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Photoredox-Mediated C–H Functionalization and Coupling of Tertiary Aliphatic Amines with 2-Chloroazoles

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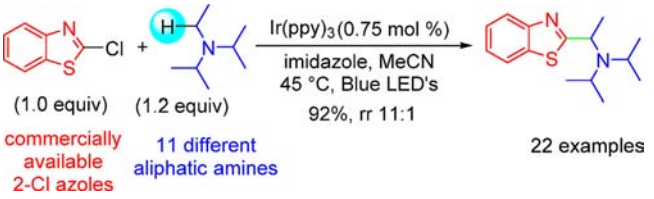
ABSTRACT



Herein, conditions for C–H functionalization of tertiary aliphatic amines and their subsequent coupling with a number of 2-chloroazole derivatives are reported. The reaction is facilitated by a catalytic amount of tris-*fac*-Ir(ppy)$_3$, with blue light irradiation and takes place under mild and convenient conditions. Most couplings take place with excellent regioselectivity. The reaction is tolerant of a number of functional groups and allows for rapid access to α-azole carbinamines commonly found in post-translationally modified peptides.

Aromatic heterocycles are a ubiquitous motif in natural products, drug molecules, and pesticides. One important subclass contains tertiary aliphatic amines adjacent to the heterocycle (Figure 1). Both in nature and in the labratory, access to this motif is often accomplished via cyclodehydration to form the heterocycle.[1] While cyclodehydration methodology is routine, it necessitates early incorporation of substituents, thus, elucidation of structural activity relationships (SAR) of ring substituents in biological studies can be a tedious process involving multistep synthesis. A more expedient disconnection would involve a late-stage direct coupling of the ring and the desired carbinamine substituent. This would reduce the number of synthetic steps needed to perform proper SAR, thus filling a real need. However, no general method exists.

With the aim of developing a late-stage coupling, we began to consider how we might access the azole carbinamine motif via this disconnection. We hoped to use abundant tertiary amines which we reasoned could be activated oxidatively.[3] Recently, a number of photoredox methods have demonstrated α-amino C–H functionalizations of both isoquinoline[4] and aniline[5] derivatives (eqs 1 and 2, Scheme 1). Unfortunately, the inherent limitation of these methods, which is that you must desire an isoquinoline or *N*-aryl group in your molecule, prevented us from using them to access our desired motif. Given the numerous methods involving isoquinoline and aniline derivatives

[†] Authors contributed equally.

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(3) There is significant overlap in the photochemical and copper-mediated processes; for an example and review of copper-mediated oxidative methods, see: (a) Deb, M. L.; Dey, S. S.; Bento, I.; Barros, M. T.; Maycock, C. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9791–9795. (b) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443–2465. (c) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490–1501. (d) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464–3484.

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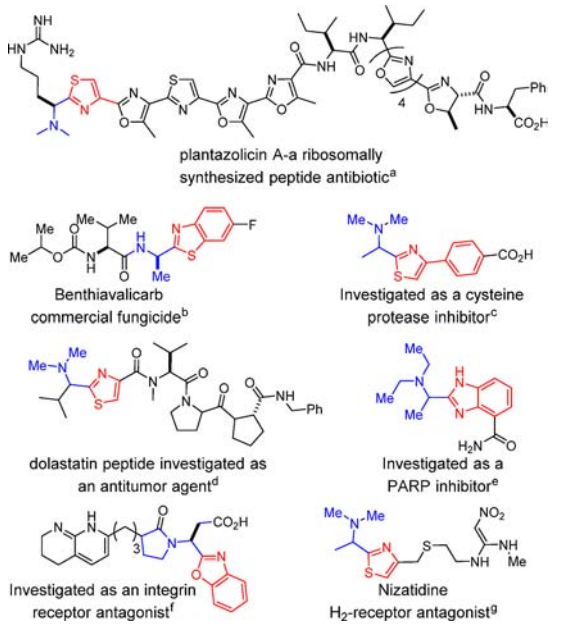
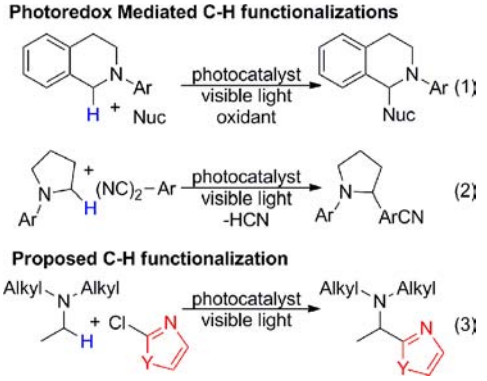


Figure 1. Some examples of natural products, drugs, and pesticides that contain an azole with a carbinamine side chain.[2]

and the frequent use of simple aliphatic amines within photoredox catalysis, it was surprising to find that the C−H functionalization of simpler and far more abundant aliphatic amines had not been developed.[5c,6] Thus, we decided to investigate whether simple aliphatic amines and heteroaryl chlorides could be cross-coupled via photoredox catalysis (eq 3).[7] Herein we report the use of tertiary aliphatic amines as coupling partners in the photocatalytic cross-coupling of 2-chlorobenzimidazoles, -benzoxazoles, -benzothiazoles, and -thiazoles and related derivatives.

