JOC Article

A Simple Cu-Catalyzed Coupling Approach to Substituted 3-Pyridinol and 5-Pyrimidinol Antioxidants

Susheel J. Nara, Mukund Jha, Johan Brinkhorst, Tony J. Zemanek, and Derek A. Pratt*

Department of Chemistry, Queen's University, Kingston, ON, Canada K7L 3N6

pratt@chem.queensu.ca

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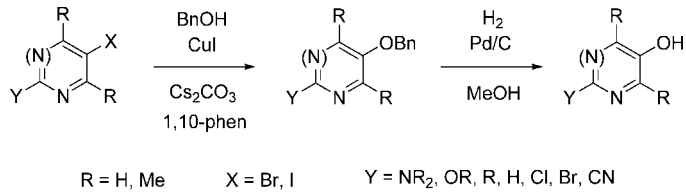
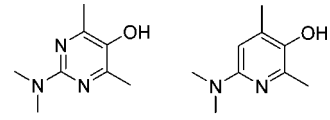


A convenient approach to 3-pyridinols and 5-pyrimidinols via a two-step Cu-catalyzed benzyloxylation/catalytic hydrogenation sequence is presented. The corresponding 3-pyridinamines and 5-pyrimidinamines can be prepared in an analogous sequence utilizing benzylamine in lieu of benzyl alcohol. The radical-scavenging ability of these derivatives are preliminarily explored and reveal that the increased acidities of the pyridinols and pyrimidinols render them susceptible to more significant kinetic solvent effects when compared to phenols.

Introduction

Phenols, ubiquitous in Nature and industry, constitute the most widely used and arguably most effective class of radical-scavenging chain-breaking antioxidants. The archetypical phenolic antioxidant, α-tocopherol (α-TOH, the most potent form of vitamin E), is believed to be the most effective natural compound of this class, reacting with peroxyl radicals with a rate constant around 3×10^6 M^{-1} s^{-1} at ambient temperature in nonpolar solvents.[1] It has long been the goal of many academic and industrial researchers to develop synthetic radical-scavenging antioxidants with even greater activities than α-TOH. Attempts to maximize the antioxidant activity of phenolic compounds have been based largely upon the extensive structure−reactivity studies of Mahoney, Ingold and Pedulli, which clearly show that electron-donating substituent groups on the aromatic ring weaken the phenolic O−H bond, leading to greater rates of H-atom transfer to autoxidation chain-carrying peroxyl radicals.[2] Unfortunately, studies with phenols that are more electron-rich than the substituted benzochromanol found in α-TOH have been disappointing since these compounds are generally reactive with air.[3] This reaction is undesired from two perspectives: first, it depletes the antioxidant, and second, it generates the superoxide radical anion, rendering the phenol a pro-oxidant, rather than an antioxidant (Scheme 1).

In recent years, we have demonstrated that phenolic compounds containing nitrogen in lieu of carbon at the 3 or 3 and 5 positions have an unprecedented balance between radical-scavenging chain-breaking antioxidant activity and stability to air oxidation.[4,5] For example, 2-amino-5-pyrimidinols such as **1** and 6-amino-3-pyridinols such as **2** react 2-fold and 5-fold faster with peroxyl radicals than α-TOH. Most importantly, **1** and **2** are indefinitely stable to degradation when exposed to air, conditions under which the equivalently substituted phenols rapidly decompose.



1 **2**

Unfortunately, detailed structure−reactivity studies with 3-pyridinols and 5-pyrimidinols beyond **1**, **2** and closely related

* To whom correspondence should be addressed. Tel: 613-533-3287. Fax: 613-533-6669.

(1) (a) Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6472. (b) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194.

(2) See, e.g.: Mahoney, L. R.; DaRooge, M. A *J. Am. Chem. Soc.* **1975**, *97*, 4722. (b) Brigati, G.; Lucarini, M.; Mugaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 4828. (c) Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334.

(3) (a) Burton, G. W.; Doba, T.; Gabe, E.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053. (b) Barclay, L. R. C.; Vinqvist, M. R.; Mukai, K.; Itoh, S.; Morimoto, H. *J. Org. Chem.* **1993**, *58*, 7416.

(4) (a) Pratt, D. A.; DiLabio, G. A.; Brigati, G.; Pedulli, G. F.; Valgimigli, L. *J. Am. Chem. Soc.* **2001**, *123*, 4625. (b) Valgimigli, L.; Brigati, G.; Pedulli, G. F.; DiLabio, G. A.; Mastragostino, M.; Arbizzani, C.; Pratt, D. A. *Chem.−Eur. J.* **2003**, *9*, 4997.

(5) (a) Wijtmans, M.; Pratt, D. A.; Valgimigli, L.; DiLabio, G. A.; Pedulli, G. F.; Porter, N. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4370. (b) Wijtmans, M.; Pratt, D. A.; Brinkhorst, J.; Swerza, R.; Valgimigli, L.; Pedulli, G. F.; Porter, N. A. *J. Org. Chem.* **2004**, *69*, 9215.

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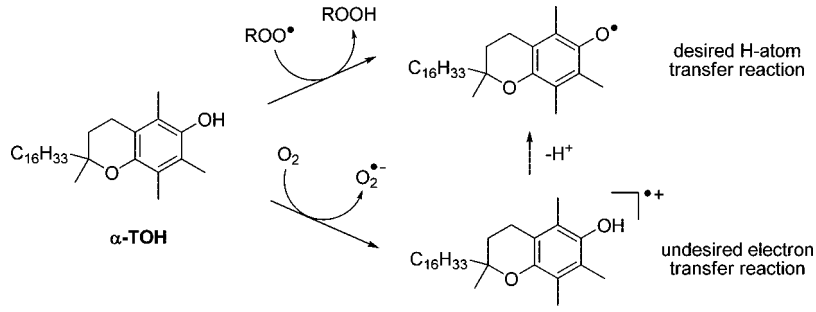
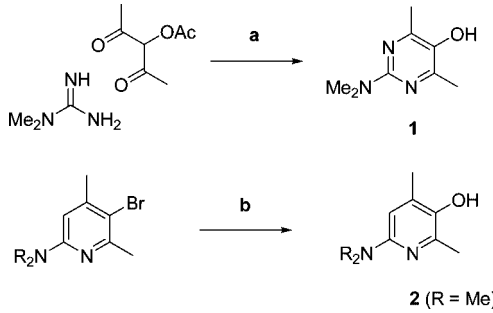
SCHEME 1. Desired Peroxyl Radical Trapping Reaction of α-Tocopherol (α-TOH) and the Competing Undesired Reaction with Molecular Oxygen



SCHEME 2. Previous Routes to 2-Amino-5-Pyrimidinols 1 and 6-Amino-3-Pyridinols 2[a]



[a] Key: (a) NaOAc, DMF, 100 °C, 4 h, 30%[4]; (b) (i) BuLi, THF, −78 °C, 30 min, (ii) 2-nitro-*m*-xylene, THF, −78 °C, 2 h, (iii) aq HCl, 25−63%.[5]

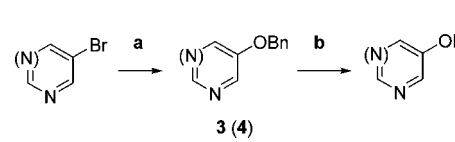
compounds have yet to be carried out, and their suitability for various applications has yet to be explored because of a lack of commercial availability and convenient synthetic routes for their preparation. For example, the approaches we employed to prepare **1** and **2** (Scheme 2) are restrictive in the substitution that they tolerate, they are low-yielding (ca. 20−30% for most examples) and can be quite costly.

