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Preparation of Heteroaryl Ethers from Azine *N*-Oxides and Alcohols

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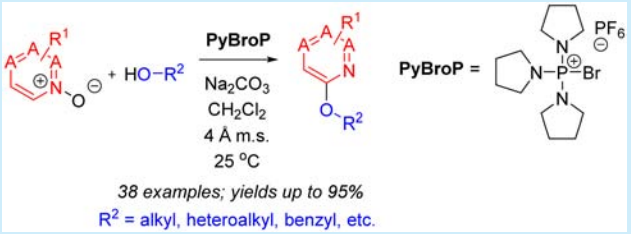
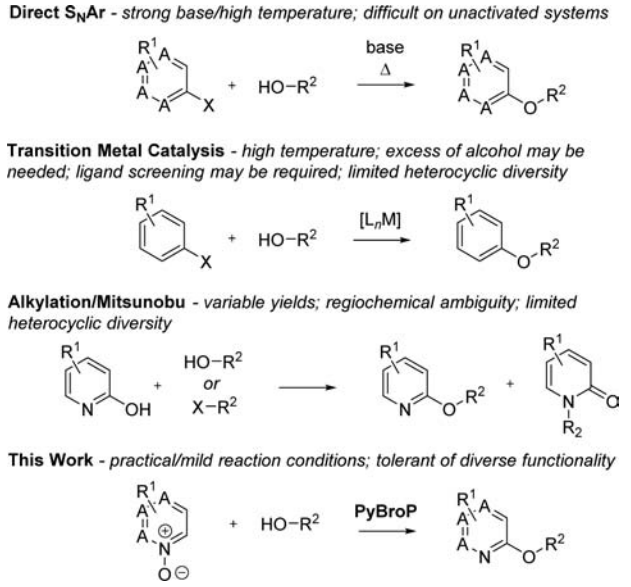
Supporting Information

ABSTRACT: The heteroaryl ether is an important structural feature in molecules of biological interest, yet it remains a challenge to synthesize. A new and practical method for the synthesis of heteroaryl ethers is reported. In the presence of PyBroP, a variety of nonaromatic alcohols readily add to azine *N*-oxides to afford the corresponding heteroaryl ethers. The reaction conditions are mild, economical, chemoselective, and compatible with a broad range of substrates. Thirty-eight examples are provided, as is a discussion of reaction optimization and mechanism.



The heteroaryl ether is a structural feature found in numerous pharmaceuticals and molecules with biological activity.[1] Despite this prevalence, de novo synthesis of heteroaryl ethers remains especially challenging (Scheme 1).[2]

Scheme 1. Challenges and Approaches to the Synthesis of Heteroaryl Ethers



Highly activated heteroaryl halides can undergo direct displacement with alcohols to afford the corresponding heteroaryl ethers. Such S_NAr reactions, however, are not broadly applicable and require forcing conditions due to the poor nucleophilicity of alcohols. The copper-mediated Ullmann coupling[3] is an alternative approach but is usually specific to phenols, which are used in stoichiometric excess. More recently, Buchwald,[4] Maligres,[5] and others[6] have shown that both copper and palladium can effectively catalyze C−O bond formation between a variety of alcohols and aryl halides. These reactions, though useful, require high temperatures and specific ligands and are not always compatible with heterocyclic diversity. MacMillan[7] and co-workers have also explored such C−O bond disconnections with photoredox catalysis. Direct alkylation[8] of aromatic alcohols can also be used to prepare the corresponding ethers, but this approach is nonspecific with heterocyclic substrates and can be complicated by regioisomerism. Perhaps with the exception of the latter preparation, all heteroaryl ether bond formations require a heteroaryl halide as a reactant. This inherent limitation combined with comparatively few synthetic approaches necessitates the development of new and improved methodologies.

During the course of our research, we required a simple and direct procedure for the coupling of primary and secondary alcohols with pyridines to afford 2-alkoxypyridines. We found that this was a very challenging C−O bond to reliably synthesize using contemporary methods, particularly via transition-metal catalysis. We were therefore interested in developing a new methodology that would be more compatible with the polar heterocycles common to our research while overcoming the limitations mentioned above.

