Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Minisci-Photoredox-Mediated α-Heteroarylation of N-Protected Secondary Amines: Remarkable Selectivity of Azetidines

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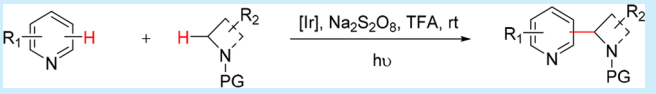
Supporting Information

ABSTRACT: The development of a general, mild, and functional-group-tolerant direct functionalization of N-heteroarenes by C−H functionalization with N-protected amines, including azetidines under Minisci-mediated photoredox conditions, is reported. A broad scope of substituted azetidines, including spirocyclic derivatives, and heterocycles were explored. This reaction enables the production of sp3-rich complex druglike structures in one step from unactivated feedstock amines and heterocycles.

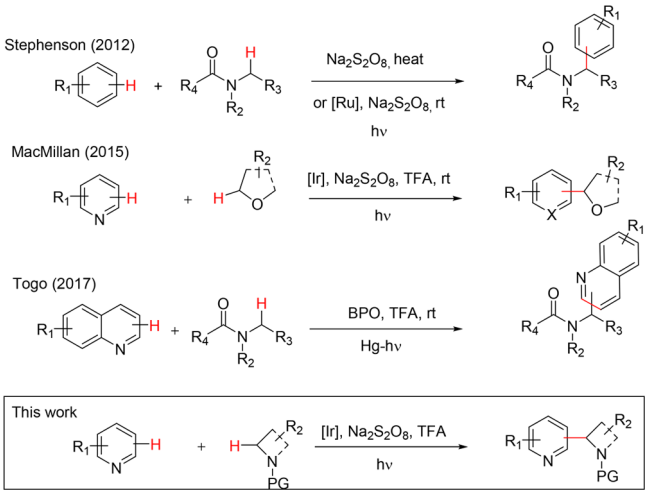


Recently, the rapidly evolving field of photoredox catalysis has revolutionized C−C and C−X bond formation. The high functional group tolerance and versatility of these transformations make them directly applicable to elaborated compounds at the very last stage of synthesis.[1]

The C−C couplings of (a)cyclic amines with N-heteroarenes yield scaffolds that are of great interest to drug discovery because of their broad pharmacological activity and ability to tune physicochemical properties.[2] Numerous applications have been developed to functionalize azaarenes with an array of moieties such as ether,[3] alcohol,[4] and functionalized alkyl chains.[5,6] C−H functionalization of N-heteroarenes by N-protected amines remains challenging. Early attempts[7,8] through Minisci-type reactions[9] suffered from harsh conditions and narrow scope. Stephenson et al.[10] reported a Friedel−Crafts amidoalkylation under radical or thermal conditions with a scope limited to electron-rich arenes and with photocatalysis providing higher yields and better selectivity. The scope was extended to heterocycles and ethers when MacMillan merged the photoredox with the Minisci reaction.[3] More recently, small amides were reacted with quinolines and isoquinolines, but still >10 equiv of the amide coupling partner was necessary.[11,12] The photoredox-mediated strategy of direct α-aminoalkylation remains an area rich in possibilities for novel chemistry and chemotypes.

The development of a general, mild, and functional-group-tolerant direct functionalization of *N*-heteroarenes by C−H functionalization with a variety of *tert*-butoxycarbonyl (Boc)-protected aliphatic and cyclic amines under Minisci photoredox conditions in only one step from unactivated coupling partners is reported.

The photoredox-mediated coupling of 2-methylquinoline with *N,N*-dimethylacetamide (DMA) was investigated first (see the Supporting Information (SI) for details). Following conditions already reported in the literature[3] successfully



produced α-aryl amide **SI-1a** in 76% yield after 21 h of irradiation, but still required >10 equiv of amide coupling partner, which is less than reported previously with ethers.

