Photocatalysis *Hot Paper*

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Photoinduced Copper-Catalyzed C–H Arylation at Room Temperature

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Dedicated to Professor Jochen Mattay

Abstract: *Room-temperature azole C–H arylations were accomplished with inexpensive copper(I) compounds by means of photoinduced catalysis. The expedient copper catalysis set the stage for site-selective C–H arylations of non-aromatic oxazolines under mild reaction conditions, and provides step-economical access to the alkaloid natural products balsoxin and texamine.*

Catalyzed C–H activation has emerged as a powerful platform for the step-economical diversification of heteroarenes.[1] Particular progress in C–H activation chemistry was accomplished using earth-abundant copper catalysts,[2] with early contributions to copper(I)-catalyzed C–H arylations by the groups of Daugulis,[3] Miura,[4] and Gaunt,[5] as well as Ackermann[6] among others.[2] Despite these undisputed advances, copper(I)-catalyzed C–H arylations with easily accessible aryl halides continue to face major limitations in that they require rather harsh reaction conditions with typical reaction temperatures ranging from 120 to 160 °C.

In recent years, photocatalysis[7] has been recognized as an increasingly viable tool to realize one-electron-transfer cross-coupling reactions, with key contributions by the groups of Reiser,[8] König,[9] and Glorius,[10] among others.[11–14] The photocatalysis reaction manifold was also merged with precious second-row transition-metal C–H activation catalysts, such as palladium, ruthenium, and rhodium complexes, as elegantly elaborated by among others Sanford[15] and Rueping,[16] exploiting entropically favored intramolecular reactions[16c] or Lewis-basic directing groups.[15,16a,b] In contrast, photoinduced copper-catalyzed C–H arylations with organic halides have thus far proven elusive. Within our program on sustainable C–H activation by base-metal catalysis,[17] we have now devised a protocol for unprecedented photoinduced C–H arylation by copper(I) catalysis, on which we report herein. Notable features of our approach include a) photoinduced base-metal[18] catalysis for C–H activation, b) copper-catalyzed C–H arylations at room temperature, c) ligand acceleration by amino acids[19] in photoinduced C–H activation, and d) versatile copper catalysts that proved effective for aromatic azole and nonaromatic oxazoline substrates—key structural motifs of chiral ligands[20] and natural products (Figure 1).

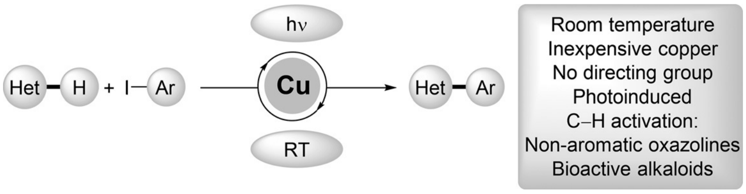

Figure 1. Photoinduced copper-catalyzed C–H activation.

We initiated our studies by probing reaction conditions for the envisioned C–H activation on the substrate **1a** by using photoinduced copper catalysis (Table 1; and see Tables S-1 and S-2 in the Supporting Information).[21] Preliminary experiments revealed CuI and Et_2O to be the catalyst and solvent of choice, respectively (entries 1–5). While the photo-assisted C–H arylation occurred under ligand-free reaction conditions (entries 4–6), here a higher catalyst loading was required to ensure a satisfactory performance (entry 5). Among a set of representative ligands, a significant rate acceleration was exerted by amino acid derivatives (entries 7–12), and the best results were obtained with the aid of *N*,*N*-dimethylglycine (entries 11 and 12). Control experiments confirmed the essential role of the copper catalyst (entry 13), and unambiguously illustrated the photocatalytic nature of the C–H functionalization process (entry 14).

With the optimized reaction conditions in hand, we tested the versatility of the photoassisted C–H arylation with benzannulated heteroarenes **1** (Scheme 1). Thus, the broadly applicable copper(I) catalyst enabled efficient C–H functionalizations of benzothiazoles and benzoxazoles **1** which were devoid of directing groups. The chemoselectivity of the robust catalyst was reflected by its tolerance of valuable functional groups, such as chloro or ester substituents.

