C-H Alkylation

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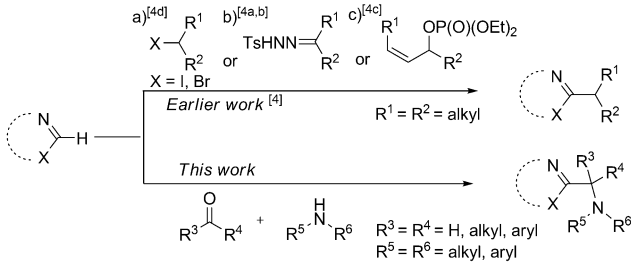
Copper-Catalyzed Direct Secondary and Tertiary C–H Alkylation of Azoles through a Heteroarene–Amine–Aldehyde/Ketone Coupling Reaction**

*Dipak D. Vachhani, Abhishek Sharma, and Erik Van der Eycken**

The transition-metal-catalyzed direct C–H functionalization of heteroarenes has emerged as a powerful approach for streamlining the synthesis of biologically important heterocyclic frameworks.[1] In this context, considerable progress has been achieved in the direct arylation, alkenylation, and alkynylation of heteroarenes using aryl halides and psuedohalides as coupling partners.[2] In contrast, the corresponding direct C–H alkylation,[3] especially the installation of secondary alkyl groups on azoles, has remained a much more challenging proposition. Recently, some attractive methods have emerged for the direct secondary alkylation of azoles using tosylhydrazones,[4a,b] allylic phosphates,[4c] and secondary halides[4d] as coupling partners (Scheme 1). However, it



Scheme 1. Strategies for direct secondary/tertiary C–H alkylation of heteroarenes.

would be highly desirable if readily available alkyl donors could be employed for the introduction of diversly substituted secondary or even tertiary alkyl groups on azoles. For example, azoles bearing an alkylamine side chain at the C2 position constitute an integral component of biologically important natural products.[5] Currently available direct C–H alkylation methods do not allow the installation of substituted alkylamine moieties on azoles.[6]

On the other hand, the copper-catalyzed aldehyde–amine–alkyne (A^3) coupling[7] is a highly useful multicomponent reaction for the synthesis of propargylamines. This proceeds through the initial formation of a metal acetylide followed by its coupling with an imine formed in situ.[7] In the course of our ongoing research into the synthetic utility of A^3 couplings[8a] and the direct C–H functionalization of heteroarenes,[8e–f] we wondered if the metal–azole complex formed by the C–H activation can be trapped by an imine formed in situ. Such a combination of two contemporary C–C bond forming approaches[2,7] would not only allow the facile installation of a diverse range of secondary, and even tertiary, alkyl groups on azoles, but also furnish unprecedented access to azoles bearing alkylamine side chains. Herein, we describe the realization of this goal through a novel copper-catalyzed heteroarene–amine–aldehyde/ketone (HA^2/HAK) coupling (Scheme 1).

To test our initial hypothesis for a copper-catalyzed HA^2 coupling, cyclohexylcarboxaldehyde (**2a**, 0.4 mmol, 1 equiv) was treated with piperidine (**1a**, 1.2 equiv) and 2-phenyloxadiazole (**3a**, 1 equiv) in the presence of CuI (15 mol%) in toluene at 110°C under microwave irradiation. Although this reaction afforded the desired secondary alkylated product (**4a**) in only 8% yield (Table 1, entry 1), this result motivated us to further explore the conditions.

A careful analysis of the above transformation revealed that the amine-promoted ring-opened azole was the major side product,[9] aside from unreacted azole. In light of this, the ratio of the reactants **1a**/**2a**/**3a** was changed to 1:1.5:1.2, which enhanced the yield of **4a** to 23% (Table 1, entry 2). A further screening of the reaction conditions revealed that replacement of toluene with xylene, THF, or acetonitrile led to lower yields (Table 1, entries 3–5). However, increasing the temperature to 140°C considerably improved the reaction performance (68% yields; Table 1, entry 6). The reaction was also feasible under neat conditions, albeit in lower yield (38%; Table 1, entry 16). Furthermore, among the different copper catalysts tested (Table 1, entries 7–14), CuCl was found to be optimal (78% yield, Table 1, entry 14) whereas the absence of any copper source afforded only a trace of **4a** (Table 1, entry 15).