While the aryl bromide to aryl alcohol conversion employed to prepare **2** was low yielding, this type of approach was most desirable because we could then make use of the vast substitution chemistry known to pyridines and pyrimidines to construct precursors to a wide variety of pyridinols and pyrimidinols and then convert them to the aryl alcohols in a final step. Unfortunately, efforts to improve the lithiation/oxidation sequence by changes in reaction conditions were futile. Herein we present the results of our attempts to find a more general, inexpensive and higher yielding approach to convert pyridyl and pyrimidyl halides to pyridyl and pyrimidyl alcohols for the detailed kinetic and thermodynamic studies we have long desired to carry out.

Results and Discussion

Pyri(mi)dyl Halides to Pyri(mi)dyl Alcohols. We envisioned a two-step sequence involving the formation of an aryl ether followed by cleavage of the ether to yield the desired aryl alcohol. Hartwig[6] and Buchwald[7] have shown that the Pd-catalyzed etherification of electron-poor aryl bromides can be accomplished in good yields and given the greater electron-deficiency of the pyridine and pyrimidine rings relative to their

SCHEME 3. Benzyloxylation/Hydrogenation Sequence to 3-Pyridinols and 5-Pyrimidinols[a]



X	Y	% Yield[b]
CH	CH	0
CH	N	86
N	N	88

[a] Key: (a) BnOH, Cs_2CO_3, CuI, 1,10-phenanthroline, toluene, 110 °C, overnight; (b) H_2, Pd/C, MeOH, rt, 2 h. [b] Isolated yield.

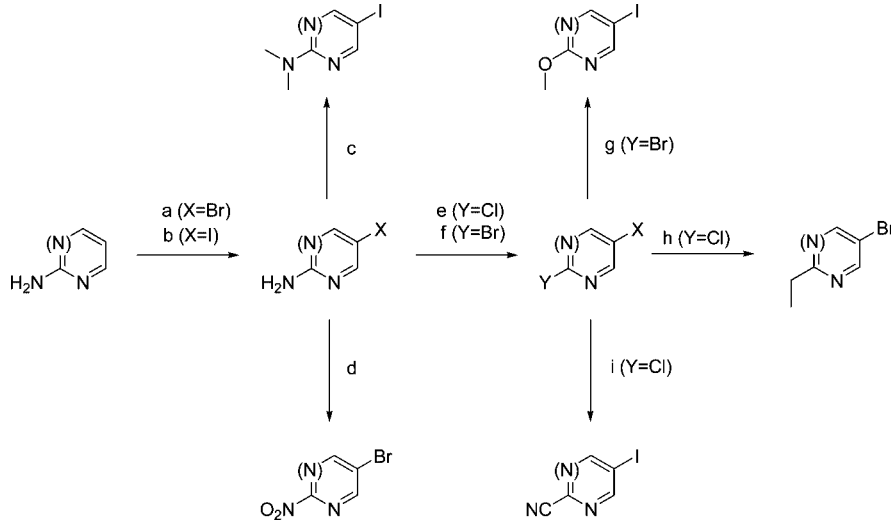
phenyl counterparts, we enthusiastically pursued this chemistry. Our attempts centered on the use of *tert*-butyl alcohol or benzyl alcohol to facilitate mild removal of the *tert*-butyl or benzyl moiety in a subsequent step and included a variety of different commercially available Pd sources and ligand combinations in differing catalyst loadings. Unfortunately, this approach did not afford encouraging results, with only trace amounts of product formed from either 3-bromopyridine or 5-bromopyrimidine.

We next turned our attention to a Cu-catalyzed approach. The Cu-mediated Ullmann ether synthesis[8] is a classical method to effect aryl carbon-heteroatom bond formation and Buchwald has shown that it can be done catalytically with aryl iodides.[9] Again, we hoped that the increased electron deficiency of the pyridine and pyrimidine rings would make the accessible pyridyl and pyrimidyl bromides good substrates for this reaction. Indeed, we found that 3-bromopyridine and 5-bromopyrimidine are smoothly converted to their cooresponding benzyl ethers (Scheme 3) and that catalytic hydrogenation to remove the benzyl group and yield the 3-pyridinol and 5-pyrimidinol is quantitative. In comparison, bromobenzene could not be converted to benzyl phenyl ether under the same conditions.

Monosubstituted Pyri(mi)dyl Halides as Substrates. To our surprise, exploring the substrate scope of this approach in order to prepare a series of pyridinols and pyrimidinols for detailed structure−reactivity studies required the de novo preparation of almost all of the pyridyl halides and pyrimidyl halides we examined since many were not available through commercial suppliers, nor were synthetic routes for their preparation described in the literature. We desired a wide range of substitution: electron-donating groups such as amino, alkoxy, and alkyl and electron-withdrawing groups such as halo, cyano and nitro. Furthermore, we hoped to prepare them all via 2-aminopyri(mi)dine, one of the most inexpensive monofunctionalized pyri(mi)dines. The transformations are summarized in Scheme 4.

(6) See, e.g.: Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718.
(7) See, e.g.: Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770.
(8) Ullman, F. *Chem. Ber.* **1904**, *37*, 853. For a general review, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
(9) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.

