Photoinduced Copper-Catalyzed Cross-Coupling of Acylsilanes with Azoles

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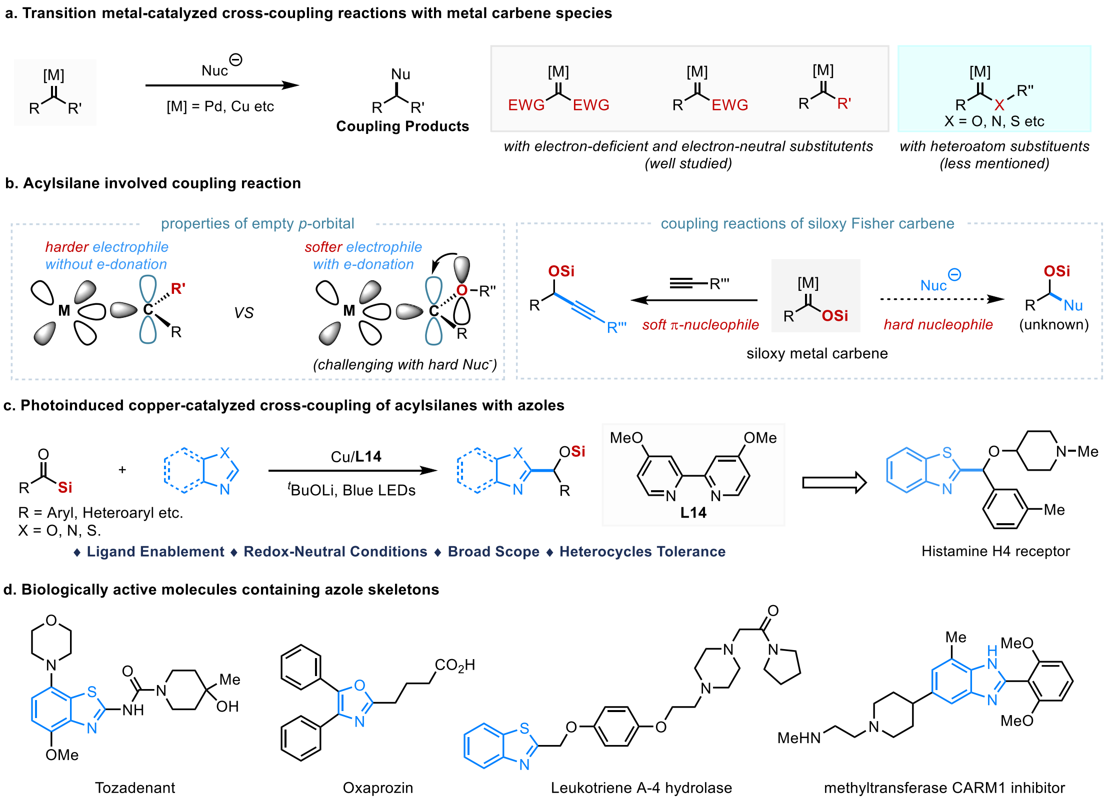
Supporting Information Placeholder

ABSTRACT: The transition metal-catalyzed direct coupling reactions involving electron-rich Fisher carbene species are largely underdeveloped and remain a big challenge. Here, we report a direct coupling reaction of azoles with Fisher copper carbene species bearing an α-siloxy group, which could be in-situ generated from acylsilanes catalytically under photoirradiation and redox-neutral conditions. This reaction features mild conditions and remarkable heterocycle compatibility. Notably, this protocol tolerates a series of azole derivatives, including benzoxazole, benzothiazole, benzoimidazole, benzoisoxazole, oxazole, oxadiazole, triazolo[4,3-*a*]pyridine, purine, caffeine etc., which is highly synthetic useful in organic synthesis and pharmaceutical discovery. Preliminary mechanistic studies and kinetic analysis implied a bimetallic relay process.

Metal carbenes have emerged as highly versatile intermediates, involving in many efficient reactions, such as cyclopropanation, C–H and C–X bonds insertion reactions, tandem cyclization etc.[1-4] In view of the great success in this context, metal carbene species with an electron-deficient (carbonyl, nitro group etc.) and electron-neutral (aryl, alkenyl, alkynyl group etc.) substituents have been well established due to the readily accessibility of corresponding stable carbene precursors including diazo compounds and their analogs (*N*-tosylhydrazones).[1-4] In sharp contrast, the investigations on catalytic reactions involving the metal carbene species bearing electron-rich heteroatom (O, N, S etc.) substituents are considerably limited, primarily due to the lack of readily available and stable metal carbene precursors. The corresponding diazo compounds bearing electron-rich heteroatoms are highly unstable and explosive, and the use of stoichiometric isolable Group VI metal (Cr, Mo, or W) carbene bearing methoxy group[5], normally prepared by using strictly dry anaerobic operation technique, obeys the principles of atom-economy and green chemistry. Only a few catalytic approaches for the access of electron-rich Fisher carbenes with heteroatom functionalities have been mentioned[6], including the attack of heteroatomic nucleophiles to tungsten vinylidene intermediate[7], metal-carbene bearing a leaving group[8], and in-situ trap of transient siloxycarbenes with transition metal catalyst[9,10]. Undoubtedly, to further develop novel strategies for the generation of electron-rich heteroatom metal carbenes catalytically as well as their novel synthetic applications is still highly desired and remains a big challenge.