Other substrates such as formamide-, benzamide-, and carbamate-type compounds, even urea and sulfonamide, proved to be reactive (see the SI). The inefficiency of *N,N*-dimethyltrifluoroacetamide may be attributed to the reduced reactivity of the α-positions of the amine when bearing a strongly electron-withdrawing group such as trifluoroacetyl. Products from dimethylbenzylamine and dimethylaniline were not detected. Thus, deactivation of the nitrogen lone pair via amide or carbamate seemed mandatory for the reaction to proceed. Theoretical calculations were performed on $BocNMe_2$, dimethylacetamide (DMA), and *N,N*-dimethyltri-

Received: July 12, 2018

DOI: 10.1021/acs.orglett.8b00991
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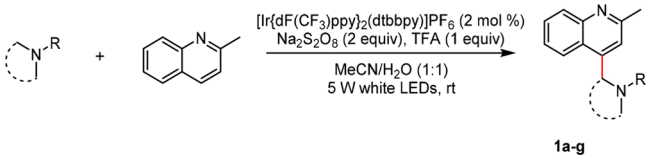
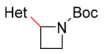
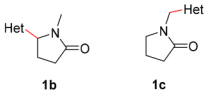
fluoroacetamide (see the SI) in an attempt to rationalize these results. Calculation of the bond dissociation energy (BDE) indicated that the N-protecting groups have limited influence on the strength of the C−H bonds α to the nitrogen atoms. Indeed, the calculated BDE for $BocNMe_2$, DMA, and *N,N*-dimethyltrifluoroacetamide are similar. The calculated energy of the SOMO orbital of the *N,N*-dimethyltrifluoroacetamide radical intermediate (−151.3 kcal/mol) was found to be much lower than those for $BocNMe_2$ and DMA (−134.2 and 138.4 kcal/mol, respectively). As it may be correlated to the reactivity as a nucleophile of the carbon-centered radical, it may explain the lack of reaction of *N,N*-dimethyltrifluoroacetamide.

Next, we studied the α-heteroarylation of protected cyclic amines bearing different ring sizes (see Table 1). Only

Table 1. Influence of the Nature of the Amine on the Outcome of the Reaction[a]



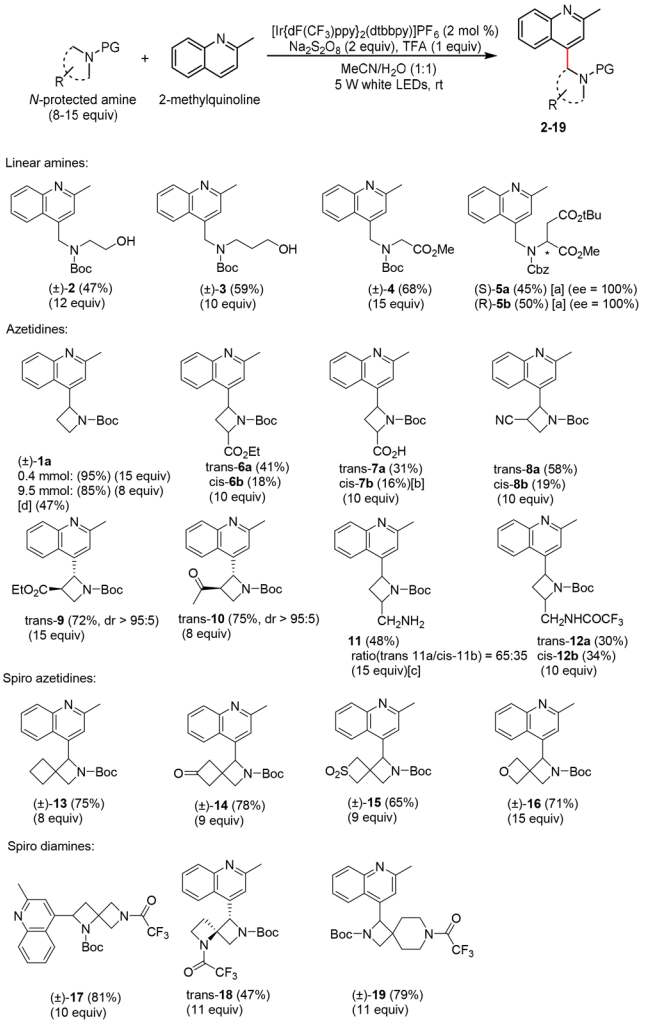
entry	Het–N(R)	1a-g (yield /%)
1		**1a** (95)
2	 1b 1c	**1b** (58), **1c** (85)[b] **1b**/**1c** = 56:44
3		**1d** (12)[b]
4		**1e** NR[c]
5		**1f** NR[c]
6		**1g** NR[c]

