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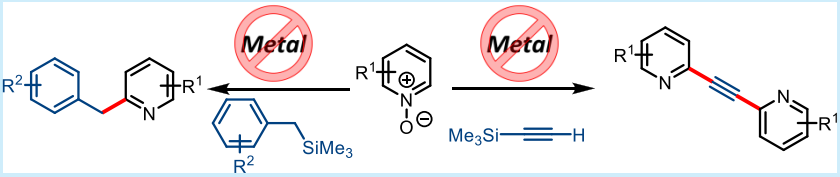
Catalytic Selective Metal-Free Cross-Coupling of Heteroaromatic *N*-Oxides with Organosilanes

Mahesh Puthanveedu,[†,‡] Vasiliki Polychronidou,[†,‡] and Andrey P. Antonchick*[,†,‡]

[†]Abteilung Chemische Biologie, Max-Planck-Institut für Molekulare Physiologie, Otto-Hahn-Straße 11, 44227 Dortmund, Germany

[‡]Fakultät für Chemie und Chemische Biologie, Technische Universität Dortmund, Otto-Hahn-Straße 4a, 44221 Dortmund, Germany

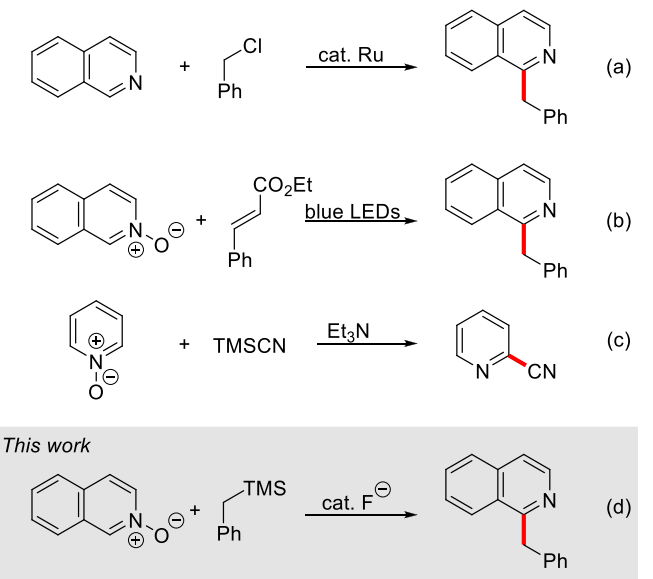
Supporting Information



ABSTRACT: A metal-free, regioselective C−H functionalization of heteroaromatic *N*-oxides has been developed. The method enables the synthesis of various benzylated and alkynylated N-heterocycles in a transition-metal-free manner employing organosilanes as coupling partners. The unanticipated reactivity has been exploited for the synthesis of a number of symmetrical disubstituted acetylenes from ethynyltrimethylsilane via carbon−silicon bond metathesis.

The direct functionalization of C−H bonds has found rapid development over the past few decades.[1] While the transition-metal-catalyzed C−H bond activation approaches for the functionalization of N-heterocycles faced extensive progress, the area of metal-free C−H functionalization remains comparatively underexplored.[2] The abundance of N-heterocyclic scaffolds like isoquinoline and quinoline in bioactive compounds has attracted the attention of chemists over the years. Among them, C1-benzylated isoquinolines represent the privileged core of a number of alkaloids and drugs with a wide variety of structures.[3] The traditional routes to access these scaffolds are metal-catalyzed cross-coupling reactions like the Bischler−Napieralski cyclization.[4] The radical alkylation of N-heteroarene C(sp^2)−H bonds are attributed to their innate electron-deficient nature and are often referred as Minisci-type reactions.[5] However, the selective C−H functionalization of these heterocycles could be challenging, as they often have more than one reactive position toward the nucleophilic attack.[5] Additionally, the radical process demands stoichiometric amounts of explosive peroxides and harsh reaction conditions.[6] A metal- catalyzed direct C−H bond benzylation of isoquinoline was reported recently (Scheme 1a).[7] Heteroaryl *N*-oxides are well-studied precursors in C−H functionalization chemistry.[8] Even though metal-catalyzed methods are predominant, there are a few reports of metal-free, direct C−H functionalization of azaarene *N*-oxides. In 2015, our group revealed a regioselective, metal-free cross-coupling of quinoline *N*-oxides with boronic acids and was the first instance of Petasis reaction application in the direct C−H functionalization of heterocycles.[9] Very recently, Murakami and co-workers reported a one-step conversion of pyridine *N*-oxides into alkylated heteroarenes through a photocatalyzed alkene cleavage (Scheme 1b).[10]