For some time, our laboratory has been exploring the utility of azine *N*-oxides as surrogates to heterocyclic halides. In previous communications,[9] we described the addition[10] of various nucleophiles to pyridine *N*-oxides facilitated by the phosphonium salt PyBroP.[11] We found that amines, sulfides, sulfonamides, enolates, and phenols were all suitable reaction partners under very mild reaction conditions. However, under no circumstances were we able to utilize nonaromatic alcohols in the transformation. We hoped that through a careful examination of reaction conditions we would be able to make appropriate modifications to include this valuable class of nucleophile. To the best of our knowledge, the generic addition

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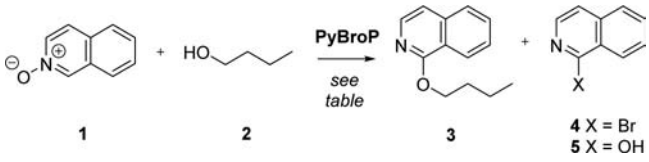
of nonaromatic alcohols to azine *N*-oxides is virtually unprecedented. The few reports[12] that do appear in the literature describe harsh reaction conditions and are applicable only to singular or limited substrates. Additionally, the alcohol component is almost always used in large excess or as solvent.

We initiated a reaction optimization study with isoquinoline *N*-oxide and *n*-butanol (Table 1). Isoquinoline *N*-oxide was found that sodium carbonate compared favorably with silver carbonate (entry 15) to afford **3** in 83% yield. More importantly, under identical conditions, only a single equivalent of *n*-butanol (entry 16) was necessary to achieve an 81% yield of the desired product.

As shown in Scheme 2, we applied the optimized reaction conditions to a series of azine *N*-oxides (**6**) and were pleased to

Table 1. Reaction Optimization[a]