Transition metal-catalyzed cross-coupling reactions relied on metal carbene intermediates have attracted increasing attention for the efficient construction of carbon-carbon and carbon-heteroatom bonds (Scheme 1a).[4] In this area, our group has proven that the electron-rich α-siloxy Fisher cupper carbenes, in-situ generated from readily accessible acylsilanes under photoirradiation in the presence of a suitable copper catalyst, could be employed in the coupling reaction with the soft π-nucleophile (alkyne).[10d] In principle, this approach should be compatible with a series of nucleophiles, thus rendering this approach potentially broadly applicable. However, the transformation achieved currently with soft nucleophile raises a question if hard nucleophiles could be employed in the transition metal-catalyzed coupling reaction with α-siloxy Fisher carbene species. In comparison to the well-studied metal carbene species containing electron-deficient or electron-neutral groups, the α-siloxy Fisher carbene species from acylsilane which contains the electronically donating α-siloxy group adjacent to electron-neutral group led to a more “softer” electrophile of the empty *p*-orbital (Scheme 1b). As a result, the coupling of α-siloxy Fisher carbene with a hard nucleophile, such as a carbanion, is more challenging due to the Hard-Soft acid-base (HSAB) principle. Here, we demonstrate the Cu-catalyzed coupling reaction of electron-rich siloxy carbene species with a hard carbon nucleophile generated from azoles in the presence of strong base (Scheme 1c). This method offers a general method for the preparation of various azole-containing alcohols in high efficiency under mild conditions.

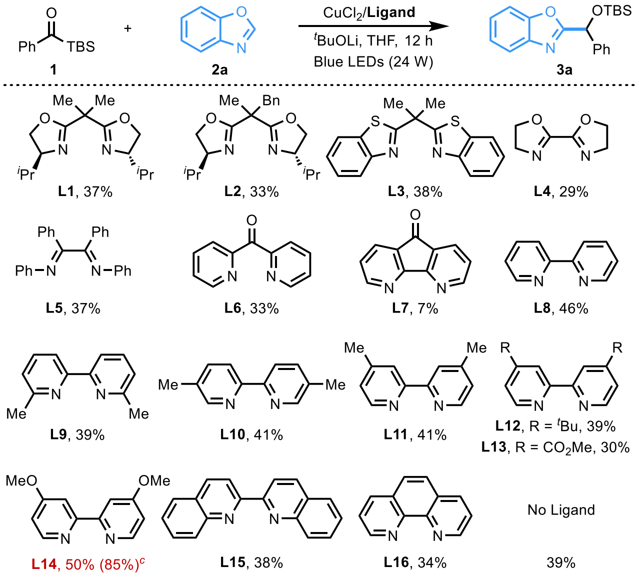
Scheme 1. Photoinduced Copper-Catalyzed Cross-Coupling of Acylsilanes with Azoles



With the assistance of an electron-rich bipyridine ligand, this protocol could tolerate a wide range of azoles, including benzoxazole, benzothiazole, benzoimidazole, benzoisoxazole, oxazole, oxadiazole, triazolo[4,3-*a*]pyridine, purine, caffeine etc., which is unusual in Cu-catalyzed carbene-involved coupling reaction[11]. Given the azole-containing motif are privileged in a large number of pharmaceutically active molecules (Scheme 1d)[12], this reaction might find wide applications in pharmaceutical industry and drug discovery. Preliminary mechanistic studies indicated this reaction might undergo a bimetallic relay process, thus opening a new avenue for the development of novel coupling reactions of electron-rich heteroatom Fisher carbenes.