Having established the optimized conditions, the substrate scope was evaluated. The secondary alkylation proceeded well with various biologically important heteroarenes, such as substituted oxadiazoles,[10a–c] thiadiazole,[10d] and oxazole[10e] (Scheme 2).

[*] D. D. Vachhani, Dr. A. Sharma,[+] Prof. Dr. E. Van der Eycken
Department of Chemistry, University of Leuven (KU Leuven)
Celestijnenlaan 200F, 3001 Leuven (Belgium)
E-mail: erik.vandereycken@chem.kuleuven.be

[+] Present address: Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801 (USA)

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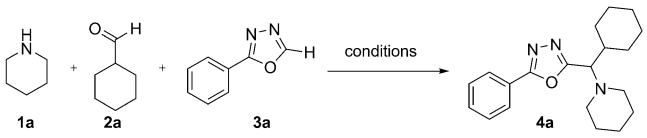
Table 1: Optimization of conditions for the copper-catalyzed direct alkylation of 5-phenylthiadiazole.[a]



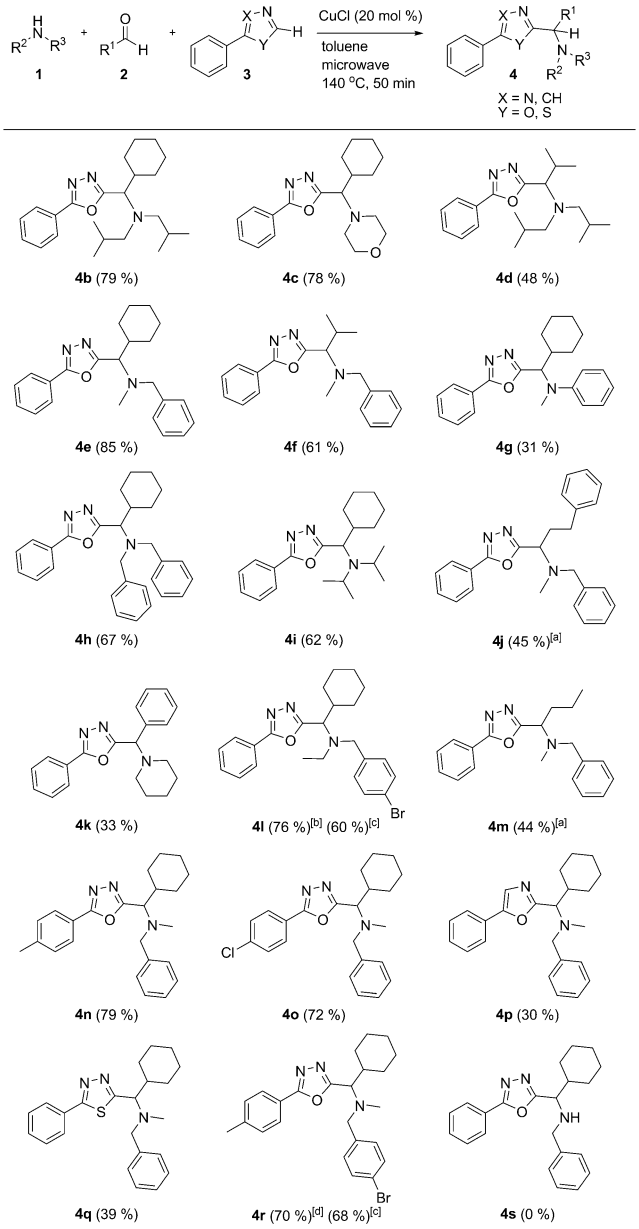
Entry	Copper source	Solvent	*T* [°C]	Yield [%][b]
1	CuI	toluene	110	8[c]
2	CuI	toluene	110	23
3	CuI	xylene	110	9
4	CuI	THF	110	11
5	CuI	MeCN	110	18
6	CuI	toluene	140	68
7	CuBr	toluene	140	74
8	CuCl	toluene	140	76
9	Cu(OTf)·0.5 toluene	toluene	140	57
10	$Cu(MeCN)_4PF_6$	toluene	140	58
11	Cu(OAc)	toluene	140	20
12	$CuCl_2·2H_2O$	toluene	140	32
13	$CuBr_2$	toluene	140	23
14	**CuCl**	**toluene**	**140**	**78[d]**
15	–	toluene	140	trace[e]
16	CuCl	–	140	38
17	CuCl	toluene	140[f]	52