Scheme 1. Regioselective C−H Functionalization of N-Heterocycles



On the other hand, organosilanes have emerged as a viable alternative to conventional reagents. Stability, low cost, and low toxicity of this class of compounds makes them very useful in cross-coupling reactions.[11] Trimethylsilyl cyanide (Scheme 1c), trimethylsilylphenyacetylene, benzyltrimethylsilane, allyltrimethylsilane etc. have been studied in metal-free cross-

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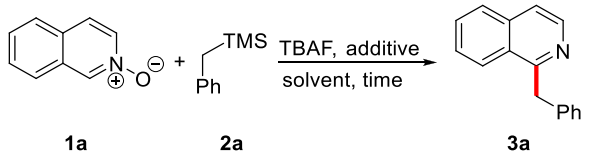
coupling reactions with azaarene 1-oxides.[12] But it is quite evident that, despite being an important building block in the biosynthesis of naturally occurring alkaloids and a privileged scaffold among pharmaceuticals, metal-free functionalization of C−H bonds of isoquinoline remains comparatively underexplored. With our continuing research interest in the area,[13] we envisioned that an oxidant-free, metal-free direct C−H bond functionalization using organosilanes as coupling partners for the synthesis of 1-benzylisoquinolines would be highly desired (Scheme 1d).

We started our study by examining the coupling of isoquinoline *N*-oxide (**1a**) with benzyltrimethylsilane (**2a**) (Table 1). We observed the formation of trace amounts of the

Table 1. Optimization of Reaction Conditions for C−H Benzylation[a]



1a **2a** **3a**

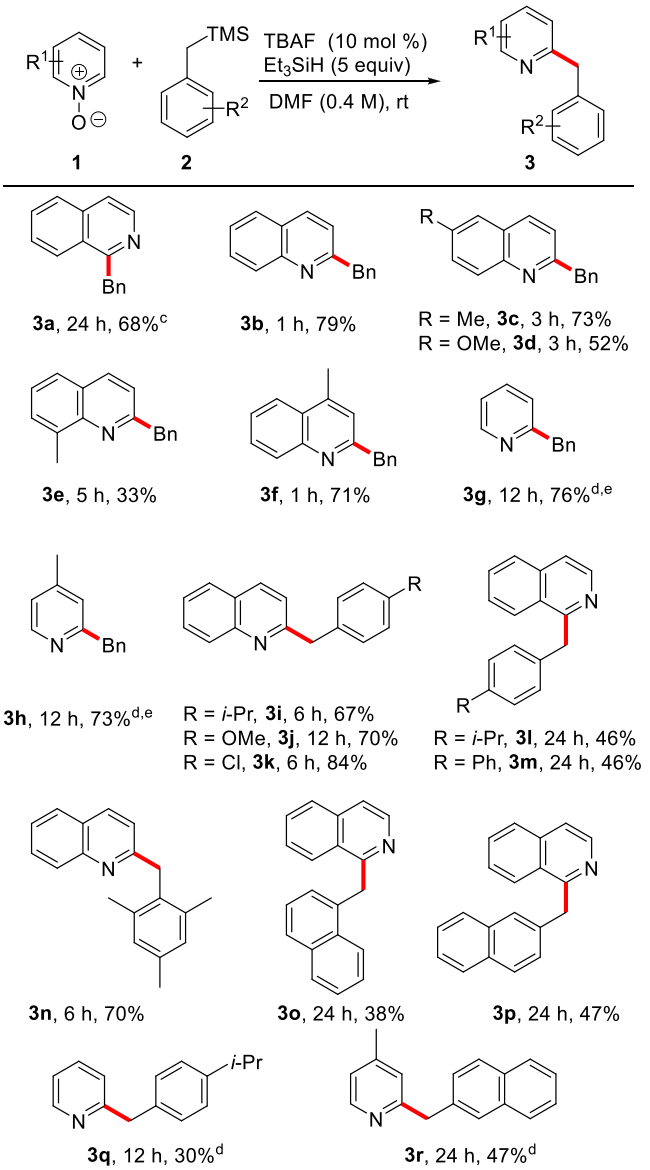
entry	additives	solvent	time (h)	yield[b] (%)
1[c,d]	–	DMF	24	trace
2	–	DMF	6	45
3[e]	–	DMF	6	19
4[f]	Et_3SiH	DMF	24	78
5[f,g]	Et_3SiH	DMF	24	30
6[f]	Et_3SiH	THF	24	7
7[f]	Et_3SiH	DCE	24	n.r
8[f]	Et_3SiH	EtOAc	24	12
9[h]	$PhMe_2SiH$	DMF	24	58
10[i]	$Me_3Si\text{-}SiMe_3$	DMF	24	42