SCHEME 4. Preparation of Substrates for Cu-Catalyzed Benzyloxylation of Pyridines and Pyrimidines[a]



[a] Key: (a) pyr: NBS, CH_3CN, rt, overnight, 87%; pym: NBS, CH_3CN, reflux, overnight, 85%; (b) HIO_4-2H_2O, I_2, HOAc, H_2SO_4, 80 °C, 4 h, pyr: 83%; pym: 63%; (c) pyr: HCO_2H, formalin, reflux, overnight, 45%; pym: NaH, MeI, DMF, 4h, 82%; (d) concd H_2SO_4, H_2O_2, 5 °C, rt, overnight, pyr: 62%; pym: no reaction; (e) $Et_3(Bn)NCl$, *t*-BuONO, CH_2Cl_2, rt, 1−12 h, pyr: 79−85%; pym: 35−40%; (f) $Me_3(Bn)NBr$, *t*-BuONO, CH_2Br_2, rt, 1−12 h, pyr: 80−85%; pym: 35−40%; (g) NaOMe, MeOH, rt, overnight, pyr: 69%; pym: 77%; (h) Et_2Zn, 2 mol % of $PdCl_2$ and dppf, dioxane, 50°C, overnight, pyr: 42%; pym: 36%; (i) pyr: ref 10; pym: NaCN, $Et_3(Bn)NCl$, DMF, rt, 7 h, 52%. Complete details are provided in the Supporting Information.

2-Aminopyridine was first brominated with NBS in CH_3CN or iodinated with I_2/HIO_4 in HOAc to provide the handle for the eventual Cu-catalyzed benzyloxylation/hydrogentation sequence. The amine could be reductively alkylated with formaldehyde to yield the 2-*N*,*N*-dimethylaminopyridine or oxidized with Caro's acid to yield the 2-nitropyridine. To provide a handle for nucleophilic substitution or cross-coupling, the aminopyridine could be easily halo-dediazotized under nonaqueous conditions to yield the 2-chloro or 2-bromo species. Subsequent treatment with NaOMe and NaCN lead to the 2-cyanopyridine and 2-methoxypyridine, respectively, while the 2-ethylpyridine was obtained by Pd-catalyzed cross-coupling with diethylzinc. The nonaqueous diazotization improves the yield over traditional Sandmeyer approaches due to both better conversion and ease of workup and isolation.

The pyrimidyl halide substrates could be prepared in a similar fashion from 2-aminopyrimidine, but with a few notable differences due to the lower inherent nucleophilicity of the amino group. First, reductive alkylation with formaldehyde was quite slow and abandoned in favor of treatment with NaH/MeI. The reduced reactivity also precluded the oxidation of the 2-aminopyrimidine to the 2-nitropyrimidine—a transformation that has yet to be reported in the literature. Not surprisingly, the halo-dediazotizations were consistently lower yielding, but the subsequent substitutions and cross-couplings were quite facile. With these substrates in hand, we explored the generality of the Cu-catalyzed benzyloxylation approach. The results are presented in Table 1.

To our satisfaction, essentially all of the pyridyl halides were good substrates for this reaction. Conventionally, aryl iodides are the best substrates for the Ullmann reaction and, indeed, for electron-rich pyridines, such as the 2-*N*,*N*-dialkylamino- and 2-alkoxy-substituted compounds, iodides were found to be much better substrates than bromides. However, in the case of the less electron-rich pyridines, such as the 2-alkyl-, unsubstituted, and 2-halosubstituted compounds, bromides proved to be good substrates as well.

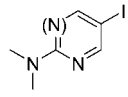
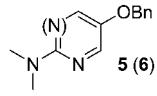
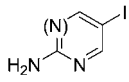
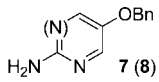
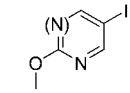
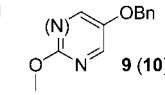
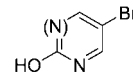
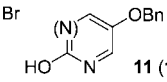
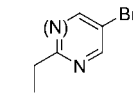
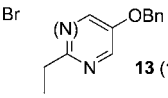
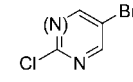
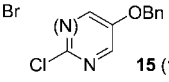
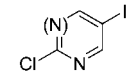
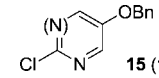
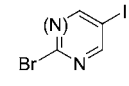
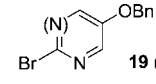
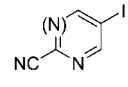
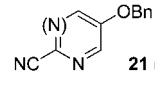
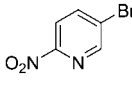
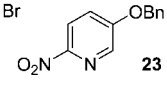
The halogenated 2-aminopyridine and 2-hydroxypyridine (the keto tautomer predominates in the latter) were poor substrates (entries 2 and 4, respectively) presumably due to deprotonation, and therefore, deactivation under the basic conditions employed. 2-Aminopyridine has a pK_a of 14.3 (measured in CH_3CN),[11] and 2-hydroxypyridine (2-pyridone) has a pK_a of 11.6 (in H_2O).[12] This further prevented efficient couplings of base-labile protected precursors (e.g., acylated amines or alcohols) due to alcoholysis. In the end, we found that an amine protected as the 2,5-dimethylpyrrole[13] could be efficiently coupled and then the amine readily deprotected as in Scheme 5.[14] Any *O*-protecting group stable to base would presumably be useful for the preparation of the pyridinone, but this was not explored. The other problematic pyridyl halide, 5-bromo-2-nitropyridine (entry 10), surprisingly underwent *ipso* substitution of benzyloxy for the nitro group, yielding 2-benzyloxy-5-bromopyridine in 55% yield.

While some of the pyrimidyl halides were also good substrates for the Ullmann reaction (2-dialkylamino, 2-alkyl, unsubstituted), any which presented a reasonable leaving group at the activated 2-position (alkoxide, halide, cyanide) underwent preferential substitution at this position, leading to 2,5-dibenzyloxy substituted compounds. In order to access the pyrimidine derivatives with these groups intact at the 2-position, the 2,5-dibenzyloxypyrimidine (**24**) then had to be subjected to nucleophilic substitutions, e.g. with NaOMe to yield the 2-methoxy-5-benzyloxy derivative (77% yield).

Ortho Alkylated Pyri(mi)dyl Halides as Substrates. Many of the radical-scavenging chain-breaking phenolic antioxidants used in industry and found in Nature contain alkyl substitution in the *ortho* positions relative to the phenolic hydroxyl group, e.g., methyl in α-TOH and *tert*-butyl in butylated hydroxytoluene (BHT). Hence, we expanded our studies of the substrate

(10) Song, J. J.; Yee, N. K.; Tan, Z.; Xu, J.; Kapadia, S. R.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4905.
(11) Kaljurand, I.; Rodina, T.; Leito, I.; Koppel, I. A.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 6202.
(12) Albert, A.; Phillips, J. N. *J. Chem. Soc.* **1956**, 1294.
(13) Lützen, A.; Hapke, M.; Staats, H.; Bunzen, J. *Eur. J. Org. Chem.* **2003**, *394*, 8–3957.
(14) Alternatively, one could envision a Pd-amination of the 6-halo-3-benzyloxypyridine to arrive at the 6-amino-3-benzyloxypyridine, but this approach is not useful for the pyrimidines, *vide infra*.