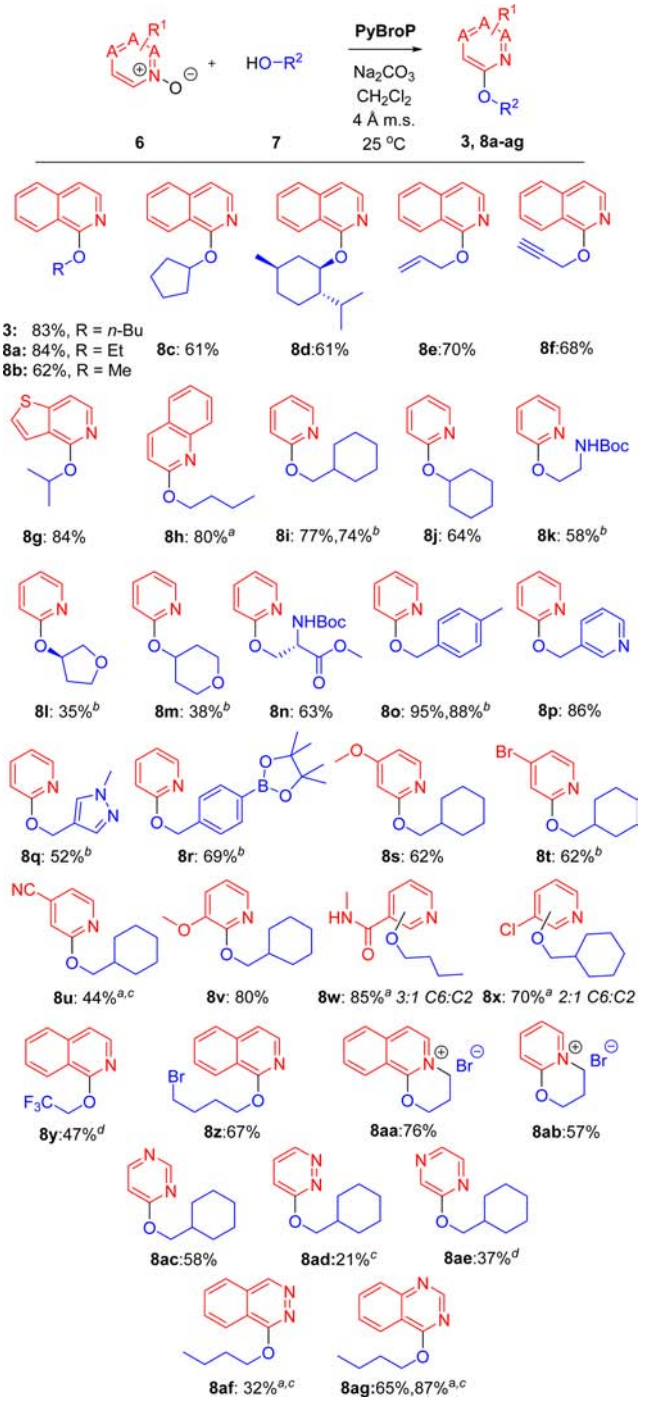


entry	base	solvent	**2** (equiv)	additive[b]	% yield[c] of **3**
1	iPr_2EtN	THF	3.0		31
2	Ag_2CO_3	THF	3.0		53
3	Ag_2CO_3	*n*-butanol			19
4	Ag_2CO_3	THF	15.0		71
5	Ag_2CO_3	THF	3.0	$MgSO_4$	51
6	Ag_2CO_3	THF	3.0	4 Å MS	78
7	Ag_2CO_3	1,4-dioxane	3.0	4 Å MS	82
8	Ag_2CO_3	CH_2Cl_2	3.0	4 Å MS	83
9	Ag_2CO_3	toluene	3.0	4 Å MS	70
10	Ag_2CO_3	EtOAc	3.0	4 Å MS	62
11	Ag_2CO_3	DMF	3.0	4 Å MS	29
12	Cs_2CO_3	THF	3.0	4 Å MS	48
13	K_2CO_3	THF	3.0	4 Å MS	38
14	Na_2CO_3	THF	3.0	4 Å MS	75
15	**Na_2CO_3**	**CH_2Cl_2**	**3.0**	**4 Å MS**	**83**
16	**Na_2CO_3**	**CH_2Cl_2**	**1.0**	**4 Å MS**	**81**
17	Na_2CO_3	CH_2Cl_2	3.0		61

[a]Unless otherwise noted, all reactions were conducted in 2-dram vials under normal atmospheric conditions with **1** (1.00 equiv), **2**, base (2.00 equiv), PyBroP (1.40 equiv) and solvent (0.25 M) at 25 °C for 18−24 h. [b]10% (w/v). [c]Isolated yield.

chosen on the basis of its privileged reactivity profile[13] compared to other heterocyclic *N*-oxides. Using standard conditions from our past work (entry 1), we were both pleased and surprised to observe the formation of desired product **3**, albeit in low yield (31%). This result was contrary to our prior examination of nonaromatic alcohols as substrates in this transformation. When we attempted the analogous reaction with pyridine *N*-oxide (not shown), which was used formerly as an optimization substrate, no reaction occurred. This discrepancy suggested that further work would indeed be required to generalize the reaction conditions. Careful examination of the reaction mixture in entry 1 revealed two significant byproducts (**4** and **5**) derived from the consumption of PyBroP and the inadvertent addition of extraneous water in the reaction mixture. With further experimentation, we determined that **4** could be attenuated by using silver carbonate as base, though byproduct **5** was still present. Gratifyingly, with a 15-fold excess of *n*-butanol, we were able to isolate the desired product in 71% yield, with minimal byproducts, though the practicality of such a protocol was unappealing. The addition of 4 Å molecular sieves (entry 6) proved very successful at minimizing **5** and, when combined with silver carbonate as base, suppressed all side reactions to afford 78% yield of **3**. Solvents other than THF were well tolerated, with dichloromethane (entry 8) optimal. Somewhat serendipitously, we

Scheme 2. Reaction Substrate Scope



*Unless otherwise noted, all reactions were conducted in 2-dram vials under normal atmospheric conditions with **6** (1.00 equiv), **7** (3.00 equiv), Na_2CO_3 (2.00 equiv), PyBroP (1.40 equiv) and 4 Å m.s (10% (w/v)) at 25 °C in CH_2Cl_2 (0.25 M) for 18−24 h. [a]THF as solvent. [b]7 (1.00 equiv). [c]55 °C. [d]Ag_2CO_3 as base.