We began our study with 2-chlorobenzothiazole, diisopropyl ethyl amine (Hünig's base,) and tris-*fac*-Ir(ppy)$_3$ as the photocatalyst (Table 1, entry 1). Initial solvent screening (entry 2) revealed that dichloromethane, toluene, tetrahydrofuran, and nitromethane gave trace conversion at best, while several polar solvents (entry 3) facilitated the reaction with acetonitrile being optimal and giving smooth

Scheme 1. Previous and Current Work



conversion using only 0.75 mol % of catalyst. In all cases, the major product was the coupled product **3a** arising from coupling with the carbon of the methylene rather than the methine carbon (**3a**′).[8] The photocatalyst was a necessary component of the reaction, and furthermore, popular Ru(bpy)$_3$Cl$_2$ did not facilitate the reaction (entry 4). While initial results indicated (entry 5) that rigorous exclusion of air was not essential, we found this to be more of the exception and not universally true. While most reactions still worked in air, reaction with some amines gave substantial byproducts. Therefore, we opted to run all of the substrates under an atmosphere of argon.

In an effort to improve the reaction conditions, we sought to minimize the amount of amine needed. We envisioned that at least 1 equiv was simply serving as a base and might be replaced with a convenient alternative. Indeed, we found that while the reaction would stall out without the extra equivalents of amine (entry 6), simply replacing the extra equivalents with pyridine, imidazole, or carbonates worked well (entries 7−10) while DBU (entry 11) gave decreased conversion and increased amounts of side products. Again, in an attempt to simplify the reaction procedure, we looked at the effect of water (entry 12). We were pleased to find water had little effect on the reaction, implying that rigorous drying of reagents and solvents is not necessary for a successful reaction.

Finally, we investigated temperature as a control element. We found that the rate of reaction was dependent on temperature up to a point (entries 13−15), above which the conversion dropped severely and was accompanied by a change in the color of the reaction solution (it turned black, entry 15). However, the regioisomeric ratio (rr) proved to be relatively insensitive to temperature and thus allowing temperature to be used as a handle for sluggish reactions. Thus, we ultimately settled on running the reaction under argon, at 45 °C, with 1.2 equiv of amine and 2.0 equiv of imidazole.

With ideal conditions in hand, we next attempted to explore the scope (Scheme 2). Gratifyingly, we saw that the

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(6) Ohashia has shown that direct UV photolysis can lead to formation of the coupled product, and later MacMillan (see ref 5c) showed that under photocatalysis a single example of a tertiary aliphatic amine which, contrary to what we have observed, was highly endoselective. Ohashi, M.; Miyake, K.; Tsujimoto, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1683–1688.

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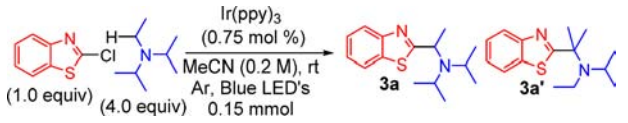
(8) This is not unprecedented; for examples, see: (a) Kotani, S.; Osakama, K.; Sugiura, M.; Nakajima, M. *Org. Lett.* **2011**, *13*, 3968–3971. (b) Schreiber, S. L. *Tetrahedron Lett.* **1980**, *21*, 1027–1030.

Table 1. Identification of the Optimal Conditions



entry	modification of experimental conditions	GC/MS conversion[a]	GC/MS 3a/3a'[a]
1	none, 13 h	67%	9:1
2	DCM, CH_3NO_2, Tol or THF	<6%	nd[b]
3	DMF, DMSO, or DMA	29–44%	nd[b]
4	no photocatalyst or $Ru(bpy)_3CI_2$	0%	nd[b]
5	MeCN exposed to air	57%	9:1
6	1.2 equiv of amine at 24 h	21%	9:1
7	2.0 equiv of pyridine and 1.2 equiv of amine	63%	9:1
8	2.0 equiv of imidazole and 1.2 equiv of amine	68%	13:1
9	2.0 equiv of Cs_2CO_3 and 1.2 equiv of amine	69%	9:1
10	2.0 equiv o f K_2CO_3 and 1.2 equiv of amine	59%	9:1
11	2.0 equiv of DBU and 1.2 equiv of amine	32%	9:1
12	up to 15% v/v H_2O	65%	9:1
13	reaction run at 27 °C, 7 h	46%	9:1
14	reaction run at 45 °C, 7 h	62%	12:1
15	reaction run at 65 °C, 7 h	22%	8:1