TABLE 1. Copper-Catalyzed Benzyloxylation of 3-Halopyridines and 5-Halopyrimidines[a]

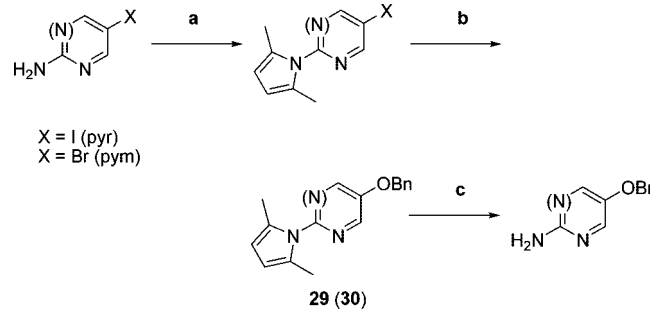
Entry	Aryl Halide	Aryl Ether	% Yield[b]
1		 **5 (6)**	92 (95)
2		 **7 (8)**	35 (0)
3		 **9 (10)**	88 (89)[c]
4		 **11 (12)**	0 (0)
5		 **13 (14)**	84 (74)
6		 **15 (16)**	83 (79)[c]
7		 **15 (16)**	91 (85)[d]
8		 **19 (20)**	88[e](88)[d]
9		 **21 (22)**	91 (92)[c]
10		 **23**	55[f]

[a] Conditions: 10 equiv of BnOH, 1.5 equiv of Cs_2CO_3, 10 mol % of CuI, 20 mol % of 1,10-phenanthroline, toluene, 110 °C, 24 h. [b] Isolated yield following purification. [c] Substitution occurs at both the 2- and 5-positions to yield 2,5-dibenzyloxypyrimidine (**24**). [d] Substitution occurs at both the 2- and 5-positions to yield **24**. Reactions at 60 °C led to 2-benzyloxy-5-iodopyrimidine **25**. [e] Substitution occurs at both the 2- and 5-positions to yield the 2,5-dibenzyloxypyridine (**26**). Reactions at 60 °C led to 2-benzyloxy-5-iodopyridine (**27**). [f] Substitution occurs only at the 2-position to give 2-benzyloxy-5-bromopyridine (**28**).

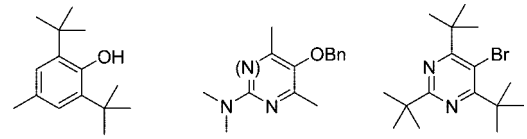
scope of the Cu-mediated benzyloxylation to include pyridyl and pyrimidyl halides with *o*-methyl and *tert*-butyl substitution. In doing so, we discovered that even electron rich pyrimidyl and pyridyl halides with methyl substitution at the *ortho* position were reasonable substrates for the two-step conversion to pyridinols and pyrimidinols. For example, the benzyl ethers **31** and **32** could be prepared from the corresponding aryl iodides and subsequently converted to pyridinol **2** and pyrimidinol **1** in 68% and 62% isolated yield over both steps. Unfortunately, *tert*-butylated substrates such as the accessible pyrimidine **33**[15] proved too hindered for the Cu-catalyzed coupling reaction (or a Cu-catalyzed halogen exchange[16] to afford the corresponding aryl iodide).

Pyri(mi)dyl Halides to Pyri(mi)dyl Amines. Aromatic amines are probably the most important industrial radical-scavenging chain-breaking antioxidants, and we have wondered if incorporating nitrogen atoms in the aromatic ring of these compounds would help stabilize them to air oxidation, as we have demonstrated for phenols.[4,5] This would allow the preparation of more effective aromatic amine antioxidants, since they would tolerate substitution with more electron-donating groups without being too reactive to air to be useful. Unfortunately, there is a paucity of precedent to these classes of compounds in the literature. We are therefore encouraged that the benzyloxylation/hydrogenation approach can be extended to prepare the analogous arylamines from the same halogenated precursors in a two-step process involving first a Cu-catalyzed coupling to benzylamine followed by catalytic hydrogenation. We found that changing the base, solvent, and ligand to K_3PO_4, DMSO, and proline, respectively, as suggested by Zhang and coworkers,[17] resulted in better yields for the preparation of the *N*-benzylamines and subsequent catalytic hydrogenation often proceeded better at higher temperatures with ammonium formate as the reductant.[18] For example, we prepared the *N*,*N*-dimethylamino-substituted pyridyl and pyrimidyl *N*-benzylamines **34** and **35** in 80% and 81% yield, respectively, and subsequently debenzylated them to give the pyri(mi)dinamines **36** and **37**. The approach is contrasted with that used to prepare the analogous pyri(mi)dinols **38** and **39** in Scheme 6.

SCHEME 5. Preparation of Substrates for Cu-Catalyzed Benzyloxylation of Pyridines and Pyrimidines[a]



[a] Key: (a) 2,5-hexanedione, *p*-TsOH, toluene, Dean−Stark, overnight, pyr: 82%; pym: 91%; (b) 10 equiv of BnOH, 1.5 equiv of Cs_2CO_3, 10 mol % of CuI, 20 mol % of 1,10-phenanthroline, toluene, pyr: 86%; pym: 82%; (c) $NH_2OH \cdot HCl$, Et_3N, EtOH, water, reflux, 20 h, pyr: 81%; pym: 76%.



Pyri(mi)dyl Halides to Pyri(mi)dyl Thiols. We also investigated whether this approach could be applied to the synthesis of the analogous arylthiols from the same halogenated precursors. A recent computational study has recommended that 3-pyridinethiols be pursued as antioxidants based on their low S−H bond strengths.[19] Indeed, the Cu-catalyzed coupling of the *N*,*N*-dimethylamino-substituted pyridyl and pyrimidyl iodides with benzyl mercaptan was possible (isolated yields, pyr: 87%, pym: 65%), but cleavage of the resulting *S*-benzyl thioethers **40** and **41** was cumbersome (Scheme 7). While it could be accomplished for the pyridine using titanocene

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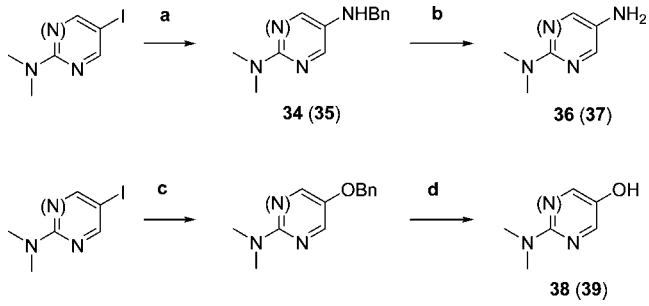
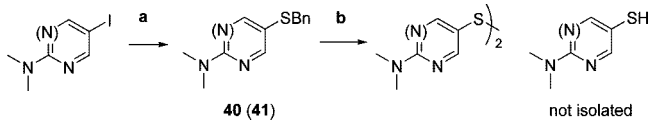
SCHEME 6. Comparing the Benzylamination/Hydrogenation Sequence to 3-Pyridinamines and 5-Pyrimidinamines and the Benzyloxylation/Hydrogenation Sequence to 3-Pyridinols and 5-Pyrimidinols[a]



[a] Key: (a) $BnNH_2$, K_3PO_4, CuI, proline, DMSO, 80 °C, 48 h; (b) pyr: NH_4HCO_2, Pd/C, HOAc, rt, 16h, 80%; pym: NH_4HCO_2, Pd/C, MeOH, reflux, 30 min, 81%; (c) BnOH, Cs_2CO_3, CuI, 1,10-phenanthroline, toluene, 110 °C, overnight, pyr: 92%; pym: 95%; (d) H_2, Pd/C, MeOH, rt, overnight, pyr: 89%; pym: 93%.