The versatile copper catalyst was not limited to the benzannulated substrates **1**. Indeed, the azoles **4** bearing various aromatic C–H bonds proved to be amenable for site-selective C–H arylations (Scheme 2a). Hence, we were

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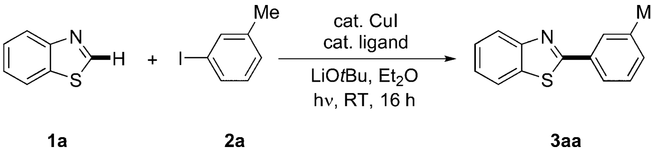
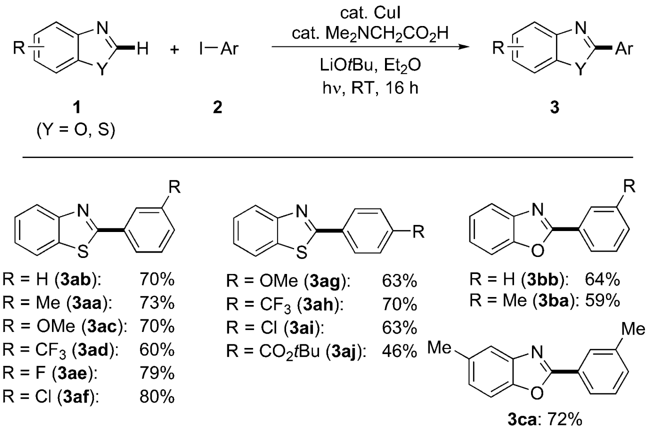
Table 1: Validation of photoinduced copper-catalyzed C—H arylation.[a]



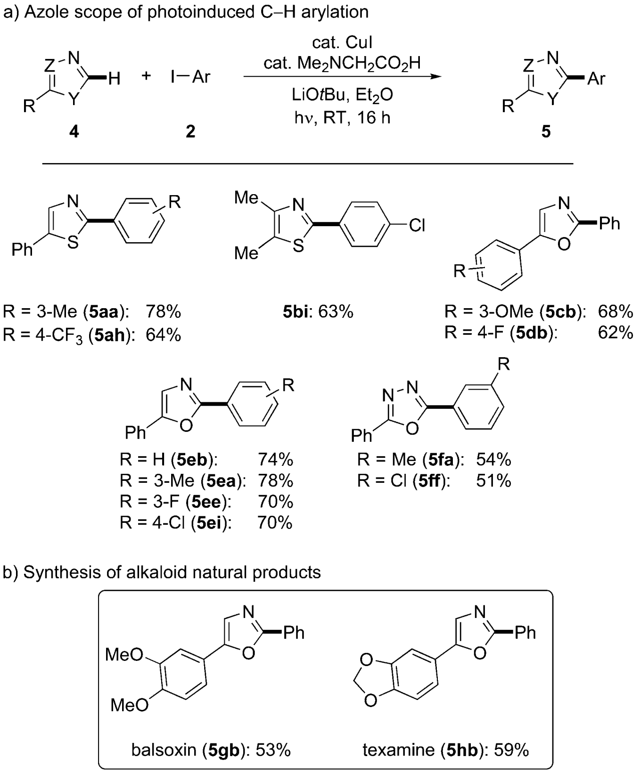
Entry	Ligand	Solvent	Yield [%][b]
1	–	DMA	37[c,d]
2	–	1,4-dioxane	10[d,e]
3	–	THF	30[d,e]
4	–	Et$_2$O	48[d]
5	–	Et$_2$O	80[f]
6	–	Et$_2$O	57
7	TMEDA	Et$_2$O	36
8	bpy	Et$_2$O	39
9	L-Pro-OH	Et$_2$O	62
10	L-Ala-OH	Et$_2$O	67
11	$Me_2NCH_2CO_2H$	Et$_2$O	67
12	$Me_2NCH_2CO_2H$	Et$_2$O[g]	73
13	$Me_2NCH_2CO_2H$	Et$_2$O	0[h]
14	$Me_2NCH_2CO_2H$	Et$_2$O	0[i]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (1.25 mmol), CuI (20 mol %), ligand (30 mol %), 254 nm, LiO*t*Bu (0.75 mmol), Et$_2$O (1.5 mL). [b] Yield of isolated product. [c] 50 °C. [d] CuI (10 mol %). [e] Conversion determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [f] CuI (50 mol %). [g] Et$_2$O (1.0 mL). [h] Without CuI. [i] In the dark. bpy = 4,4′-bipyridine, DMA = *N*,*N*-dimethyl acetamide, RT = room temperature (25–27 °C),[21] THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.



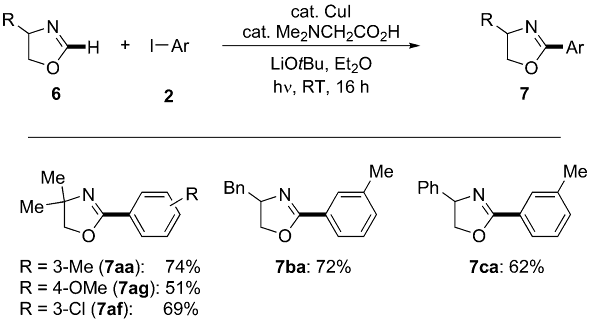
Scheme 1. Photoinduced copper-catalyzed C—H arylation of benzoxazoles **1**.

delighted to observe that a set of differently decorated thiazoles, oxazoles, and oxadiazoles **4a–f** was converted with comparable catalytic efficacy. It is particularly noteworthy that the photoinduced C—H arylation strategy provided step-economical access to the alkaloid natural products balsoxin (**5gb**) and texamine (**5hb**)[22] at room temperature (Scheme 2b). Thus far, the syntheses of these natural products by C—H functionalization technology largely called for either palladium or nickel catalysts, typically at reaction temperatures between 120 and 150 °C,[23] or stoichiometric amounts of copper compounds at 160 °C,[24] thus reflecting the unique potential of the photoinduced copper-catalysis approach.