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obtain a diverse array of 2-azaheteroaryl alcohols (**8a**–**ag**) in modest to excellent yields. The reactions were performed in capped 2-dram vials without atmospheric controls and were usually complete within 18–24 h at room temperature. For most examples, a solution of **6** was prepared in dichloromethane and sequentially treated with **7**, sodium carbonate, 4 Å molecular sieves, and PyBroP. A slight color change to yellow was commonly noted as the reaction progressed. A large variety of alcohols and azine *N*-oxides were effective in the transformation. Usually, more precious alcohols were utilized in a 1:1 ratio with the azine *N*-oxide, while commodity-type alcohols were used in 3-fold excess. Direct comparisons in yield to the equivalents of alcohol were again made (**8i** and **8o**) and were consistent with the results from Table 1. In instances where electron-deficient or sterically hindered[14] azine *N*-oxides were used, THF was the preferred solvent, sometimes with gentle heating (vide infra). In general, primary alcohols were more effective than secondary alcohols as were electron-rich alcohols vs electron-poor alcohols.

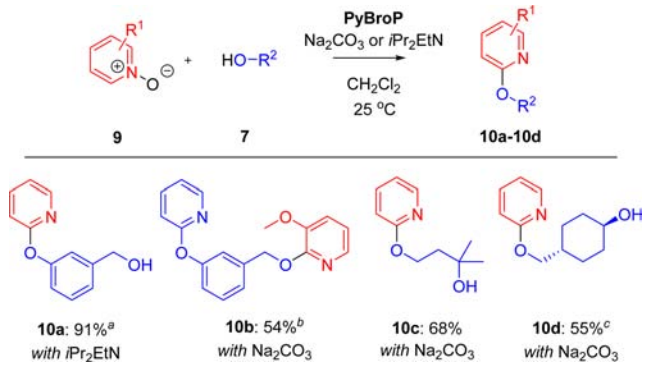
Highly sensitive functionality was successfully incorporated into multiple reaction substrates. Of particular note are the examples containing an alkyne (**8f**), reactive halide (**8t** and **8z**), and boronic ester (**8r**). Additionally, *N*-Boc-L-serine methyl ester was readily heteroarylated (**8n**) without any racemization,[15] suggesting a general compatibility with base-sensitive functionality. When 1-bromopropanol was used as a reactant (**8aa**,**ab**), concomitant ring closure was observed resulting in the pyridinium bromide salts. Remarkably, trifluoroethanol was also effective[16] in the transformation (**8y**), though it proceeded in somewhat lower yield. In instances where regioisomeric products were possible (**8v**–**x**), the electron density[17] of the azine *N*-oxide was predictive of the major product. In all cases, alcohol addition occurred ortho to the N–O bond.[18]

Pleasingly, all varieties of diazine *N*-oxides that we examined as substrates in this reaction also afforded the corresponding ethers (**8ac**–**ag**). These represent the first examples of diazine *N*-oxides acting as electrophiles in any analogous PyBroP-mediated transformation examined thus far. In general, pyrimidine-based *N*-oxides performed best.

Based on the observations that aromatic and nonaromatic alcohols react under different conditions[19] and that primary and secondary alcohols proceed at different reaction rates, we examined whether chemoselective etherification was possible (Scheme 3). The reaction of 3-(hydroxymethyl)phenol with pyridine *N*-oxide was studied first. With *N*,*N*-diisopropylethylamine as base, complete chemoselectivity for the aromatic oxygen resulted (**10a**, 91%). Interestingly, when sodium carbonate was employed with the same substrates, **10a** was again obtained exclusively, albeit in attenuated yield,[20] demonstrating an enhanced reactivity profile of aromatic alcohols vs aliphatic. Once isolated, benzylic alcohol **10a** was subjected to the sodium carbonate protocol with 3-methoxypyridine *N*-oxide to afford **10b** in fair yield. In example **10c**, complete selectivity for a primary vs tertiary alcohol was observed. In fact, tertiary alcohols were found to be unreactive in this procedure. Finally, excellent chemoselectivity between primary and secondary alcohols was seen in example **10d**.