Based on our experiences on the Cu-catalyzed coupling reaction of acylsilanes with alkynes, we commenced our studies by choosing 1,3-benzoylsilane **1** and benzoxazole **2a** as the model substrates in the presence of a catalytic amount of Cu(OTf)$_2$ and a strong base ^{t}BuOLi under the irradiation of blue light. To our delight, the desired coupling product **3a** was observed in 35% yield with the assistance of a bisoxazoline (Box) ligand **L1**. The optimization of bases indicates this novel coupling reaction could only happened in the presence of strong bases, such as ^{t}BuOLi, ^{t}BuONa, and ^{t}BuOK (See supporting information for more information), which could deliver the azole anion or azole cupper species via deprotonation. Next, systematically ligand effects on this reaction have been evaluated using CuCl$_2$ as the catalyst precursor (Scheme 2), as CuCl$_2$ gave a slight better yield than

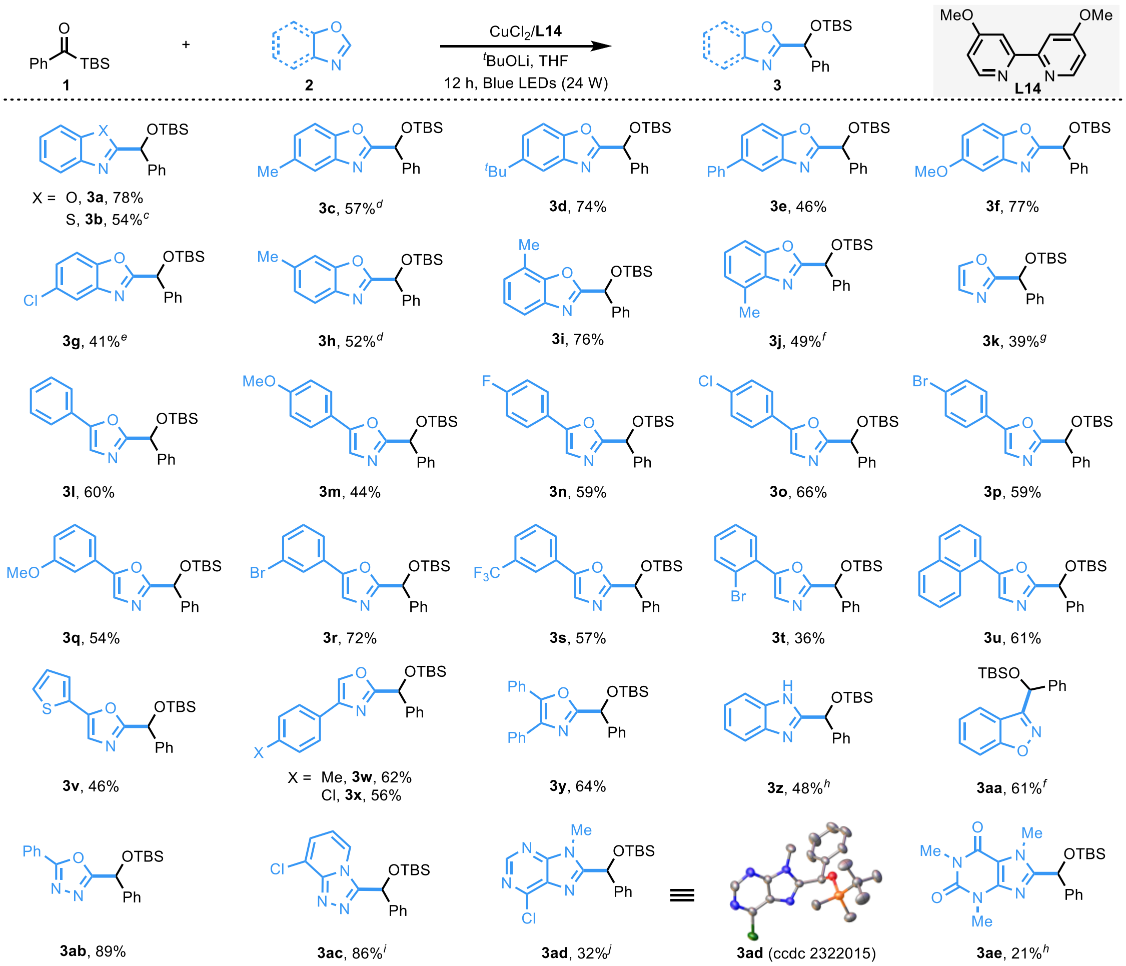
Scheme 2. Ligand Evaluation for Copper-Catalyzed Coupling of Acylsilanes with Azoles[a,b]



[a]Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **2a** (0.1 mmol, 1.0 equiv.), CuCl$_2$ (10 mol %), Ligand (12 mol %), ^{t}BuOLi (0.1 mmol, 1.0 equiv.), THF (1.0 mL), Blue LEDs (450-470 nm, 24 W), 12 hours. [b]Yield was determined by ^{1}H NMR using CH$_2$Br$_2$ as the internal standard. [c]**2a** (0.2 mmol, 2.0 equiv.) was used.