[a]Reactions were performed with 15 equiv of the *N*-protected amine, [b]50 equiv of *N*-protected amine was used. [c]No reaction.

azetidine gave the desired compound **1a** and in excellent yield (95%). *N*-Methylpyrrolidone had lower reactivity (58% overall yield), and due to the presence of two activated positions, a mixture of regioisomers **1b** and **1c** was obtained in a 56:44 ratio in favor of the arylation on the cyclic methylene of NMP. Only trace amounts (12% of **1d**) were obtained for *N*-Boc-pyrrolidine, while no product was observed for *N*-Boc-piperidine after 48 h. In addition, acyclic partners such as *N*-Boc-diethylamine and *N*-Boc-diisopropylamine showed no reactivity. It is known that high regioselectivities can be observed on substrates possessing several activated positions.[3] Through their work on HAT on tertiary amides, Bietti et al.[13] described *N*-acetylpyrrolidine as a much more reactive compound than acyclic tertiary amides, thanks to a reduced steric hindrance and a more rigid geometry, where α C−H bonds are aligned with the amide π-system. The unexpected high reactivity of *N*-Boc azetidine, NMP, and to a lesser extent *N*-Boc-pyrrolidine could thus be explained by ring strain and rigidity, which make these molecules adopt an optimal conformation where α C−H bonds are aligned with the nitrogen lone pair.

The functional group tolerance of the amine partner was then studied by treating a range of functionalized N-protected aliphatic amines and azetidines with 2-methylquinoline under photoredox conditions (Scheme 1). Primary alcohols **2** and **3**

Scheme 1. Scope of the *N*-Protected Amine Partner



[a]70% conversion by LCMS analysis on the crude mixture. [b]16% of decarboxylated product **1a** was also obtained. [c]Sixteen equiv of TFA were used. [d]No Iridium catalyst, no irradiation, no TFA, with $Na_2S_2O_8$ and heating at 50 °C.

as well as α-amino ester **4** were successfully synthesized. Coupling of enantiopure aspartic acid derivatives provided the corresponding chiral amines (*S*)-**5a** and (*R*)-**5b** with complete retention of chiral integrity. It is worth noting that the reaction exhibits a very good regioselectivity toward the α-aminomethyl group in each case.

The synthesis of Boc-azetidine **1a** was confirmed on a larger scale (9.5 mmol), delivering compound **1a** in excellent yield (85%). Gratifyingly, just heating the reaction at 50 °C in the presence of the oxidant alone also provided a useful conversion to **1a** (47% yield). Although this needs to be confirmed with additional examples, this result seems to be in line with

DOI: 10.1021/acs.orglett.8b00991
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previous findings[10] where photocatalysis gave higher yields compared to thermal conditions. The transformation shows an impressive functional group tolerance; ester or carboxylic acid at the C2 position of the azetidine resulted in the formation of 2,4-disubstituted products **6a,b** and **7a,b** in 59% and 47% yield, respectively, whereas C3-substituted azetidines efficiently furnished nitrile **8a,b**, ester **9**, and ketone **10** (72−77% yields). Given the strong redox environment of the reaction, it is remarkable to observe tolerance toward a ketone functional group. When full protonation of the basic function (using excess TFA) of 2-(aminomethyl)azetidine is achieved, product **11** could be obtained in 48% yield. The reduced reactivity of *N,N*-dimethyltrifluoroacetamide offered an opportunity for chemoselective α-arylation of diamines via orthogonal protection using trifluoroacetamide. As such, compounds **12a,b** were obtained in good total yield (64%).