SCHEME 7. Benzylthiolation of 2-*N*,*N*-Dimethylaminopyri(mi)dyl Iodide[a]



[a] Key: (a) BnSH, Cs_2CO_3, CuI, 1,10-phenanthroline, toluene, 110 °C, overnight, pyr: 87%; pym: 65%; (b) pyr: $Ti(Cp)_2Cl_2$, Bu_2Mg, diglyme, 0°C, 1 h, 23%; pym: (i) Bu_3SnH, AIBN, benzene, reflux, 3 h, (ii) 6 M HCl, rt, 2 h, 10%.

dichloride and dibutylmagnesium,[20] the product thiol was readily oxidized to the corresponding disulfide, which was solely isolated. Where titanocene dichloride and dibutylmagnesium failed to cleave the pyrimidyl thioether, treatment with tributyltin hydride/AIBN[21] followed by either concentrated acid or tetrabutylammonium fluoride[22] was successful, but again yielded only the disulfide.

Preliminary Kinetics Investigations. We have carried out preliminary studies of the reactivity of pyri(mi)dinols **38** and **39** and pyri(mi)dinamines **36** and **37** with peroxyl radicals using a newly developed peroxyl radical clock approach.[23,24] This approach involves the kinetic competition between the unimolecular β-fragmentation of the nonconjugated peroxyl radical **I** derived from peroxyester **42**, which occurs with a rate constant of 1.4×10^5 s^{-1}, and its trapping by a H-atom donor (XH) to yield a nonconjugated hydroperoxide (Scheme 8). Rate constants determined for XH = **36**−**39**, determined in benzene and propionitrile, are given in Table 2.

The pyridinol **38**, prepared in four straightforward steps from 2-aminopyridine (halogenation, alkylation, benzyloxylation, and hydrogenolysis), was found to be indefinitely air stable and slightly more reactive toward peroxyl radicals than α-TOH in benzene. Consistent with our previous results, the corresponding pyrimidinol **39** prepared in exactly the same way, but starting from 2-aminopyrimidine, had slightly lower reactivity compared to pyridinol **38** and α-TOH but was more reactive than air-stable monosubstituted phenols. This is due to the slightly stronger phenolic O−H bond in pyrimidinols compared to equivalently substituted pyridinols (i.e., 78.2 kcal/mol[4] in **1** and 77.0 kcal/mol[5] in **2**). The arylamine analogues **36** and **37**, prepared similarly from 2-aminopyridine and 2-aminopyrimidine, respectively, react roughly 3-fold slower with peroxyl radicals than the corresponding pyridinols and pyrimidinols in benzene. This is a similar difference in kinetics to those of reactions of phenols and anilines with radicals and is ascribed to the slightly stronger N−H bond in anilines as compared to the O−H bond in phenols.[26]

TABLE 2. Second-Order Rate Constants for the Reactions of 2-*N*,*N*-Dimethylamino-Substituted Pyri(mi)dinol and Pyri(mi)dineamine with Peroxyl Radicals in Benzene and Propionitrile at 25 °C

	$k_{ROO\bullet}$ (M^{-1} s^{-1})	
H-atom donor	benzene	propionitrile
pyridinol **38**	3.7×10^6	2.1×10^5
pyrimidinol **39**	1.4×10^6	6.7×10^4
pyridinamine **36**	1.3×10^6	5.0×10^4
pyrimidinamine **37**	4.0×10^5	7.5×10^3
α-TOH[25]	3.4×10^6	3.8×10^5

The kinetics of H-atom transfer reactions of phenols and anilines are known to be sensitive to the nature of the medium. Ingold and co-workers have clearly demonstrated that the kinetic solvent effect (KSE) on these reactions can be well described by a mechanism wherein the H-bond donating (HBD) abilities of phenols (ArOH, Scheme 9) or anilines render them less reactive in H-bond accepting (HBA) solvents (S) since the phenolic O−H (or anilinic N−H) is tied up in an H-bond and not free to react (Scheme 9).[27]

To date, there is no data on the KSEs on the H-atom transfer reactions of pyridinols and little on the pyrimidinols.[4b] This is particularly relevant for these classes of antioxidants since the increased electron-deficiency of the pyridine and pyrimidine rings would be expected to yield a more acidic O−H bond, increasing their H-bond donating ability relative to phenols, and decreasing their rates of reaction. The preliminary data we have gathered here support this idea. For example, where the rate constant for α-TOH drops by roughly 10-fold on going from benzene to propionitrile, that for pyridinol **38** drops 17-fold and that for pyrimidinol **39** drops 21-fold. This is presumably due to the greater acidity of the O−H bond along the phenol−pyridinol−pyrimidinol series (i.e., pK_a's of α-TOH, **38**, and **39** are 11.9,[28] 9.22 ± 0.09,[29] and 8.15 ± 0.04,[29] respectively), which leads to greater H-bonding interactions between the H-atom donor and the solvent. This will be explored in detail in a future manuscript.

Surprisingly, the KSEs on the reactions of the arylamines **36** and **37** were found to be even larger than those on the reactions of the pyri(mi)dinols, as seen when comparing the rate constants for the reactions in propionitrile to those in benzene (i.e., rate constants drop 26-fold and 53-fold for **36** and **37**, respectively). Since anilines are less acidic than phenols, we had expected the pyri(mi)dinamines to have weaker interactions with HBA solvents than the pyri(mi)dinols, and consequently smaller KSEs. This will also be explored in detail in a future manuscript.