Cu(OTf)$_2$. Unlike our previous reaction with soft nucleophile, the side-arm modified mono-benzyl ^{i}Pr-Box **L2** could not enhance the efficiency of this coupling reaction, giving the coupling product **3a** in 33% NMR yield. Despite the use of bis-benzothiazole ligand (**L3**), bioxazoline ligand (**L4**), and diimine ligand (**L5**) cannot further increase the reactivity of this reaction, bipyridine **L8** accelerated this reaction in some extent (46% NMR yield). On this basis, a series of modified bipyridines (**L8-L15**) and phenanthroline (**L16**) ligands were investigated. We found that the electron-rich bipyridine ligand (**L14**) bearing a *para*-methoxy group gave the best outcome (50% NMR yield). The yield of **3a** could be further optimized to 85% NMR yield, when the loading of **2a** increased to 2.0 equivalent. Control experiments unveiled that the use of electron-rich bipyridine ligand is crucial, and inferior result was obtained in the absence of **L14**.

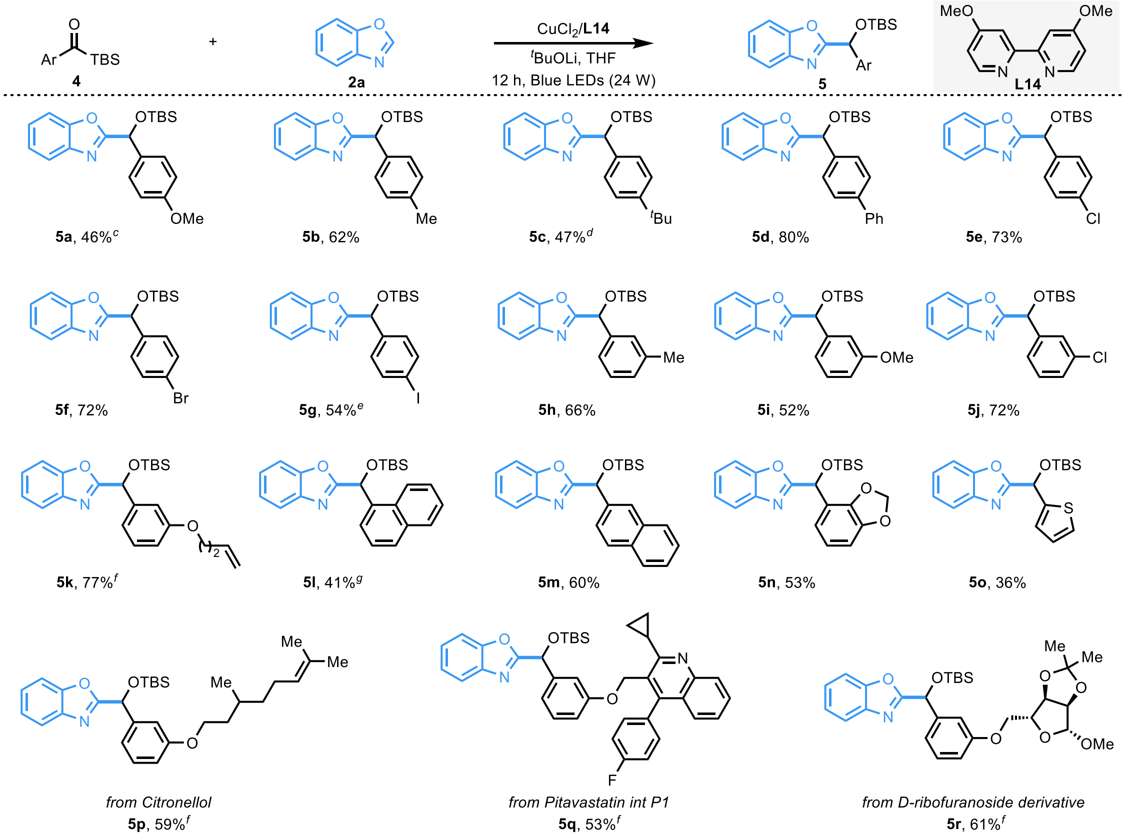
Scheme 3. Scope of Azoles[a,b]