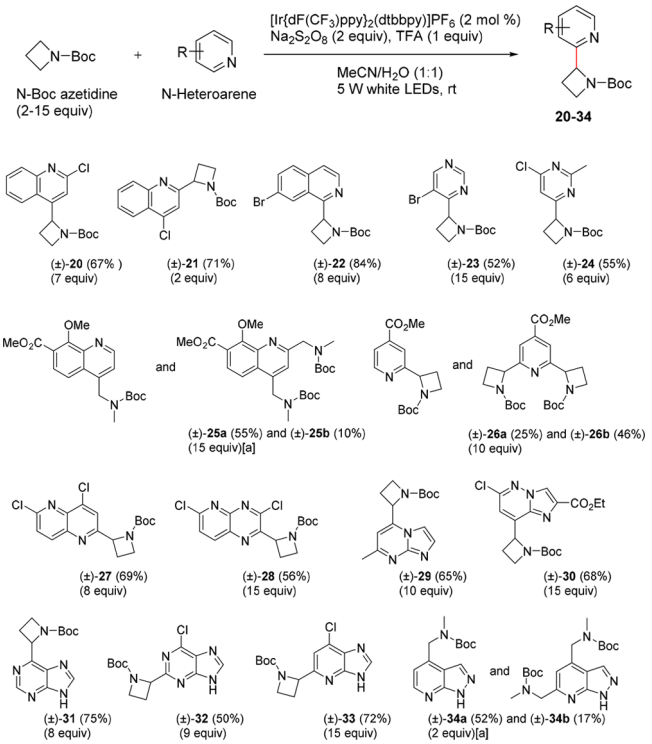
Notably, for compounds **6a,b** and **7a,b**, formation of the *trans*-2,4-isomer (approximately 2:1) was preferred, except for compound **12a,b** where no selectivity was obtained. For the 2,3-isomers **8a,b**, even better diastereoselectivity was obtained (approximately 3:1), and for compounds **9** and **10**, excellent diastereoselectivity (dr >95:5) was obtained, presumably due to steric hindrance.

Spirocyclic scaffolds have established an important presence in the toolbox of modern medicinal chemistry.[14] Our results with azetidine prompted us to consider spirocyclic azetidine α-arylation, which offers significant advantages over traditional synthetic approaches.[17] While Boc-protected 3,3-spirocyclic azetidines gave a different level of steric challenge, the targeted compounds **13**, ketone **14**, and sulfone **15** were all prepared in good yields. Unexpectedly, remarkable selectivity was observed in the case of spiro ether **16**, as the arylation occurred only at the α-position the nitrogen affording compound **16** (71% yield). Simple treatment of the carbamates **1a**, **9**, as well as spiro **13** and **15** with TFA in CH_2Cl_2 at room temperature provided the corresponding amines azetidines.[15]

The trifluoroacetamide protecting group does not activate the α-position of the nitrogen, avoiding the formation of mixtures in the presence of *N*-Boc moieties; thus, spiroazetidines **17** (84%), **18** (47%) and **19** (79%) were obtained in moderate to good yields. These results are remarkable both from a chemoselective as well as a sterical hindrance point of view. The presence of orthogonal protecting groups on the nitrogen atoms enabled the removal of the trifluoroacetamide moiety in **17** in the presence of K_2CO_3 in MeOH, opening an additional vector to introduce diversity.[14]

A variety of electron-deficient nitrogen-containing heteroaromatics bearing additional functional groups (Scheme 2) was probed. Chlorine and bromine substituents were compatible (**20**−**23**, 52−84% yields). Reaction on the most electrophilic position of the heteroarene was preferred in **22**, **23**, **25a**, and **34a**. The highly electron-deficient 4-pyridinecarboxylic acid methyl ester, however, gave more disubstituted compound **26b** (46%) than monosubstituted **26a** (25%). Despite the multiple activated positions and complexity of the N-heteroaromatics, a wide array of substituted heteroarenes was prepared (**27**−**33**, Scheme 2) with excellent selectivity and moderate to good yields (50−75%). The presence of an NH moiety on the heteroarene is compatible with the insertion of an *N*-Boc-azetidine substituent at the C4 position of purine and at the C6 position of 4-chloropurine, providing **31** and **32** in 75% and 50% yield, respectively. Finally, imidazopyridine and pyrazolopyridine afforded the corresponding alkylated compounds **33** and **34a,b**.