Scheme 2. Photoinduced C—H arylation of azoles **4**. a) Scope with respect to azoles **4**. b) Synthesis of alkaloids.

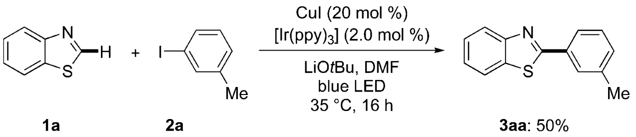
Accomplishing C—H arylations of non-aromatic substrates is difficult, because these substrates lack the aromatic moiety which engages in attractive interactions with the transition metal.[25] Hence, we were particularly delighted to observe that the photoinduced copper(I)-catalyzed C—H arylation strategy proved applicable to the diversification of non-aromatic oxazolines **6** (Scheme 3), which are important structural motifs in various chiral ligands.[20] It is noteworthy that the inexpensive photoinduced copper catalysis compares favorably with the previously reported C—H arylation of oxazolines (**6**) by expensive palladium catalysts at a reaction temperature of 100 °C.[26] Moreover, our approach is complementary to outer-sphere radical-based catalysts, which target



Scheme 3. Photoinduced copper-catalyzed C—H arylation of non-aromatic oxazolines **6**.

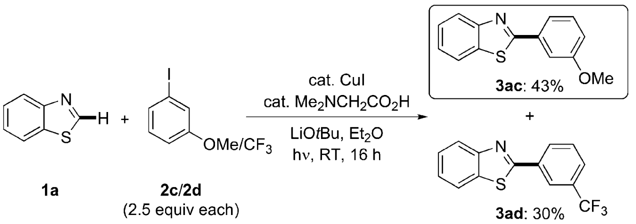
the weakest benzylic C–H bond in proximity to the nitrogen atom in the substrates **6b**,**c**.

Interestingly, the photoassisted C–H arylation could be achieved by using visible light (Scheme 4), provided that an iridium photoredox catalyst was employed in a hetero-bimetallic cooperative catalysis regime (see Table S-3).



Scheme 4. Visible-light photoredox-catalyzed C–H arylation.

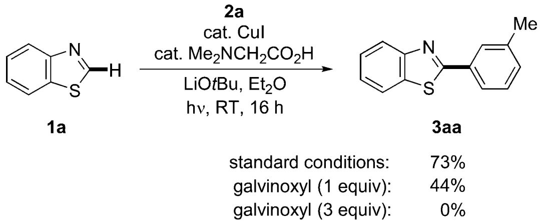
Given the versatility of the photoinduced copper-catalyzed C–H arylation, we became intrigued by performing preliminary mechanistic studies to delineate its mode of action.[21] To this end, intermolecular competition experiments highlighted electron-rich electrophiles to be preferentially converted (Scheme 5), thereby rendering an oxidative C–I addition unlikely to be operative as the kinetically relevant elementary step.



Scheme 5. Competition experiment between aryl iodides **2c** and **2d**.

Finally, we probed an SET-type reaction regime by the addition of the representative radical scavenger galvinoxyl (Scheme 6), and it resulted in a significant inhibition of the catalytic performance.

In summary, we have reported on the first photoinduced[28] C–H arylation by the action of inexpensive copper catalysts. Thus, C–H functionalization with organic electrophiles enabled direct arylations of various aromatic and non-aromatic heterocycles with ample scope. The C–H arylation process is operative on substrates being devoid of directing groups under exceedingly mild reaction conditions[27] at room temperature. Furthermore, our studies reveal the notable rate acceleration of amino acid ligands for photoinduced copper catalysis, which set the stage for the efficient synthesis of the naturally occurring alkaloids balsoxin and texamine by room-temperature C–H arylation.



Scheme 6. Probing an SET-type mechanism.

Acknowledgements

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Keywords: alkaloids · C–H activation · copper · photocatalysis · total synthesis

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[28] The photoinduced C–H arylations were performed in a Luzchem LZC-ICH2 photoreactor equipped with a temperature control unit. We have recorded a reaction temperature range of 25–27 °C throughout the entire C–H transformations (see Figure S-1).

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