[a]Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **2** (0.2 mmol, 2.0 equiv.), CuCl$_2$ (10 mol %), **L14** (12 mol %), LiO^{t}Bu (0.1 mmol, 1.0 equiv.), THF (1.0 mL), Blue LEDs (24 W), 12 hours. [b]Isolated yield. [c]**1** (0.12 mmol, 1.2 equiv.), **2** (0.1 mmol, 1.0 equiv.), LiO^{t}Bu (0.2 mmol, 2.0 equiv.). [d]LiO^{t}Bu (0.08 mmol, 0.8 equiv.) was used. [e]**1** (0.12 mmol, 1.2 equiv.), **2** (0.1 mmol, 1.0 equiv.), CuBr (10 mol %), **L14** (12 mol %), LiO^{t}Bu (0.08 mmol, 0.8 equiv.). [f]NaO^{t}Bu (0.1 mmol, 1.0 equiv.) was used. [g]LiO^{t}Bu (0.2 mmol, 2.0 equiv.), THF (0.5 mL). [h]NaO^{t}Bu (0.2 mmol, 2.0 equiv.) was used. [i]LiO^{t}Bu (0.2 mmol, 2.0 equiv.) was used. [j]CuCl$_2$ (20 mol %), **L14** (24 mol %), NaO^{t}Bu (0.2 mmol, 2.0 equiv.).

With the optimal reaction conditions in hand, the generality of this coupling reaction with various azole derivatives were evaluated first by employing benzoylsilane (**1**) as the model substrate. A wide range of 1,3-benzoxazoles (**2a-j**) bearing various functionalities are well tolerated, delivering the corresponding products in moderate to excellent yields. In general, the substituents with both electron-rich and electron-deficient functional groups at various positions (4-, 5-, 6-, 7-position) on the aromatic rings are all suitable for this reaction, and the electron-rich benzoxazole normally provided higher yield than the electron-deficient ones. A series of oxazoles were also evaluated (**2k-y**). Electron-donating and electron-withdrawing substituents on the aryl group of oxazole coupling partners, including methyl (**2w**), methoxy (**2m**, **2q**), fluoro (**2n**), chloro (**2o**, **2x**), bromo (**2p**, **2r**, **2t**) and trifluoromethyl (**2s**), are tolerated, furnishing coupled products in 36-72% yields. We also found that the diphenyl (**2y**), naphthyl (**2u**) and thienyl (**2v**) substituted oxazoles are suitable substrates. Notably, the reaction showed high level of compatibilities with other heterocyclic substrates, such as benzothiazole (**2b**), benzimidazole (**2z**), 1,2-benzoxazole (**2aa**), oxadiazole (**2ab**), triazolo[4,3-*a*]pyridine (**2ac**), purine (**2ad**) and caffeine (**2ae**), which further demonstrates the broad scope of this reaction.

Scheme 4. Scope of Acylsilanes[a,b]