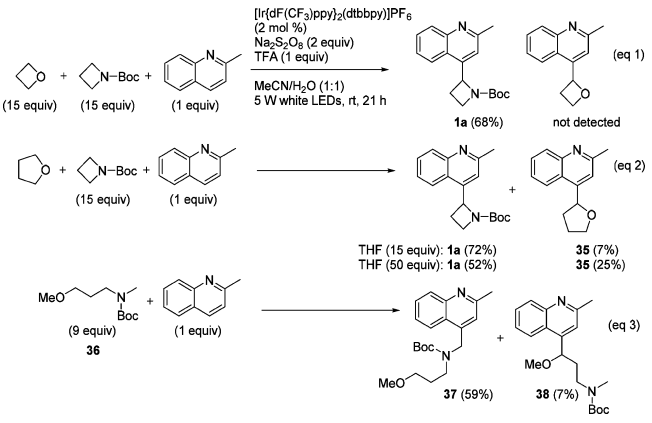
Scheme 2. Scope of the *N*-Heteroarene Partner



[a]Coupling performed with *N*-Boc-dimethylamine.

Surprisingly, no detectable α-arylation of the oxetane with spiro **16** was observed.[3] Competition between *N*-Boc-azetidine (15 equiv) and oxetane (15 equiv) confirmed this result as azetidine **1a** was the only isolated product (Scheme 3, eq 2).

Scheme 3. Reactivity Comparison of *N*-Protected Amines versus Ethers



THF (15 equiv) (Scheme 3, eq 2) also gave selectivity toward α-arylation of azetidine **1a**. A larger excess of THF resulted once again in the formation of amine **1a** (ratio **1a**/**35**: 2:1). This is consistent with MacMillan's results, which showed a higher reactivity for THF compared to oxetane.[3] Despite the presence of four activated sites (methyls and methylenes α to nitrogen and oxygen) in linear amino ether **36** (Scheme 3, eq 3), remarkable regioselectivity was obtained in favor of the methyl carbon α to the nitrogen (**37**, 59%) compared to

DOI: 10.1021/acs.orglett.8b00991
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methylene α to the oxygen (**38**, 7%). BDE and SOMO calculations did not provide an explanation for this regioselectivity (see the SI). This observed selectivity could be due to a polarity-matching effect that favors C−H bonds α to the nitrogen for the HAT in the presence of the electrophilic H atom abstractor sulfate radical.[16]

While scale-up of **1a** from 2-methylquinoline and Boc-azetidine gave high reproducibility and yield (85%), scale-up of **20** from 2-chloroquinoline was more cumbersome with slow conversion and hydrolysis of the 2-chloroquinoline. Recently, the Stephenson group has exemplified advantages of flow over batch for visible-light-induced photoredox catalysis.[18] A continuous flow procedure[19] enabled us to transform 4.0 mmol of 2-chloroquinoline in 7 h (residence time of 30 min), resulting in a productivity of 94 mg/h to prepare **20** using only 5 equiv of azetidine (see the SI).

In summary, this protocol allows α-aminoalkylation of substituted Boc-protected *N*-methylamines with a broad range of functionalized heterocycles. For substituted *N*-Boc-methylene amines, reactivity/selectivity plays in favor of constrained cyclic amine such as azetidines. This coupling does require less substrate than more traditional Minisci reactions with *N*-Boc-azetidine being a particularly active substrate that is selective toward amine over ethers and allows the use of more complex (spiro)amines. A broad range of amide or carbamate directing groups can be used, except trifluoroacetyl, which can be employed as orthogonal N-protection. A wide variety of functional groups are tolerated, enabling fine-tuning of chemical properties important to optimize ADME parameters in a drug discovery effort. Halo-substituted 6−5, 6−6 heterocycles used routinely in medicinal chemistry projects can be utilized, hence covering a wide range of pharmacological space. This protocol is also amenable to building block synthesis using flow chemistry. Synthetic efforts are currently directed toward adding those higher Fsp3 structures into our fragment library with the aim of providing high value starting points for medicinal chemistry projects.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00991.

Experimental procedures, spectral data, computational data (PDF)

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Notes

The authors declare no competing financial interest.

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(19) DMSO/H_2O (3:1) was used instead of ACN/H_2O (1:1) to avoid the formation of a biphasic mixture.

DOI: 10.1021/acs.orglett.8b00991
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