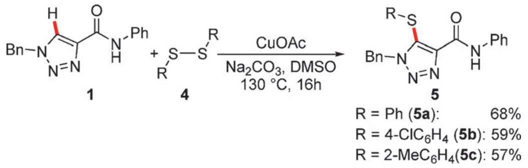
Thereafter, we investigated the C–H selenylation with structurally diverse diselenides **2** (Scheme 3). Hence, electron-donating and -withdrawing groups at the *para*-, *meta*-, and *ortho*-position were well tolerated by the optimized reaction conditions. Notably, the protocol was not restricted to aromatic diselenides **2**. Indeed, heteroaryl and alkyl derivatives **2z** and **2aa** were also efficiently converted as well to deliver products **3z** and **3aa**, respectively.



Scheme 3. C–H functionalization with diselenides **2**.

The robustness of the widely applicable protocol also enabled the challenging C–H sulfurylation on substrates **1** (Scheme 4), again with weak *O*-coordination overriding the bidentate *N*,*N*-coordination mode.

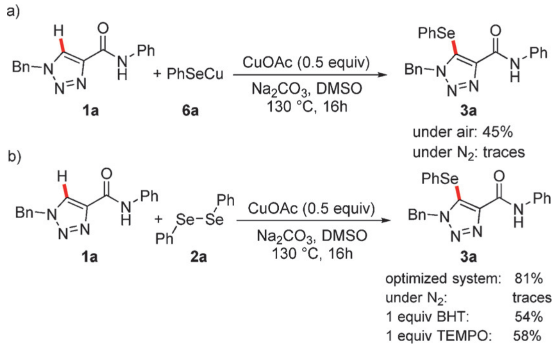
In consideration of the unique features of the C–H chalcogenation by preferential weak *O*-coordination, we became intrigued by delineating its mode of action. To this end, reac-



Scheme 4. C–H sulfurylation by weak *O*-coordination.

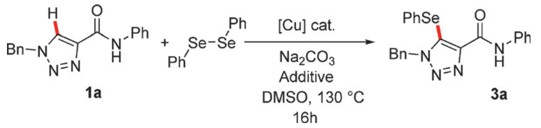
tions with the well-defined copper(I) selenide PhSeCu (**6a**) as the selynylation reagent furnished the desired product **3a** under an atmosphere of air (Scheme 5a). Furthermore, the stoichiometric use of the radical inhibitors 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) and butylated hydroxytoluene (BHT) led to a slight, yet notable decrease in efficacy (Scheme 5b).

Finally, the C–H selenylation proved viable with catalytic amounts of CuOAc provided that PhI(OAc)$_2$ was employed as the additive (Table 2).



Scheme 5. Mechanistic studies.

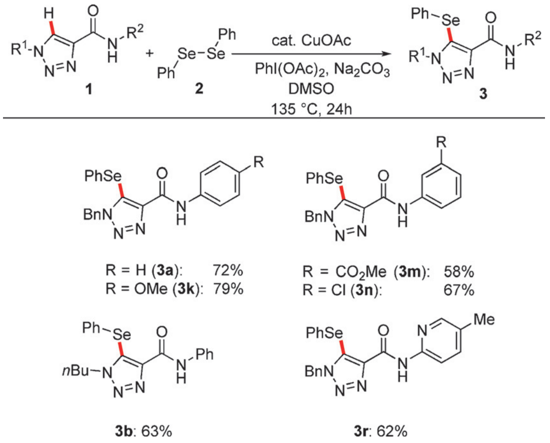
Table 2. Copper(I)-catalyzed C–H selenylation.[a]



Entry	[Cu]	Additive	Yield [%]
1	CuOAc	O_2	42
2	CuOAc	MnO_2	34
3	CuOAc	PhI(OTFA)$_2$	–
4	Cu(OAc)$_2$	PhI(OAc)$_2$	38
5	**CuOAc**	**PhI(OAc)$_2$**	**72**

[a] General reaction conditions: **1a** (0.2 mmol), Ph$_2$Se$_2$ (0.4 mmol), [Cu] (0.04 mmol), base (0.2 mmol), additive (0.4 mmol), DMSO (0.5 mL), air, 130 °C, 16 h.

The optimized copper-catalyzed C–H chalcogenation proved broadly applicable (Scheme 6). Hence, a variety of substituted diselenides **2** enabled the site-selective C–H functionalization on substrates **1** by weak mono *O*-coordination (Scheme 3).



Scheme 6. Catalytic C–H selenylation by weak *O*-coordination.

In summary, we have shown that the weak monodentate *O*-assistance can outcompete strong *N*,*N*-bidentate directing groups in catalyzed C–H activation technology. Thus, efficient copper(I)-promoted C–H chalcogenations were viable by an amide assistance, furnishing fully decorated 1,2,3-triazoles with excellent chemo- and positional selectivities. The optimized protocol proved broadly applicable to C–H selenylation as well as C–H sulfenylation with ample scope, and was accomplished by means of cost-effective copper catalysis though weak *O*-assistance.

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Keywords: C–H activation · copper · selenylation · sulfenylation · triazoles

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