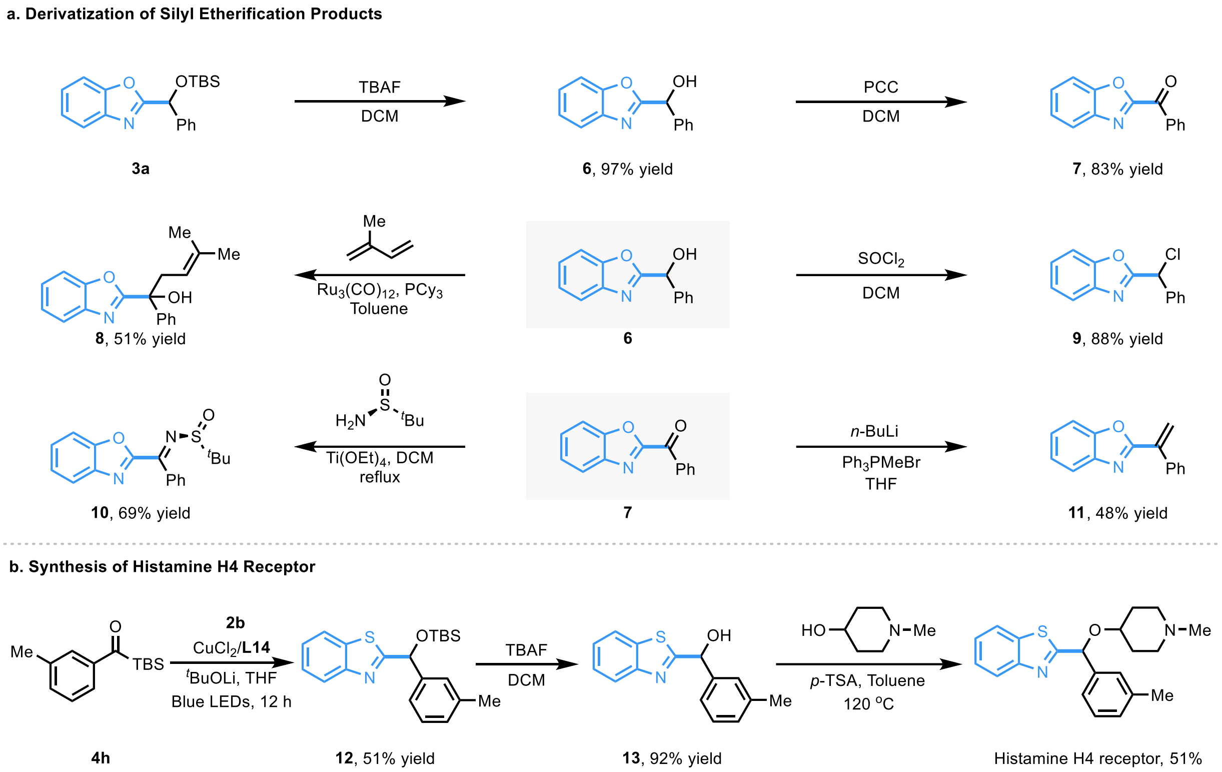


[a] Reaction Conditions: **4** (0.1 mmol, 1.0 equiv), **2a** (0.2 mmol, 2.0 equiv), $CuCl_2$ (10 mol %), **L14** (12 mol %), LiO^{t}Bu (0.1 mmol, 1.0 equiv), THF (1.0 mL), Blue LEDs (24 W), 12 hours. [b] Isolated yield. [c] $CuCl_2$ (20 mol %), **L14** (24 mol %), NaO^{t}Bu (0.1 mmol, 1.0 equiv), 24 hours. [d] $CuCl_2$ (20 mol %), **L14** (24 mol %), 24 hours. [e] LiO^{t}Bu (0.06 mmol, 0.6 equiv). [f] $CuCl_2$ (20 mol %), **L14** (24 mol %). [g] LiO^{t}Bu (0.08 mmol, 0.8 equiv).

Next, we turned to investigate the substrate scope of acylsilanes (Scheme 4). Employing 1,3-benzoxazole (**2a**) as the model substrate, a wide range of acylsilanes were well tolerated, providing the corresponding products in moderate to excellent yields. This protocol is compatible with a variety of aryl acylsilanes bearing both electron-rich and electron-deficient functional groups. As listed in Scheme 4, functional groups such as methoxy (**4a**, **4i**), methyl (**4b**, **4h**), *tert*-butyl (**4c**), phenyl (**4d**), chloro (**4e**, **4j**), bromo (**4f**) and iodo (**4g**) etc., are all tolerated, providing corresponding coupling products in 46-80% yields. In addition, polycyclic aromatic substituted acylsilanes including 1-naphthyl (**4l**) and 2-naphthyl (**4m**) are also suitable substrates, delivering the corresponding products in moderate yields. Notably, this coupling reaction underwent with high chemoselectivity when acylsilane substrate **4k** containing a terminal alkene was employed. The cyclopropanation of terminal alkene was not observed with electron-rich siloxy cupper carbene species under our conditions. The piperonyl substituted acylsilane **4n** couple with benzoxazole in 53% yield. The acylsilane bearing thienyl group (**4o**) is also reactive under our conditions. It is noteworthy that our protocol could be used in the late-stage installation of azoles in bioactive molecules. Substrates derived from citronellol (**4p**), pitavastatin int P1 (**4q**) and D-ribofuranoside derivative (**4r**) are all reactive, providing corresponding products in 53-61% yields.

The azole-containing products are synthetically useful, which could be further derivatized for the preparation of valuable compounds (Scheme 5a). Using our Cu-catalyzed coupling product **3a** as substrate, the benzo[*d*]oxazol-2-yl(phenyl)methanol (**6**) was obtained in 97% yield with TBAF as the desilylative reagent, which could be further oxidized to corresponding ketone **7** in 83% yield by employing PCC as the oxidant. Treatment of **6** with isoprene using $Ru_3(CO)_{12}$ as catalyst under redox neutral conditions, the 1-(benzo[*d*]oxazol-2-yl)-4-methyl-1-phenylpent-3-en-1-ol (**8**) could be obtained in 51% yield. The corresponding benzyl chloride **9** could be also readily accessed in 88% yield by the reaction of **6** with $SOCl_2$. In addition, the condensation reaction of benzo[*d*]oxazol-2-yl(phenyl)methanone (**7**) with (*S*)-*tert*-butanesulfinamide gave (*S*, *E*)-*N*-(benzo[*d*]oxazol-2-yl(phenyl)methylene)-2-methylpropane-2-sulfinamide (**10**) in 69% yield in the presence of $Ti(OEt)_4$. This chiral sulfinamide is a potential ligand in transition metal-catalyzed asymmetric reactions. The 2-(1-phenylvinyl)benzo[*d*]oxazole (**11**) could be synthesised through Wittig reaction in 48% yield. To further demonstrate the synthetic utility of this newly developed methodology, the efficient synthesis of histamine h4 receptor, an inflammatory mediator,[13] was synthesized using current method as the key step (Scheme 5b). The coupling of *m*-tolyl acylsilane **4l** with benzothiazole gave the 2-((((*tert*-butyldimethylsilyl)oxy)(*m*-tolyl)methyl)benzo[*d*] thiazole (**12**) in 51% yield. The corresponding alcohol **13** could be readily prepared in 92% yield after removal of the silyl protecting group. The histamine h4 receptor was then obtained in 51% yield via etherification mediated by stoichiometric *p*-TSA.