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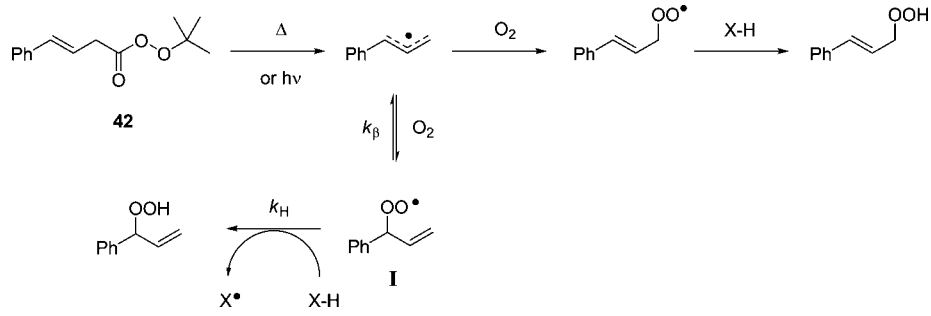
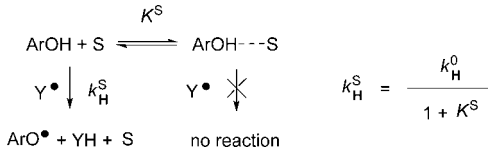
SCHEME 8. Peroxyester-Based Approach for the Determination of Peroxyl Radical Kinetics[23,24]



SCHEME 9. Kinetic Solvent Effects on H-Atom Transfer Reactions of Phenols



In conclusion, we have explored the use of a simple Cu-catalyzed coupling approach to 3-pyridinols and 5-pyrimidinols and the analogous arylamines. This two-step sequence, along with the means to prepare a variety of pyri(mi)dyl halide precursors, now permits us to pursue detailed studies of the exciting radical-scavenging activities of these compounds, in particular, the importance of kinetic solvent effects on their reactivities.

Experimental Section

General Procedure for Benzyloxylation of Pyri(mi)dyl Halides. To a mixture of CuI (0.40 mmol), 1,10-phenanthroline (0.80 mmol), cesium carbonate (6.00 mmol), and bromo- or iodopyri(mi)dine (4.00 mmol) in a dry Schlenk flask (evacuated and nitrogen purged) were added 5 mL of toluene and benzyl alcohol (40 mmol) and heated in an oil bath at 110 °C for 24 h. The reaction mixture was filtered through a silica plug and solvent removed under reduced pressure. The crude residue obtained was subjected to flash chromatography (eluent: ethyl acetate/hexanes) and the purified product characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

3-Benzyloxypyridine (3). The characterization data is consistent with literature values.[30] Yield: 86%.

5-Benzyloxypyrimidine (4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (s, 2H), 7.34−7.41 (m, 5H), 8.46 (s, 2H), 8.85 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.7, 127.4, 128.9, 129.7, 135.2, 144.0, 151.7, 152.8 ppm. HRMS (ES^+) calcd (M) 186.0793, obsd 186.0795. Yield: 88%.

2-*N*,*N*-Dimethylamino-5-benzyloxypyridine (5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (s, 6H), 5.03 (s, 2H), 6.49−6.51 (d, J = 9.2, 1H), 7.19−7.22 (dd, J = 9.2, 3.2), 7.33−7.45 (m, 5H), 7.99−8.00 (d, J = 9.2, 2.8 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.8, 71.7, 106.5, 126.5, 127.6, 128.0, 128.6, 135.0, 137.2, 147.0, 155.4 ppm. HRMS (ES^+) calcd (M) 228.1263, obsd 228.1255. Yield: 92%.

2-*N*,*N*-Dimethylamino-5-benzyloxypyrimidine (6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (s, 6H) 5.02 (s, 2H), 7.40−7.41 (m, 5H), 8.14 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.6, 72.6, 127.7, 128.3, 128.7, 136.5, 144.7, 146.6, 158.7 ppm. HRMS (ES^+) calcd (M) 229.1215, obsd 229.1217. Yield: 95%.

2-Amino-5-benzyloxypyridine (7). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 (bs, 2H), 5.03 (s, 2H), 6.48−6.50 (d, J = 8.8 Hz, 1H), 7.16−7.19 (dd, J = 8.8, 3.2 Hz, 1H), 7.33−7.44 (m, 5H), 7.85−7.86 (d, J = 2.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.5, 109.4, 127.0, 127.6, 128.1, 128.6, 134.5, 136.8, 148.7, 153.2 ppm. HRMS (ES^+) calcd (M) 200.0950, obsd 200.0952. Yield: 35% from coupling. Yield: 81% from deprotection of pyrrole **24** (vide infra).

2-Amino-5-benzyloxypyrimidine (8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (bs, 2H), 5.04 (s, 2H), 7.35−7.42 (m, 5H), 8.10 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 72.2, 127.7, 128.4, 128.7, 136.1, 146.6, 146.64, 158.4 ppm. HRMS (ES^+) calcd (M) 201.0902, obsd 201.0903. Yield: 0% from coupling. Yield: 76%. From deprotection of pyrrole **25** (vide infra).

2-Methoxy-5-benzyloxypyridine (9). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 4.97 (s, 2H), 6.59−6.62 (d, J = 9.2 Hz, 1H), 7.17−7.35 (m, 6H), 7.79−7.80 (dd, J = 2.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.6, 71.3, 111.1, 127.6, 127.9, 128.2, 128.7, 132.4, 136.6, 150.2, 158.9 ppm. HRMS (ES^+) calcd (M) 215.0946, obsd 215.0947. Yield: 88%.

2-Methoxy-5-benzyloxypyrimidine (10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 5.11 (s, 2H), 7.42−7.43 (m, 5H), 8.26 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.0, 69.8, 125.6, 126.5, 126.8, 133.7, 144.7, 146.6, 158.6 ppm. HRMS (ES^+) calcd (M) 216.0899, obsd 216.0906. Yield: 77% from NaOMe treatment of 2,5-dibenzyloxypyrimidine (**24**, vide infra).

2-Ethyl-5-benzyloxypyridine (13). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23−1.27 (t, J = 7.6 Hz, 3H), 2.58−2.63 (q, J = 7.6 Hz, 2H), 5.40 (s, 2H), 6.77−6.80 (d, J = 8.4 Hz, 1H), 7.32−7.50 (m, 6H), 8.03 (d, J = 2.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 25.2, 67.6, 110.9, 127.8, 127.9, 128.5, 132.3, 137.5, 138.8, 145.3, 162.0 ppm. HRMS (ES^+) calcd (M) 213.1154, obsd 213.1152. Yield: 84%.

2-Ethyl-5-benzyloxypyrimidine (14). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25−1.28 (t, J = 6.0 Hz, 3H), 2.58−2.62 (q, J = 6.0 Hz, 2H), 5.45 (s, 2H), 7.31−7.34 (m, 2H), 7.37−7.40 (m, 2H), 7.50−7.52 (d, J = 6.0 Hz, 2H), 8.39 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 22.7, 68.9, 127.9, 128.4, 129.1, 130.0, 136.8, 158.5, 163.8 ppm. HRMS (ES^+) calcd (M) 214.1106, obsd 214.1106. Yield: 74%.