[a] Determined by integration of GCMS trace. [b] Not determined.

reaction worked well for benzothiazole (**3a**, 92%, rr 11:1) and a number of substituted benzothiazole substrates including those substituted with a bromide (**3c**) and a chloride (**3d**), which provides opportunity for further elaboration of the products via more traditional cross-coupling methodologies. The fact that neither 6-Br nor 6-Cl reacted suggests the reaction is highly chemo- and regioselective for the 2-Cl position. Survival of the aryl bromide under these conditions is somewhat surprising considering that reduction of electron-deficient aryl bromides has been observed under similar conditions.[9] The reaction also works well for more electron-rich benzothiazole **3e**, 61% 13:1 rr, albeit dilution was found to be necessary to achieve reasonable reaction rates. Importantly, exploration of other related heterocycles revealed that the method was not limited to benzothiazole but could be applied to benzoxazoles (**3b**, **3h**, **3n**, **3p**, **3s**, **3u**), Boc-protected benzimidazole (**3k**), as well as simple thiazole derivatives (**3f**, **3i**, **3j**, **3l**, **3v**). In all the heterocycles studied, similar regioselectivity was observed in which coupling of the less hindered C−H dominated.

Gratifyingly, the reaction proved tolerant of a number of functional groups, including a cyano group (**3l**), ester (**3j**), halogens (**3c**, **3d**, **3f**, **3h**, **3n**, **3p**, **3s**, **3u**), and methyl ethers (**3e**) as well as terminal olefins (**3r**). Finally, Boc groups (**3k**) survived, albeit loss of the Boc group was initially problematic but was easily circumvented by replacing the imidazole with Cs_2CO_3.

The regioselectivity appears to be sensitive, in part, to further substitution of the aryl chloride. Comparison of benzothiazole **3a** to functionalized benzothiazoles (**3c**, **3d**, **3e**) suggests that substitution at the 6-position results in increased selectivity. On the other hand, simplification of benzothiazole (**3a**) to simple thiazole (**3v**) results in diminished selectivity (11:1 vs 2:1). However, additional substitution of the thiazole causes the selectivity to return to more desirable levels. Substitution with an ester or a cyano group increases the regioselectivity from 2:1 to 4:1 (**3v** vs **3j** and **3l**), while substitution with a chloride or phenyl ring results in even more dramatic increases from 2:1 to 9:1 (**3v** vs **3f** and **3i**). However, coupling of phenyl-substituted thiazole **3i** proved to be sluggish, giving incomplete conversion and an isolated yield of only 24%.

The reaction also worked well with less hindered linear amines such as tributyl amine (**3n**, **3o**). However, an increase in the amount of the amine was used to prevent a second arylation of the product as the reaction neared completion. Pyrrolidyl amines also proved to be competent coupling partners (**3g**, **3m**). We observed excellent selectivity (> 20:1 rr) for the acyclic methylene over the cyclic pair of methylenes. This selectivity is particularly interesting since the vast majority of examples of N-oxidation[10] initiated functionalizations as well as photochemical[11] couplings in the literature are highly selective for the endocyclic position. This finding suggests a different controlling element in this coupling reaction when compared to these processes which seem related. The reaction also works well using amines with three different groups (**3t**) and highlights the advantage of this coupling method which provides facile access to a product that would be difficult to access via other methods. Finally, while substrate **3p** derived from a methyl amine offers less complexity than other substrates, it shows that the reaction also works with simpler methyl amines giving the product as a single regioisomer.

We suspected that our method would be ideal for rapidly assessing the SAR of heterocycles substituted with an aliphatic carbinamine. Take for instance the drug Nizatidine, which is an H-2 histamine agonist developed by Eli Lilly[2g,12] and sold under the trade names Taxzad and Axid and was one of the most widely used drugs for a number of years in combating health issues related to the overproduction of stomach acid. In the development of this drug, SAR of the carbinamine was determined by variation of the amine in the acetonitrile component in the initial step of the reaction sequence (Scheme 3, eq 1). With regard to the carbinamine side group, Eli Lilly only looked at five