Scheme 5. Synthetic Applications

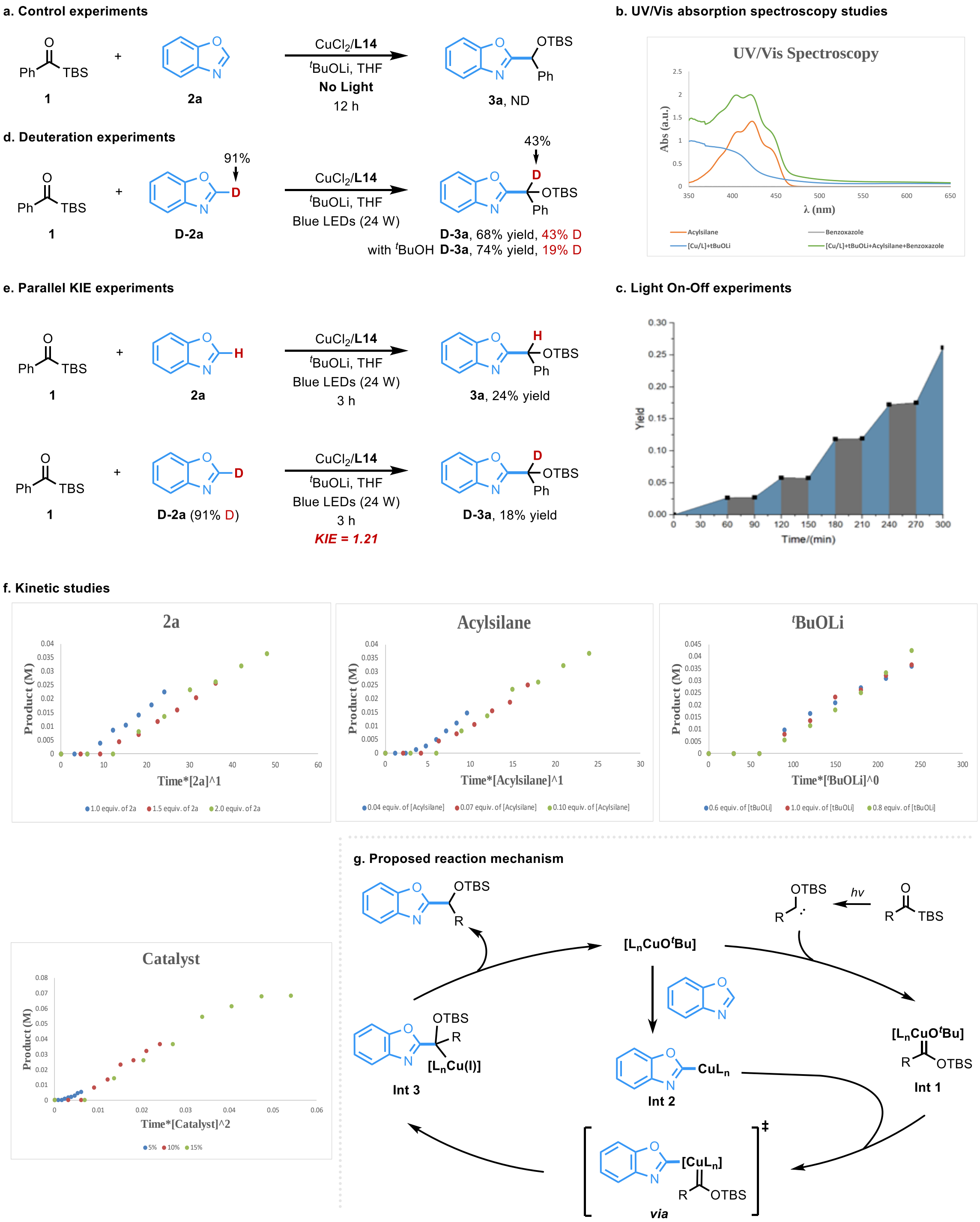


Preliminary mechanistic studies were conducted to shed light on the mechanism of this novel Cu-catalyzed photoinduced coupling reaction with azoles. Control experiments indicated the reaction could not happen without photoirradiation, thus ruled out the nucleophilic addition pathway to acylsilanes by azole anion or azole-copper nucleophiles generated in the presence of strong bases and copper catalyst (Scheme 6a). The UV/VIS analysis of the individual reaction components and the reaction mixture revealed that the acylsilane was the only absorbing species in the visible range, therefore excluded the role of other species as photocatalyst (Scheme 6b). Moreover, the light on-off experiment was conducted and the desired product **3a** formed only under continuous irradiation, which ruled out the possibility of a radical chain propagation pathway (Scheme 6c). The photochemical quantum yield ($\Phi = 0.019$) for current reaction is less than 1.0, which is consistent with α-siloxy copper carbene-involved coupling mechanism[10d] (For more details, see Supporting Information).

To confirm the hydrogen sources in the products, the experiment using deuterium-labelled benzoxazole (**D-2a**) was performed. Although only 43% deuteration rate was observed in the target product, it still revealed that the acidic proton in the benzoxazole could serve as one of the hydrogen sources for this reaction. The low deuteration might originate from the trace amount of water in the solvent or alcohol in the presence of lithium tert-butoxide, as the deuteration rate was reduced to 19% by the addition of a small amount of tert-butanol (Scheme 6d). The KIE experiments with deuterium-labelled benzoxazole (**D-2a**) unveiled that the $C(sp^2)$–H cleavage of benzoxazole might not be involved in the rate-determining step ($k_H/k_D = 1.21$) (Scheme 6e).

To further understand the reaction mechanism, the reaction progress kinetic analysis (RPKA) was preformed (For details, see Supporting Information). The kinetic data indicated the reaction rate is second order to Cu/**L14** catalyst, first order to benzoxazole and acylsilane, which indicated the acylsilane, benzoxazole and copper catalyst are all involved in rate determining step (Scheme 6f). The second order to **Cu/L14** catalyst disclosed a bimetallic relay process in the catalytic cycle. On the basis of our experimental observations and previous studies, a possible mechanism was proposed as depicted in Scheme 6g. As Cu(I) catalysts are also reactive under our standard conditions, we believe that our reaction underwent a Cu(I)-catalyzed coupling process, which could be in-situ generated via the reduction of

Scheme 6. Preliminarily Mechanistic Studies



Cu(II) by carbene species[14]. The ligand attached Cu(I)-O^{t}Bu species could be generated in the presence of LiO^{t}Bu and siloxyl carbene species. α-siloxy Fisher Cu-carbene species **Int 1** was then formed by trapping the in situ generated α-siloxy carbene from acylsilane under photoirradiation. Meanwhile, Cu(I)-O^{t}Bu species was reacted with benzoxazole to reach a copper-azole intermediate **Int 2** which was via the bimetallic relay process, transmetalation process between two organocopper species (**Int 2** and **Int 1**), delivering a key intermediate **Int 3**. Sequentially migratory insertion and protonation were followed to give the desired product. Notably, this bimetallic relay process is the rate-determining step according to the reaction progress kinetic analysis.

In summary, we have demonstrated a photoinduced copper-catalyzed coupling reaction of acylsilanes with azoles, delivering a series of azole-containing secondary alcohols with broad substrate scopes and remarkable heterocycle and functional group compatibility under redox-neutral conditions. This reaction represents the first example of Cu-catalyzed coupling reaction of electron-rich Fisher carbene species with hard nucleophiles. The development of novel coupling reactions with the in-situ generated electron-rich Fisher carbenes are ongoing in our laboratory.

ASSOCIATED CONTENT

Experimental procedures, complete characterization data, copies of ^{1}H and ^{13}C NMR spectra, and ^{19}F NMR spectra. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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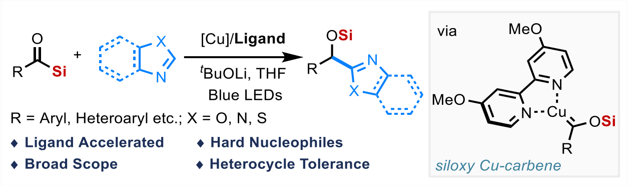
[Cu]/Ligand
tBuOLi, THF
Blue LEDs
R = Aryl, Heteroaryl etc.; X = O, N, S
◆ Ligand Accelerated
◆ Hard Nucleophiles
◆ Broad Scope
◆ Heterocycle Tolerance
via
MeO
MeO
siloxy Cu-carbene