2-Chloro-5-benzyloxypyridine (15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (s, 2H), 7.23−7.28 (m, 2H), 7.36−7.43 (m, 5H) 8.15−8.16 (d, J = 2.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.9, 124.5, 125.4, 127.5, 128.5, 128.8, 135.7, 137.1, 142.8, 154.1 ppm. HRMS (ES^+) calcd (M) 219.0451, obsd 219.0446. Yield: 83% from 2-chloro-5-bromopyridine and 91% from 2-chloro-5-iodopyridine.

2-Cyano-5-benzyloxypyridine (21). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (s, 2H), 7.30−7.33 (dd, J = 8.8, 3.2 Hz, 1H) 7.38−7.46 (m, 5H), 7.64−7.66 (d, J = 8.8 Hz, 1H), 8.46−8.47 (d, J = 2.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.8, 117.4, 120.9, 125.6, 127.6, 128.8, 128.9, 129.5, 134.8, 140.7, 157.0 ppm. HRMS (ES^+) calcd (M) 210.0793, obsd 210.0800. Yield: 91%.

2,5-Dibenzyloxypyrimidine (24). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 (s, 2H), 5.41 (s, 2H), 7.28−7.50 (m, 10H), 8.27 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.2, 71.7, 127.6, 127.9, 127.9, 128.4, 128.6, 128.8, 135.7, 136.8, 146.7, 148.7, 159.9 ppm. HRMS (ES^+) calcd (M) 292.1212, obsd 292.1216. Yield: 88% from

(30) Cherng, Y.-J *Tetrahedron* **2002**, *58*, 4931–4935.

2-bromo-5-iodopyrimidine, 85% from 2-chloro-5-iodopyrimidine, 89% from 2-ethoxy-5-iodopyrimidine, 85% from 2-methoxy-5-bromopyrimidine, 79% from 2-chloro-5-bromopyrimidine.

2-Benzyloxy-5-iodopyrimidine (25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (s, 2H), 7.33−7.41 (m, 3H), 7.47−7.49 (d, J = 7.2 Hz, 2H), 8.67 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.5, 82.6, 128.0, 128.2, 128.5, 136.0, 164.0, 164.4 ppm. HRMS (ES^+) calcd (M) 311.9760, obsd 311.9747. Yield: 97% at 60 °C from 2-chloro-5-iodopyrimidine, 98% at 60 °C from 2-bromo-5-iodopyrimidine.

2,5-Dibenzyloxypyridine (26). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.96 (s, 2H), 5.24 (s, 2H), 6.65−6.68 (d, J = 8.8, 1H) 7.16−7.37 (m, 11H), 7.79−7.80 (d, J = 2.8, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.8, 71.3, 111.5, 127.6, 127.8, 127.86, 127.9, 128.2, 128.5, 128.7, 132.4, 136.7, 137.6, 150.4, 158.4 ppm. HRMS (ES^+) calcd (M) 291.1259, obsd 291.1259. Yield: 88%.

2-Benzyloxy-5-iodopyridine (27). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (s, 2H), 6.66−6.68 (d, J = 8.4 Hz, 1H), 7.32−7.46 (m, 5H), 7.80−7.83 (dd, J = 8.8, 2.4 Hz, 1H), 8.36−8.37 (d, J = 2.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.9, 82.3, 113.7, 128.0, 128.0, 128.5, 136.9, 146.5, 152.6, 163.0 ppm. HRMS (ES^+) calcd (M) 310.9807, obsd 310.9806. Yield: 10%.

2-Benzyloxy-5-bromopyridine (28). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (s, 2H), 6.74−6.76 (d, J = 9.2 Hz, 1H) 7.33−7.48 (m, 5H), 7.66−7.69 (dd, J = 8.8, 2.4 Hz, 1H) 8.24 (d, J = 2.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.0, 111.9, 113.0, 128.0, 128.0, 128.5, 136.9, 141.2, 147.4, 162.4 ppm. MS (*m*/*z*, % intensity) 91 (100), 262 (9), 264 (8). Yield: 55%

2-*N*-(2,5-Dimethylpyrrolo)-5-benzyloxypyridine (29). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 6H), 5.18 (s, 2H), 5.90 (s, 2H), 7.16−7.18 (d, J = 8.4 Hz, 1H), 7.40−7.50 (m, 6H), 8.37−8.38 (d, J = 2.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 70.8, 106.4, 122.5, 123.5, 127.7, 128.5, 128.7, 128.8, 135.9, 137.1, 145.2, 154.0 ppm. HRMS (ES^+) calcd (M) 278.1419, obsd 278.1414. Yield: 86%.

2-*N*-(2,5-Dimethylpyrrolo)-5-benzyloxypyrimidine (30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 6H), 5.21 (s, 2H), 5.98 (s, 2H), 7.46−7.52 (m, 5H), 8.56 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 71.2, 107.8, 127.7, 128.8, 128.9, 129.4, 135.3, 145.0, 150.6, 151.8 ppm. HRMS (ES^+) calcd (M) 279.1372, obsd 279.1369. Yield: 82%.

5-Benzyloxy-4,6-dimethyl-2-*N*,*N*-dimethylaminopyridine (31). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.45 (s, 3H), 3.07 (s, 6H), 4.77 (s, 2H), 6.22 (s, 1H), 7.37−7.50 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 19.5, 38.4, 74.9, 105.2, 128.0, 128.03, 128.6, 137.6, 141.3, 143.8, 149.2, 155.8 ppm. HRMS (ES^+) calcd (M) 256.1576, obsd 256.1576. Yield: 81%.

5-Benzyloxy-4,6-dimethyl-2-*N*,*N*-dimethylaminopyrimidine (32). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 6H), 3.18 (s, 6H), 4.75 (s, 2H), 7.37−7.47 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 37.3, 75.4, 128.1, 128.3, 128.6, 137.1, 141.6, 158.5, 160.1 ppm. HRMS (ES^+) calcd (M) 257.1528, obsd 257.1524. Yield: 78%.

General Procedure for Benzylamination of Pyri(mi)dyl Halides. A mixture of 5-bromo-2-*N*,*N*-dimethylaminopyri(mi)dine (1.49 mmol, 0.30 g), copper iodide (0.15 mmol, 0.029 g, 10 mol%), K_3PO_4 (3.0 mmol, 0.63 g), and L-proline (0.17 mmol, 0.02 g) in DMSO was stirred at 80 °C for 48 h under nitrogen. The reaction mixture was diluted with 20 mL of ethyl acetate and filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue obtained was purified using flash column chromatography (solvent: ethyl acetate) to give the title compound.