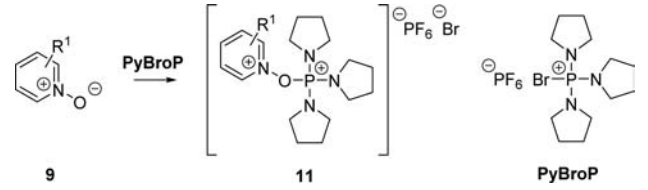
Analogous to our previous reports on the addition of nucleophiles to azine *N*-oxides activated by PyBroP, we propose intermediate **11** as the key mechanistic feature in this transformation (Scheme 4). The successful formation of this intermediate largely dictates the outcome of the reaction. For instance, in those examples from Scheme 2 where azine *N*-

Scheme 3. Chemoselective Reactions*



*Unless otherwise noted, all reactions were conducted in 2-dram vials with **9** (1.00 equiv), **7** (3.00 equiv), base (2.00 equiv), PyBroP (1.40 equiv), and 4 Å MS (10% (w/v), omitted for example **10a**) at 25 °C in CH_2Cl_2 (0.25 M) for 18–24 h. [a]Without 4 Å MS. [b]**7** (1.00 equiv). [c]10:1 primary vs secondary heteroarylation.

Scheme 4. Mechanistic Considerations



oxides (**6**) were electron-deficient or sterically hindered about the N–O bond, modified reaction conditions were beneficial, including the use of heat and/or THF as solvent. When compared to dichloromethane, THF is a superior coordination solvent and resultantly accelerates the formation of intermediate **11**. This is supported by both ^{1}HNMR and ^{31}PNMR analytical experiments.[21] Based on the points made above, similar reaction modifications with other diverse substrates can be made as necessary and should enhance overall yields of isolated products.

The most apparent difference between the reaction conditions reported here and those from our previous work is the use of sodium carbonate as base. Interestingly, sodium carbonate is optimal for primary and secondary alcohols and comparatively less effective[22] with other nucleophiles such as amines and phenols. NMR experiments[21] reveal that with sodium carbonate the lifetime of both PyBroP and **11** is significantly extended compared with *N*,*N*-diisopropylethylamine. This distinction is highly beneficial with poor nucleophiles such as alcohols. This is also consistent with the observation that reaction yields with aliphatic alcohols improve with time, whereas little change is noted after a few hours with other nucleophiles.

In conclusion, we have presented a practical and mild synthesis of varied heteroaryl ethers, which remain challenging to make via contemporary methods. Our procedure is operationally simple, is highly substrate tolerant, and takes advantage of the unique reactivity of azine *N*-oxides, which are easily obtained and synthesized.[23] This methodology should be of particular use in the synthesis of small molecule therapeutics where the incorporation of polarity is needed to increase beneficial drug/target interactions and optimize druglike properties. Our laboratory will continue to explore these new

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reaction conditions with other relevant nucleophiles, and we will report our results in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00295.

Experimental procedures and characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) "Sterically hindered" refers to substituents ortho to the nitrogen of the azine *N*-oxide.

(15) See the Supporting Information. The enantiomeric excess of **8n** was 100% compared to the racemic standard using chiral-SFC analysis.

(16) Silver carbonate was utilized in this reaction to prevent the formation of side product **4**, which was observed when sodium carbonate was used as base.

(17) See ref 9b. HOMO/LUMO electron density calculations are predictive of regiochemical outcome. The electrophilic carbon with the highest calculated LUMO index will be the major site of nucleophilic addition.

(18) See ref 9a−c. A charge association of the incoming nucleophile with the distributed cationic charge and/or lone pairs of the tris-pyrrolidino moiety in **11** (vide infra) likely directs nucleophiles to the ortho-position of the azine-*N*-oxide exclusively.

(19) See ref 9a−c. *N*,*N*-Diisopropylethlylamine was found to be the preferred base for all other nucleophiles in this transformation, including phenols.

(20) Compound **10a** was isolated in 54% yield using sodium carbonate as base.

(21) See the Supporting Information.

(22) See example **10a**. Although not shown, direct comparisons were made to other examples from our previous works. On average, yields were 10−20% lower.

(23) See the Supporting Information for examples. Other examples include: (a) Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 15877−15888. (b) Fields, J. D.; Kropp, P. J. *J. Org. Chem.* **2000**, *65*, 5937−5941. (c) Caron, S.; Do, M. N.; Sieser, J. E. *Tetrahedron Lett.* **2000**, *41*, 2299−2302. (d) Jain, S. L.; Sain, B. *Chem. Commun.* **2002**, 1040−1041.

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