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (3 equiv), TBAF (10 mol %) in solvent (0.4 M) under argon atmosphere. [b]Yields are given for isolated product (**3a**) after column chromatography. [c]Under air atmosphere. [d]2 equiv of **2a**. [e]Using TBAF (20 mol %). [f]Using Et_3SiH (5 equiv) after catalyst addition. [g]CsF (10 mol %). [h]5 equiv of $PhMe_2SiH$. [i]5 equiv of hexamethyldisilane, rt = room temperature. n.r = no reaction.

desired product, 1-benzylisoquinoline (**3a**) upon reaction of **1a** and **2a** at room temperature for 24 h in DMF, in the presence of tetrabutylammonium fluoride (TBAF) as catalyst (entry 1). Further investigations revealed that a number of side products were formed in addition to **3a**. The oxidation of the benzylic position of **3a** resulted in the formation of 1-benzoylisoquinoline and the incomplete reduction of the nitrogen−oxygen bond resulted in the formation of 1-benzylisoquinoline 2-oxide (see Supporting Information for details). Gratifyingly, performing the reaction under an inert atmosphere and an increase in loading of **2a** resulted in a significant rise of the yield of **3a** to 45% (entry 2). An increased loading of TBAF failed to facilitate the reaction (entry 3). Silyl hydrides, being good hydride donors, encouraged us to evaluate their ability to facilitate the reduction of the nitrogen−oxygen bond in 1-benzylisoquinoline 2-oxide and we were delighted to isolate **3a** in 78% yield in the presence of 5 equiv of triethylsilane (entry 4). The application of other fluorine sources such as CsF and TBAT did not lead to better results (see Supporting Information for details). Other aprotic solvents like THF, DCE, and EtOAc showed less promising results when compared to DMF (entries 5−8). The utilization of other additives such as dimethyl(phenyl)silane and hexamethyldisilane was found to be less effective providing 58% and 42% yields, respectively (entries 9, 10).

With the optimized conditions in hand, we moved on to evaluate the substrate scope of this reaction (Scheme 2). The

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol, 3 equiv), TBAF (10 mol %), DMF (0.4 M). [b]Yields are given for isolated products (**3**). [c]At 1 g scale reaction. [d]20 mol % of TBAF was used. [e]Without Et_3SiH.

scalability of this reaction was evaluated by carrying out a gram-scale transformation of isoquinoline *N*-oxide to 1-benzylisoquinoline. To our delight, the reaction proceeded smoothly to give product **3a** in 68% yield. Quinoline *N*-oxide was successfully transformed into 2-benzylated quinoline (**3b**) with 79% yield. Notably, regioselective formation of only C2-substituted quinoline was observed, while application of radical reaction conditions (Minisci reaction) would give a mixture of C2- and C4-isomers. Substituted quinoline *N*-oxides readily reacted with benzyltrimethylsilane to give the alkylated

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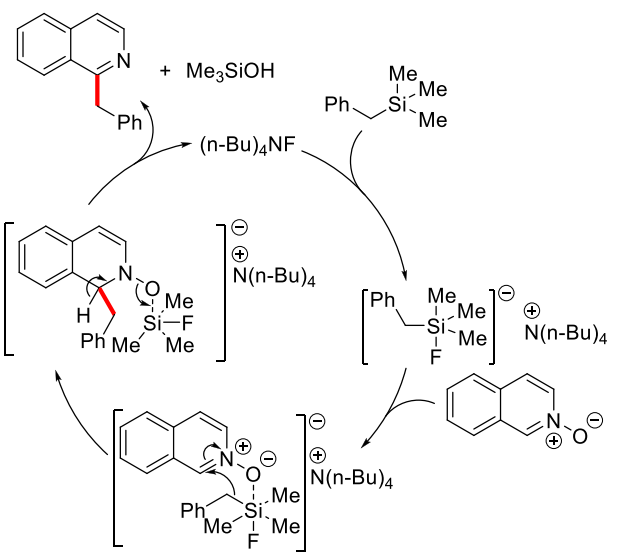
Org. Lett. XXXX, XXX, XXX−XXX