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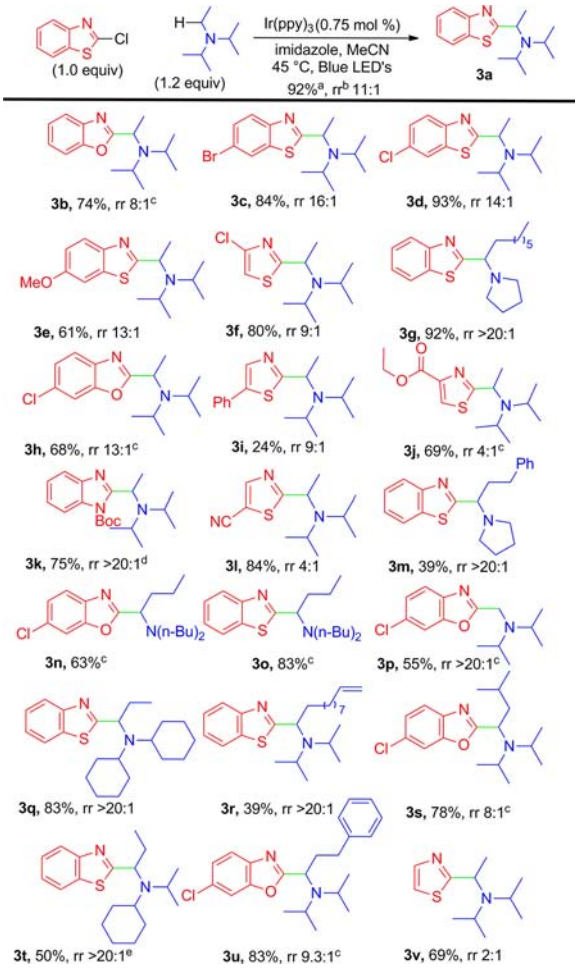
(12) Pioch, R. P. *N*-Thiazolylmethylthioalkyl-N′-alkylamidines and related compounds. Patent Appl. US4382090A, CAPLUS AN 1983:443548(Patent).

Scheme 2. Cross-Coupling of Heteroaryl Chlorides with Aliphatic Amines

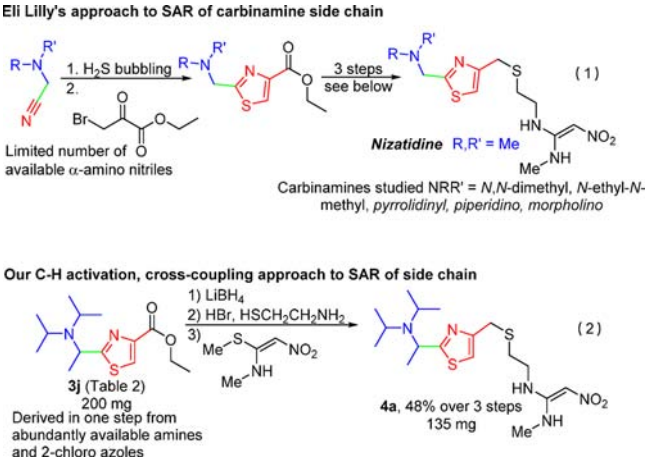


[a] Yields are of isolated products after chromatography. [b] Regioisomeric ratios were determined on crude material via ^{1}H NMR. [c] Imidazole was replaced with 4.0 equiv (total) of amine. [d] Cs_2CO_3 was used instead of imidazole. [e] No other possible regioisomer was detected by ^{1}H NMR.

variations of the nitrogen substituent and no substitution of the carbinamine methylene was explored.[2g,12] Given the minimal SAR performed on the carbinamine component, we thought this would be an ideal opportunity to demonstrate how we could use our method to rapidly make a Nizatidine analogue (**4a**).

Beginning with commercially available 2-chlorothiazole carboxylate, we coupled Hünig's base to afford **3j** (from Scheme 2). Taking 200 mg of **3j** forward (Scheme 3, eq 2), we followed the procedure of Eli Lilly.[12,13] First, we subjected our coupled product to a telescoped synthesis beginning with reduction of the ester with $LiBH_4$ followed

Scheme 3. Rapid Synthesis of Previously Unknown Nizatidine Analogue



by HBr-mediated thiol substitution and finally coupling with the active pharmacophore to afford 135 mg, 48% yield (**4a**) of the desired analogue as a single regioisomer[14] with only one purification after the final step. Thus, we were able to readily access a previously unknown analogue of Nizatidine differing at the carbinamine side chain from commercially available components in fewer steps and with greater structural diversity than previously investigated.

In summary, we highlight the enabling nature of this reaction as well as the conceptual advance it represents. First, it provides an alternative disconnection to traditional cyclodehydration which allows faster and greater carbinamine diversification. The reaction setup is simple and utilizes commercially available reagents. It has proven to be functional-group-tolerant and chemoselective. Second, this work highlights the ability of photoredox catalysis to mediate C−C bond formation with simple tertiary aliphatic amines rather than isoquinoline or aryl amine derivatives. Our future efforts will attempt to understand the mechanism[15] and expand the scope of the 2-chloroazole.

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Supporting Information Available. Experimental procedures, analytical data, and further discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The minor regioisomer was removed via chromatography after the inital coupling.

(15) For a discussion of the potential mechanism, please see the Supporting Information.

The authors declare no competing financial interest.