[a] General conditions: **1a** (0.40 mmol), **2a** (0.60 mmol), and **3a** (0.48 mmol), solvent (0.2 mL), catalyst (15 mol%), under microwave irradiation for 50 min at the specified temperature using 200 W maximum power. [b] Yield of isolated product. [c] Ratio of reactants **1a**/**2a**/**3a** was 1.2:1:1. [d] 20 mol% of catalyst was used. [e] Reaction performed without catalyst. [f] Conventional heating.

Amongst the aldehyde coupling partners, the HA^2 coupling was compatible with a diverse set of cyclic/acyclic aldehydes (Scheme 2, **4b–j**, **l–s**) as well as benzaldehyde (Scheme 2, **4k**). The method also allowed diversification of the amine component, as a variety of cyclic and acyclic secondary amines could be employed, thereby paving the way for the installation of alkaloid moieties[11] in the secondary alkyl chain of the azole (Scheme 2, **4b–e, h**, and **i**). Importantly, aniline was also tolerated (Scheme 2, **4g**). The reaction with 4-bromo-substituted *N*-ethylbenzyl amine led to the desired **4l** along with a minor, but chromatographically inseparable side product (10%, based on NMR spectroscopy). LC-MS analysis of this mixture indicated that the corresponding 4-chloro product, *N*-(4-chlorobenzyl)-*N*-(cyclohexyl(5-phenyl-1,3,4-oxadiazol-2-yl)methyl) ethanamine, was formed, presumably by halide exchange with CuCl.[12] However, pure **4l** could be readily obtained by changing the catalyst to CuBr (Scheme 2, **4l**).

Motivated by the above results, we became interested in further increasing the diversity of the alkyl group at the C2 position. Consequently, the developed coupling conditions were tested by changing the carbonyl building blocks from aldehydes to cyclic ketones (HAK coupling). This reaction proved feasible, leading to the unprecedented direct tertiary alkylation of the azole moiety (Scheme 3, **6a–c**).

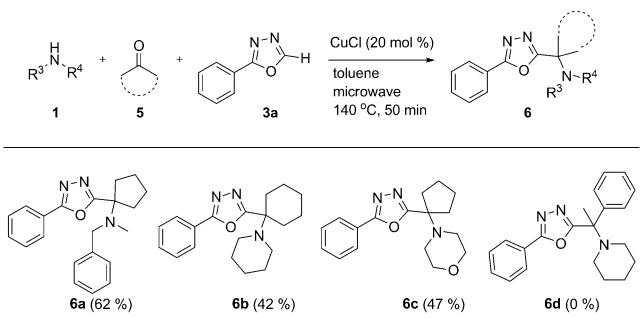
The HA^2/HAK coupling reaction plausibly proceeds through the initial condensation of the aldehyde/ketone with the amine, leading to the corresponding iminium ion (**I**; Scheme 4).[7] Subsequently, **I** is attacked by the azole–Cu



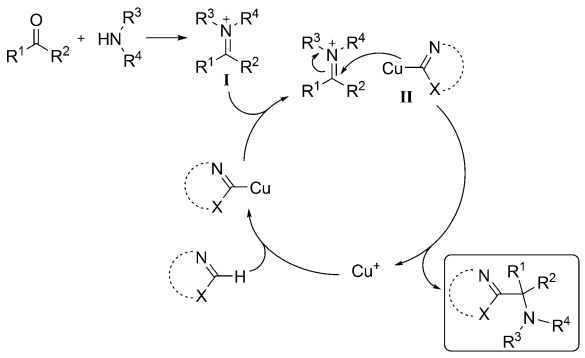
Scheme 2. Cu-catalyzed direct secondary and tertiary C–H alkylation of azoles. General conditions: unless otherwise stated, reactions were run with **1** (0.5 mmol), **2** (0.75 mmol), and **3** (0.60 mmol) in toluene (0.2 mL) using CuCl (20 mol%) under microwave irradiation (CEM Discover) for 50 min at 140°C, 200 W. [a] CuCl (30 mol%) and 40 min reaction time. [b] The 4-chloro product (10%, based on NMR spectroscopy) was also observed. [c] The reaction was carried out with CuBr (20 mol%). [d] The 4-chloro product (9%, based on NMR spectroscopy) was also observed.

complex **II**, which is formed in situ,[13] thereby installing the secondary/tertiary alkyl side chain on the azole.

The development of novel orthogonal relay catalytic reactions is greatly desired in contemporary organic synthesis.[14] To further explore the utility of the HA^2 coupling, we explored its applicability for a multicatalytic orthogonal C–H alkylation/C–H arylation sequence. Thus, amine (**1h,i**) was initially treated with aldehyde **2a** and oxadiazole **3a** in the presence of CuCl in toluene at 140°C to afford the corre-



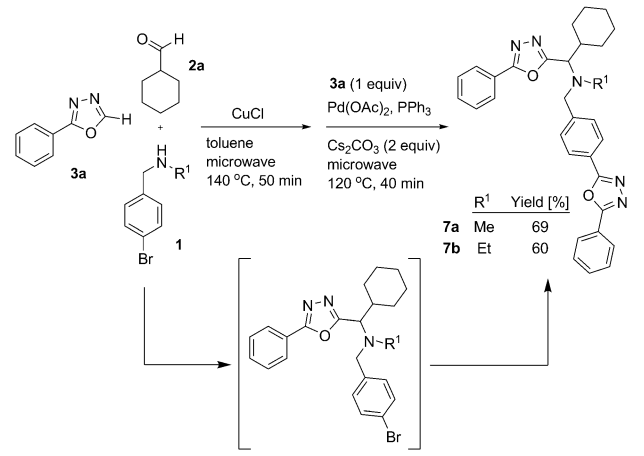
Scheme 3. Cu-catalyzed direct secondary and tertiary C–H alkylation of azoles using ketones. General conditions: **1** (0.5 mmol), **5** (1.0 mmol), and **3a** (0.60 mmol) in toluene (0.2 mL) using CuCl (30 mol%) under microwave irradiation (CEM Discover) for 50 min at 140°C, 200 W.



Scheme 4. Proposed mechanism of the Cu-catalyzed direct C–H alkylation through heteroarene–amine–aldehyde/ketone coupling.

sponding 2-alkylated oxadiazole. To the same pot, another equivalent of **3a** was added, along with $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), and Cs_2CO_3 (2 equiv), and the mixture was further irradiated at 120°C for 40 min. Gratifyingly, the above double C–H functionalization strategy led to a facile synthesis of amine tethered azoles **7** (Scheme 5).

In conclusion, a novel approach for the direct secondary and tertiary C–H alkylation of azoles through copper-catalyzed heteroarene–amine–aldehyde (HA^2) or heteroarene–amine–ketone (HAK) coupling has been elaborated. The method is operationally simple and allows the facile installation of diversely substituted, branched and nitrogen-containing alkyl or alkaloid side chains on the azole moiety using readily available starting materials. The mild conditions of the developed coupling also facilitated an orthogonal C–H alkylation/C–H arylation sequence for the synthesis of amine tethered azoles.



Scheme 5. Application of the HA^2 coupling towards an orthogonal C–H secondary alkylation/C–H arylation sequence.

Experimental Section

Representative procedure for the direct C–H alkylation of 3a: Amine **1a** (0.5 mmol) was added to an oven-dried 10 mL screw-cap vial equipped with a stir-bar, followed by the addition of aldehyde **2a** (84 mg, 1.5 equiv) and toluene (0.2 mL); the resulting mixture was stirred for 5 min at room temperature. Thereafter, heteroarene **3a** (88 mg, 1.2 equiv) and CuCl (10 mg, 20 mol%) were added and the vial was sealed with a Teflon cap. The reaction mixture was irradiated for 50 min at a preselected temperature of 140°C, with a maximum irradiation power of 200 W. After completion of the reaction, the resulting mixture was diluted with ethyl acetate (50 mL), and washed with water (50 mL) and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude sample was purified by silica gel column chromatography (10–20% ethyl acetate in heptane) to obtain compound **4a** (127 mg, 78% yield). See the Supporting Information for NMR spectra and detailed experimental procedures.

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