products **3c**–**3f** with 33–79% yield. Unfortunately, the quinoline *N*-oxides with electron-deficient functional groups were unreactive under the developed reaction conditions. Notably, the unsubstituted and substituted pyridine *N*-oxides were selectively monobenzylated to yield the corresponding 2-benzylpyridines (**3g**, **3h**) in good yields under slightly modified reaction conditions. The various substituted organosilanes were also found to be well tolerated (**3i**–**3r**). For example, the presence of a strong electron-donating group at the *para*-position of **2a** provided product **3j** in good yield. At the same time, 84% of product **3k** with electron-withdrawing group was obtained under similar conditions. Meanwhile, formation of product **3n** demonstrated the compatibility of the reaction toward highly substituted organosilanes. The scope could also be extended to simple polycyclic silanes like trimethyl-(naphthalen-1-ylmethyl)silane and trimethyl(naphthalen-2-ylmethyl)silane, providing the products **3o**, **3p**, and **3r** in moderate yields.

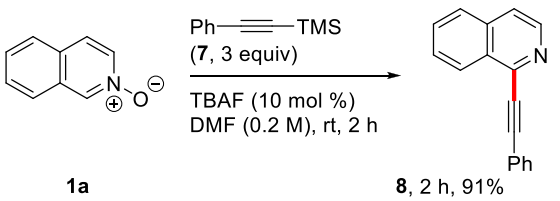
To understand the reaction mechanism, several control experiments were performed. The benzylation of isoquinoline *N*-oxide (**1a**) with **2a** did not proceed in the absence of TBAF. The application of isoquinoline instead of **1a** did not lead to formation of the product. Furthermore, the developed coupling is selective for the functionalization of heterocyclic *N*-oxides, and products of coupling are formed in the presence of a radical trap such as TEMPO. Therefore, radical pathways can be excluded. Triethylsilane facilitated the reduction of the nitrogen–oxygen bond in isoquinoline *N*-oxide in the presence of TBAF to yield 71% of isoquinoline, which indicates its role as a reducing agent in the reaction. The developed transformation occurs in absence of triethylsilane. However, utilization of triethylsilane allows to synthesize the target products with higher yields. Considering our previously reported proposal of a Petasis-type rearrangement in the cross-coupling of quinoline *N*-oxides with boronic acids,[9] a plausible mechanism has been outlined in Scheme 3. The reaction of TBAF with **2a** leads to the formation of a pentacoordinated silicon by the fluoride ion activation of organosilanes. Pentacoordinated silicon is a Lewis acid and coordinates with *N*-oxide to give a 6-coordinated silicon intermediate. Due to the increased nucleophilicity, the benzyl group undergoes a nucleophilic addition to the C1 position of isoquinoline *N*-oxide. The following rearomatization step gives the desired product **3a** with the elimination of trimethylsilanol and regeneration of the catalyst.

Scheme 3. Plausible Mechanism



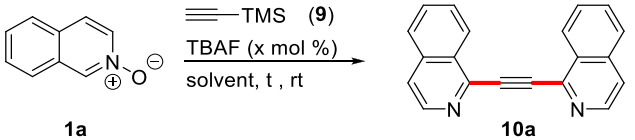
Having success in selective functionalization of *N*-oxides with benzyl trimethylsilanes, we turned our attention to organosilanes with C(sp^2)-Si and C(sp)-Si bonds. Unfortunately, aryl trimethylsilanes were not reactive under the developed reaction conditions. We were pleased to find that isoquinoline *N*-oxide reacts with trimethyl(phenylethynyl)-silane (**7**) in the presence of catalytic amounts of TBAF to give 1-(phenylethynyl)isoquinoline (**8**) (Scheme 4). The previous studies showed that the metal-free alkynylation of heteroaromatic *N*-oxides can also be realized using an organic superbase,[14] *in situ* generated onium amide base,[12a] and potassium hydroxide.[15]

Scheme 4. Synthesis of Disubstituted Acetylenes



Unexpectedly, using ethynyltrimethylsilane (**9**) as coupling partner, 1,2-di(isoquinoline-1-yl)ethyne (**10a**) was obtained in 42% yield as a product of double coupling (Table 2).

Table 2. Optimization of Reaction Conditions for C–H Alkynylation[a]



entry	**9** (equiv)	TBAF (mol %)	solvent	time (h)	yield[b] (%)
1	3	10	THF	12	42
2	3	10	DMF	12	n.r.
3	3	10	MeCN	12	n.r.
4	3	10	DCE	12	n.r.
5	6	10	THF	12	72
6	6	5	THF	3	82
7	4	5	THF	3	89
8	4	3	THF	3	35
9	3	5	THF	3	36

[a]Reaction conditions: **1a** (0.2 mmol), solvent (0.2 M). [b]Isolated yields. n.r. = no reaction.