5-*N*-Benzyamino-2-*N*,*N*-dimethylaminopyridine (34). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 6H) 4.28 (s, 2H), 6.47−6.51 (d, J = 8.9 Hz, 1H), 6.94−6.98 (dd, J = 8.9, 3.0 Hz, 1H) 7.30−7.40 (m, 5H), 7.76−7.77 (d, J = 2.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.6, 50.3, 107.6, 125.5, 127.9, 128.2, 129.3, 134.2, 136.3, 140.2, 154.9 ppm. HRMS (ES^+) calcd (M) 227.1422, obsd 227.1419. Yield: 80%.

5-*N*-Benzylamino-2-*N*,*N*-dimethylaminopyrimidine (35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.11 (s, 6H) 3.52 (bs, 1H), 4.23 (s, 2H), 7.25−7.35 (m, 5H), 7.93 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.2, 50.3, 128.1, 128.2, 129.4, 133.5, 139.6, 145.4, 158.7 ppm. HRMS (ES^+) calcd (M) 228.1375, obsd 228.1373. Yield: 82%.

General Procedure for Hydrogenolysis of 5-Benzylaminopyri(mi)dines. A mixture of 5-benzylaminopyri(mi)dine (1.0 mmol), ammonium formate (5.0 mmol, 216 mg), and Pd−carbon (10 mol%) in methanol (10 mL) was refluxed for 30 min. The reaction mixture was filtered over Celite and washed with methanol (10 mL). The filtrate was concentrated and residue was resuspended in diethyl ether (50 mL). The insoluble particles were filtered off, and the filtrate was concentrated. The residue was subjected to flash chromatography (eluent: ethyl acetate/hexanes). The purified product was characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. Although the conversion was quantitative in all the cases, the purification and isolation of the polar derivatives led to slightly reduced yields.

5-Amino-2-*N*,*N*-dimethylaminopyridine (36). The characterization data was consistent with the literature.[31] Yield: 80%.

5-amino-2-*N*,*N*-dimethylaminopyrimidine (37). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (bs, 2H), 3.13 (s, 6H), 8.00 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.6, 129.9, 146.6, 158.3 ppm. HRMS: calcd (M) 138.0905, obsd 138.0905. Yield: 81%

General Procedure for Hydrogenolysis of 5-Benzyloxypyri(mi)dines. A solution of 2-substituted and unsubstituted 5-benzyloxypyri(mi)dine (0.175 mmol) in 5 mL of MeOH was treated with 10% Pd on C (0.01 g), and the resulting black suspension was stirred at rt under H_2 atmosphere (1 atm) overnight. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography (eluent: ethyl acetate/hexanes). The purified product was characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. Although the conversion was quantitative in all the cases, the purification and isolation of the polar derivatives led to slightly reduced yields.

6-*N*,*N*-Dimethylamino-3-pyridinol (38). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (s, 6H) 6.50−6.52 (d, J = 9.2 Hz, 1H) 7.18−7.21 (dd, J = 8.8, 2.8 Hz, 1H) 7.81 (d, J = 2.8 Hz, 1H), 8.45 (bs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.3, 108.1, 128.5, 132.6, 145.1, 153.7 ppm. HRMS (ES^+) calcd (M) 138.0793, obsd 138.0790. Yield: 89%.

2-*N*,*N*-Dimethylamino-5-pyrimidinol (39). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.03 (s, 6H) 8.00 (s, 2H), 9.03 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.2, 142.9, 145.2, 157.4 ppm. HRMS (ES^+) calcd (M) 139.0746, obsd 139.0739. Yield: 93%.

General Procedure for Benzylthiolation of Pyri(mi)dyl Halides. To the mixture of CuI (0.40 mmol), 1,10-phenanthroline (0.80 mmol), cesium carbonate (6.00 mmol), and 2-*N*,*N*-dimethylamino-5-iodopyri(mi)dine (4.00 mmol) in a dry Schlenk flask (evacuated and nitrogen purged) were added 5 mL of toluene and benzyl mercaptan (40 mmol) and the mixture heated in an oil bath at 110 °C for 24 h. After the completion of reaction, as judged by TLC, the reaction was quenched by filtering the reaction mixture through silica plug and the filtrate concentrated in vacuo. The crude residue obtained was subjected to flash chromatography (eluent: ethyl acetate/hexanes). The purified product was characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

5-*S*-Benzylthio-2-*N*,*N*-dimethylaminopyridine (40). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.23 (s, 6H), 4.00 (s, 2H), 6.51−6.53 (d, J = 8.8 Hz, 1H), 7.26−7.28 (d, J = 6.4 Hz, 2H), 7.33−7.38 (m, 3H), 7.42−7.45 (dd, J = 8.8, 2.4 Hz, 1H) 8.26 (d, J = 2.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.1, 42.3, 105.7, 116.1, 127.0, 128.4, 129.0, 138.3, 143.2, 153.3, 158.7 ppm. HRMS (ES^+) calcd (M) 244.1034, obsd 244.1040. Yield: 87%.

(31) Seydel, J. *J. Med. Chem.* **1971**, *14*, 724–729.

5-*S*-Benzylthio-2-*N*,*N*-dimethylaminopyrimidine (41). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (s, 6H), 3.92 (s, 2H), 7.22−7.24 (d, J = 6.8 Hz, 2H), 7.25−7.39 (m, 3H), 8.23 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.2, 42.3, 114.1, 127.2, 128.5, 129.0, 137.8, 161.3, 163.0 ppm. HRMS (ES^+) calcd (M) 245.0987, obsd 245.0977. Yield: 65%.

Rate Constants for Reactions with Peroxyl Radicals. Stock solutions of H-atom donors (0.05−0.5 M) and *tert*-butyl 4-phenylperbutenoate (**42**, 0.1 M) were prepared in benzene. The various concentrations of H-atom donor were mixed with *tert*-butyl-4-phenylperbutenoate (0.01 M, 10 μL of 0.1 M) and diluted up to 100 μL with benzene in 2.0 mL HPLC vials. The reaction mixtures were irradiated at 300 nm for 30 min at 25 °C. After irradiation, the mixtures were reduced with PPh_3 (50 μL of 1.0 M in benzene) and diluted up to 1.8 mL with hexanes. The products of photolysis were measured by GC/FID analysis of the nonconjugated and conjugated alcohols as in ref 24. The ratio of products (conjugated/nonconjugated) was plotted versus the reciprocal of H-atom donor concentration to determine the rate constants as in ref 24.

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Note Added after ASAP Publication. A correction was made to a Table 2 column heading in the version published on November 11, 2008.

Supporting Information Available: Details of the preparation and characterization of the substrates for the Cu-catalyzed couplings in Table 1 and Scheme 5 and raw data used to determine the rate constants given in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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