Afterward, we focused on the optimization of the reaction between **1a** and **9** in the presence of TBAF. THF was found to be a better solvent than other polar aprotic solvents such as DMF, MeCN, and DCE (Table 2, entries 1–4). After careful fine-tuning of reagents and catalyst loading, along with optimization of reaction time, we were able to obtain product **10a** in 89% yield under mild conditions and in shorter reaction time (Table 2, entries 5–9).

With the optimized conditions in hand, we focused our attention toward evaluating the scope and limitations of this method (Scheme 5). Isoquinolines and quinolines *N*-oxide

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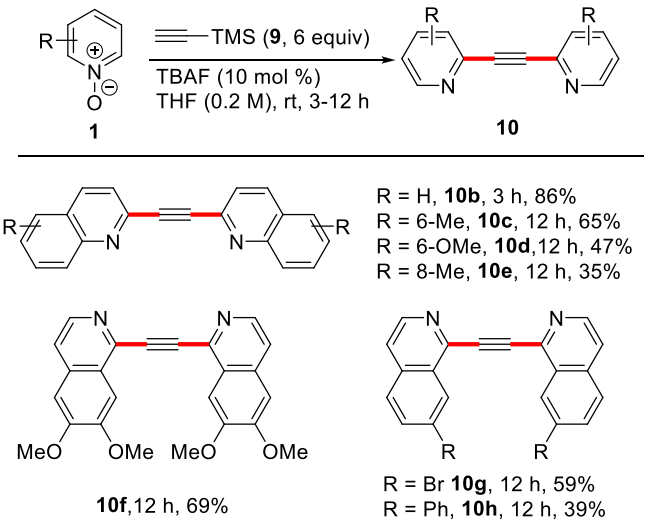
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Substrate Scope of Alkynylation[a,b]

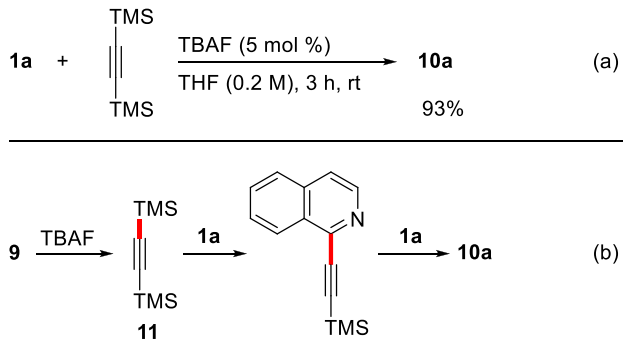


[a]Reaction conditions: **1** (0.2 mmol), **9** (0.8 mmol), TBAF (5 mol %), and THF (0.2 M), under argon atmosphere. [b]Yields are given for isolated products.

derivatives were transformed to corresponding products with moderate to high yields (**10b**–**10h**). Unfortunately, pyridine *N*-oxide did not react under similar conditions.

We speculated the silylation of terminal alkyne occurs in the presence of tetrabutylammoniumflouride.[15] Earlier reports of σ-bond metathesis of silyl alkynes supported our speculation.[16] We carried out the cross-coupling reaction of bis(trimethylsilyl)acetylene and **1a**. To our delight, the reaction proceeded smoothly to form **10a** with 93% yield. This led us to believe that the fluoride ion is acting as a base[17] to generate the alkynide ion which further attacks ethynyltrimethylsilane (**9**) to form bis(trimethylsilyl)acetylene (**11**) (Scheme 6).

Scheme 6. Control Experiment and Plausible Reaction Mechanism



Intermediate **11** was detected by GC-MS in experiment without *N*-oxide. The cross-coupling of isoquinoline *N*-oxide with bis(trimethylsilyl)acetylene gives the desired product **10a**.

In summary, we have developed a metal-free, regioselective C–H benzylation and alkynylation of heteroaromatic *N*-oxides using tetrabutylammonium fluoride as a catalyst and organosilanes as coupling partners. The method was found to be suitable for C–H functionalization of various heterocycles. The developed methodology was successfully extended to the coupling of *N*-oxides with ethynyltrimethylsilane for the synthesis of bis-heteroaryl acetylenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01141.

General procedures, detailed optimization tables, experimental data of starting materials and final products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Andrey.Antonchick@mpi-dortmund.mpg.de

ORCID

Andrey P. Antonchick: 0000-0003-0435-9443

Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX