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Preparation of Highly Reactive Pyridine- and Pyrimidine-Containing Diarylamine Antioxidants

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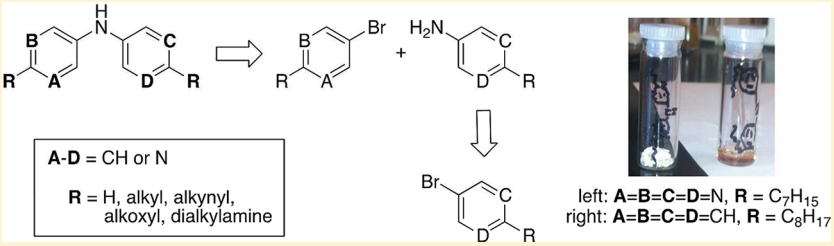
Supporting Information



ABSTRACT: We recently reported a preliminary account of our efforts to develop novel diarylamine radical-trapping antioxidants (Hanthorn, J. J. et al. *J. Am. Chem. Soc.* **2012**, *134*, 8306−8309) wherein we demonstrated that the incorporation of ring nitrogens into diphenylamines affords compounds which display a compromise between H-atom transfer reactivity to peroxyl radicals and stability to one-electron oxidation. Herein we provide the details of the synthetic efforts associated with that report, which have been substantially expanded to produce a library of substituted heterocyclic diarylamines that we have used to provide further insight into the structure−reactivity relationships of these compounds as antioxidants (see the accompanying paper, DOI: 10.1021/jo301012x). The diarylamines were prepared in short, modular sequences from 2-aminopyridine and 2-aminopyrimidine wherein aminations of intermediate pyri(mi)dyl bromides and then Pd-catalyzed cross-coupling reactions of the amines and precursor bromides were the key steps to yield the diarylamines. The cross-coupling reactions were found to proceed best with Pd(η^3-1-PhC$_3$H$_4$)(η^5-C$_5$H$_5$) as precatalyst, which gave higher yields than the conventional Pd source, Pd$_2$(dba)$_3$.

INTRODUCTION

Diarylamines (Ar$_2$NH) are among the most important additives to petroleum-derived products.[1] They are radical-trapping antioxidants which slow hydrocarbon autoxidation, the archetype free-radical chain reaction, through initial donation of their aminic H-atom to chain-carrying peroxyl radicals (eq 1).[2] Subsequent reaction of the aminyl radical with another peroxyl radical leads to nonradical products at ambient temperatures (eq 2) and nitroxide radicals at elevated temperatures (>120 °C, eq 3).[3] The latter reaction is key to the catalytic antioxidant activity of alkylated diphenylamines (**1**), which has made them the additives of choice to lubricating oils of combustion engines and in other high-temperature applications.

$$Ar_2NH + ROO^{\bullet} \rightarrow Ar_2N^{\bullet} + ROOH \quad (1)$$

$$Ar_2N^{\bullet} + ROO^{\bullet} \rightarrow \text{nonradical products} \quad (2)$$

$$Ar_2N^{\bullet} + ROO^{\bullet} \rightarrow Ar_2NO^{\bullet} + RO^{\bullet} \quad (3)$$

In a recent communication,[4] we described preliminary results of our attempts to improve the reactivity of diarylamine antioxidants. Our strategy involves the incorporation of nitrogen atoms into the aryl rings, which enables their substitution with strongly electron-donating groups to weaken the N−H bond and accelerate the rate of the formal H-atom transfer reaction in eq 1. Both modifications are believed to be key to optimizing reactivity, since ring substitution alone results in compounds that undergo one-electron oxidation by O_2 in the air or by product hydroperoxides thereby rendering them useless as antioxidants. In fact, we showed that analogues of **1** bearing either ring carbons or nitrogens at the positions indicated by X, Y, and Z in **2** were characterized by oxidation potentials that increased systematically with the number of N-atoms from less than 1 V to >1.5 V (vs NHE), while their reactivity to peroxyl radicals decreased only 6-fold at most (from 1.8×10^5 $M^{-1}s^{-1}$ for **1** to 3.0×10^4 $M^{-1}s^{-1}$ for **2** with X = Y = Z = N in chlorobenzene at 37 °C). This permitted the design of diarylamines bearing strongly electron-donating *N*,*N*-dialkylamino groups (**3**) that were stable in air and reacted with peroxyl radicals with temperature-independent rate constants up to 200-fold greater than those measured for **1** under the same conditions.

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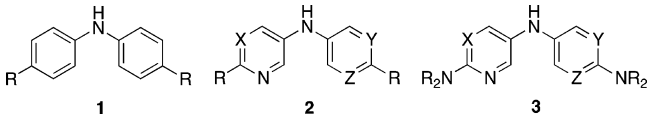
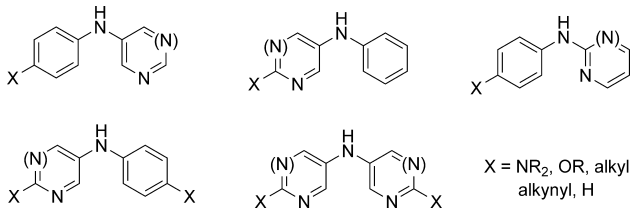


1 2 3

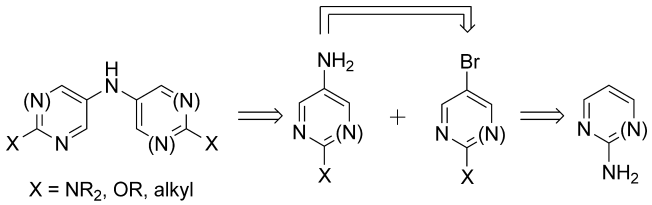
These exciting results prompted us to carry out a thorough study of the structure−reactivity relationships in these compounds. First, it was of interest to determine the optimal location of the ring nitrogen atoms. In our preliminary work, we studied only 3-pyridyl- and 5-pyrimidylamines, but clearly other arrangements are possible and should be investigated. Second, it was of interest to determine the relative reactivities of unsymmetrically substituted compounds as compared to the symmetric compounds studied to date. Third, it was necessary to expand the type of ring substituents that we have studied in order to establish well-defined structure−reactivity relationships that will provide meaningful insights into their chemistry and potential usefulness. Therefore, in addition to the alkyl- and *N*,*N*-dialkylamino-substituted compounds we studied in our preliminary report (i.e., **2** and **3**),[4] we sought to prepare alkoxyl-substituted compounds as well as the unsubstituted (parent) compounds. The compounds of interest are shown in Chart 1.

Chart 1. Target Heterocyclic Diarylamines



It should be pointed out that few of these heterocyclic diarylamines have been described in the literature,[5] and prior to our preliminary report,[4] their radical chemistry had never been explored. Diarylamines can be prepared by a variety of methods, including Smiles rearrangements of amides,[6] Chapman rearrangement of imino ethers,[7] and addition of phenylmagnesium halides to nitrobenzenes[8] or nitrosyl chlorides.[9] We sought a modular synthetic strategy involving intermediates that could be used in multiple combinations to build up a small library that could be used to survey a broad a series of ring structures and substitutions (cf. Scheme 1).

Scheme 1. Library Approach to Heterocyclic Diarylamines



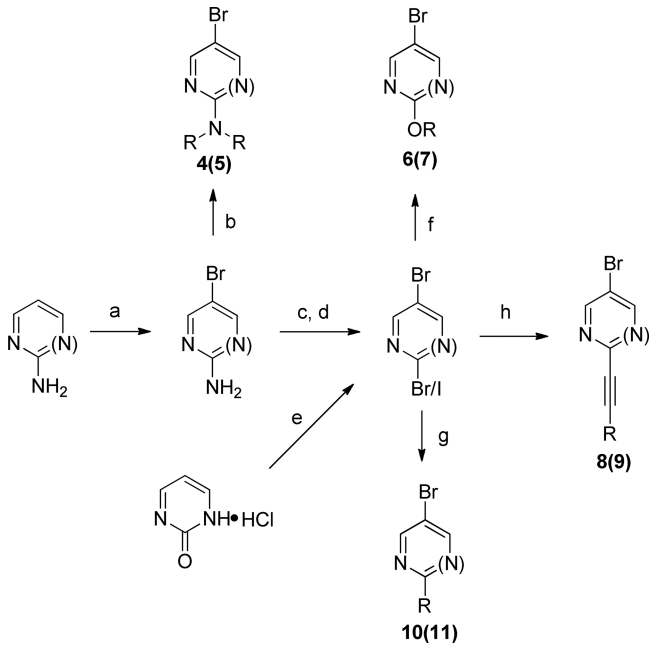
Transition-metal-catalyzed (i.e., Pd, Cu, Ni, Fe) cross-coupling reactions of aryl halides and amines appeared to be the most convenient and versatile approach to accomplish this.[10−12] Herein we describe the application of this approach to the synthesis of a library of diarylamines that has enabled detailed studies of their radical-trapping antioxidant activities (see the accompanying paper, DOI: 10.1021/jo301012x).[4,13]

RESULTS AND DISCUSSION

I. Preparation of 3-Pyridyl and 5-Pyrimidyl Bromides.

2-Aminopyridine and 2-aminopyrimidine were employed as common starting materials for each of the pyridyl and pyrimidyl halides because of their commercial availability and low cost. Synthesis of the various pyridyl bromides began with bromination of the 5-position of 2-aminopyridine using NBS/NH_4OAc.[14] This intermediate was either alkylated by reductive amination with appropriate aldehydes to prepare 5-bromo-2-*N*,*N*-dialkylaminopyridines (**4**) or subjected to nonaqueous[15] diazotization/halo-dediazoniation to afford 2,5-dibromopyridine (Scheme 2). This compound served as the precursor to all

Scheme 2. Preparation of Relevant Pyri(mi)dyl Halides 4−11[a]



[a]Key: (a) NBS, NH_4OAc, MeCN, rt, 5 min, pyr: 85−90%; pym: quant; (b) pyr: RCHO, $Na(CN)BH_3$, MeCN, reflux, 1−12 h (82%, R = C_5H_{11}); pym: NaH, RI, THF, rt, overnight (85%, R = Me); (c) $Me_3(Bn)NBr$, *t*-BuONO, CH_2Br_2, rt, overnight, pyr: 77−83%; pym: 30−40%; (d) pym: HI, CH_2Cl_2, 0 °C, 80−85%; (e) (i) NaOH, Br_2, H_2O, rt, 50−60%, (ii) $POCl_3$, $PhNEt_2$, reflux, 4h, 75−85%, (iii) HI, CH_2Cl_2, 0 °C, 80−85%; (f) ROH, Na, rt, 1−12 h, quant; (g) RZnI, $Cl_2Pd(PPh_3)_2$, DMF/THF, rt, overnight, pyr (Br): 72% (R = C_6H_{13}), pym (I) 81%, (R = C_6H_{13}); (h) alkyne, CuI, $Cl_2Pd(PPh_3)_2$, Et_3N, MeCN, rt, 1−12 h, quant.

other substituted pyridines: 2-alkoxy-5-bromopyridines (**6**) were obtained by nucleophilic substitution with an appropriate sodium alkoxide,[16] and 2-alkynyl-5-bromopyridine (**8**) and 2-alkyl-5-bromopyridines (**10**) were prepared via Sonogashira[17] and Negishi[18] cross-coupling reactions, respectively.

The pyrimidyl bromides were prepared in a similar manner, beginning with bromination of 2-aminopyrimidine. *N*-Alkylation could not be achieved by reductive amination (presumably due to the decreased nucleophilicity of the amine) and was instead accomplished using NaH and an appropriate alkyl halide to give **5**. Nonaqueous diazotization/halo-dediazoniation was used to prepare 5-bromo-2-halopyrimidines[15] but in diminished yield relative to the analogous reaction with the 2-aminopyridine (again, presumably due to the decreased

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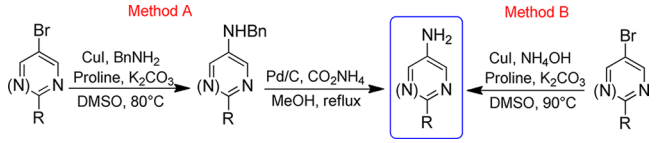
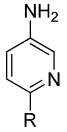
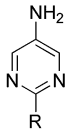
Table 1. Copper-Catalyzed Amination of 2-Substituted 5-Bromopyridnes and 5-Bromopyrimidines[a]



Compound		R	Method	Yield[b]	Compound		R	Method	Yield[b]
	**12**	NMe_2	A	74		**19**	NMe_2	A	82
	13	$N(C_5H_{11})_2$	A	87		**20**	NEt_2	A	72
	14	OMe	A	62		**21**	OEtPh	A	51
	15	OBu	A	80		**22**	OCy	B	69
	16	C_6H_9	B	95		**23**	C_6H_9	B	84
	17	C_6H_{13}	B	89		**24**	C_6H_{13}	B	58
	18	H	B	93		**25**	H	B	66

[a]Method A: 1.2 equiv of $BnNH_2$, 1.5 equiv of K_2CO_3, 0.1 equiv of CuI, 0.2 equiv of L-proline, DMSO (1 mL/1.2 mmol of ArBr) heated to 80 °C under argon. Method B: 1.5 equiv of NH_4OH, 1.5 equiv of K_2CO_3, 0.2 equiv of CuI, 0.4 equiv of L-proline, DMSO (1 mL/1 mmol ArBr) heated to 90 °C in a sealed tube. [b]Isolated yields.

nucleophilicity of the amine group). Alternatively, 2-pyrimidinone could serve as a precursor to 5-bromo-2-halopyrimidines[19] or as a substrate for alkylation to generate 5-bromo-2-alkoxypyrimidines (**7**).[20] Introduction of an alkyne substituent at the 2-position to give **9** proceeded satisfactorily under Sonogashira conditions, but alkylation using Negishi conditions was unselective. Since reduction of the 2-alkynylpyrimidyl bromide **9** to the corresponding 2-alkylpyrimidyl bromide **11** was complicated by competing removal of the bromine, we turned to 5-bromo-2-iodopyrimidine as a precursor for the cross-coupling reactions and saw a dramatic improvement in selectivity and yields.

II. Preparation of 3-Aminopyridines and 5-Aminopyrimidines. With the substituted pyridyl and pyrimidyl bromides in hand, we attempted to install the amine functionality using a two-step procedure involving first a copper-catalyzed amination with benzylamine followed by reductive cleavage of the benzyl group.[15] This method is attractive because the *N*-benzyl intermediate is stable to oxidative degradation, an attribute lacking in the more electron-rich primary amines, which can undergo significant degradation upon prolonged storage. We found that CuI, L-proline, and K_2CO_3 in DMSO at 80 °C were general conditions that afforded benzyl-protected amines in good yields from each of **4**−**11** as well as the unsubstituted 3-bromopyridine and 5-bromopyrimidine. While removal of the benzyl group to afford the corresponding primary amines was easily achieved using Pd/C and ammonium formate in refluxing methanol for the more electron-rich compounds (R = NR_2, OR), these conditions were ineffective for the less electron-rich compounds (R = H, alkyl, alkynyl). Increasing catalyst loading, or changing to $Pd(OH)_2$ or Raney nickel as catalyst, did not improve the outcome up to several atmospheres of H_2.

To circumvent this problem, we attempted to install the desired primary amine directly. After screening reported conditions for the amination of aryl bromides with "NH_2 equivalents" LiHMDS,[21] ZnHMDS,[22] Li/$NaNH_2$,[12] and *tert*-butyl carbamate[23] with either copper or palladium as catalysts with mixed results, we found that aqueous ammonia, in combination with CuI, L-proline, and K_2CO_3 in DMSO at 90 °C, was most effective.[24] Coincidently, this procedure was only successful for those pyridyl and pyrimidyl bromides for which the two-step benzylamination/hydrogenation sequence had failed at the latter step, presumably since the less electron-rich substrates are more reactive to substitution. The results are summarized in Table 1. Although the reactions generally proceeded with excellent conversions, the isolated yields reflect the difficulty associated with the purification of the more polar and/or oxidizable substrates and as such, the more electron-rich amines were generally carried through without purification.

III. Preparation of Diarylamines. A large number of phosphine ligands have been developed for Pd-catalyzed C−N bond-forming reactions, and indeed, our original ligand screen showed a broad structural variety of phosphines were useful when coupling substituted bromopyri(mi)dines with aniline (e.g., BINAP, Josiphos, SPhos, DPPF). However, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos)[11] gave consistently good results, showing the least sensitivity to the electronics of the aryl bromides, and had the added benefit of being air-stable and therefore easily handled. Based on these results, we settled on a catalytic system of 2 mol % of $Pd_2(dba)_3$ as a palladium source along with 4 mol % of XPhos as a ligand. A series of dialkylamino-substituted pyridine- and pyrimidine-based diarylamines were prepared, with varied alkyl groups to improve solubility in hydrocarbons, as shown in Table 2. The conversions were very good for nearly all of the substrates shown, the exception being 2-aminopyrimidine **30**; however, the isolated yields in some cases do not reflect the conversion because of difficulty with purification and/or sensitivity to oxidation in solution. We surmise that the poor reactivity of 2-aminopyrimidine is due its relatively low pK_a (6.8)[25] and corresponding poor nucleophilicity. Switching nucleophile and electrophile by using *N*,*N*-dimethylbenzene-1,4-diamine and 2-bromopyrimidine as the coupling partners also resulted in poor yields due to competing reduction of the aryl bromide by the highly electron-rich arylamine.

A similar set of compounds were prepared having alkyl substituents that will allow us to explore the effect of heteroatom incorporation on stability and reactivity using the industry standards (4,4′-dialkyldiphenylamines) as a baseline for comparison (Table 3). The isolated yields for these compounds are generally quite good. As noted previously, compounds with unsubstituted pyrimidines (e.g., **45**) can be difficult to purify by chromatography.

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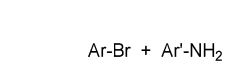
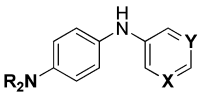
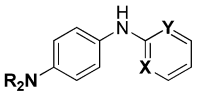
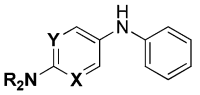
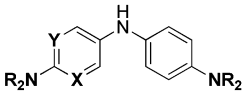
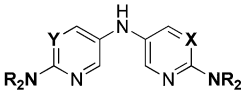
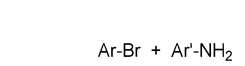
Table 2. *N,N*-Dialkylamino-Substituted Diarylamines Prepared by Palladium-Catalyzed Cross-Couplings of Aryl Bromides and Arylamines

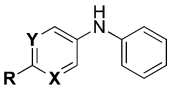
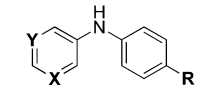
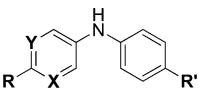
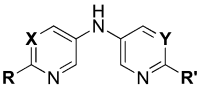


Ar-NH-Ar'		X	Y	R	Yield[a]
	**26**	CH	CH	Me	93 b
	27	N	CH	Me	74 b
	28	N	N	Pr	77 b
	**29**	N	CH	Me	80 b
	30	N	N	Pr	45 b
	**31**	N	CH	Me	94
	32	N	N	Me	93
	**33**	CH	CH	Me	89
	34	N	CH	Me	62
	35	N	N	Pr	87 b
	**36**	CH	CH	Me	72
	37	N	CH	Et/Me	91
	38	N	N	Et	81 b

[a]Conditions: ArBr (1.0 mmol), $ArNH_2$ (1.1 mmol), Pd (2 mol %), XPhos (4 mol %), NaO^tBu (1.4 mmol) in degassed toluene (2 mL) heated to 90 °C. [b]Reactions done using $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$ (**65**).

Table 3. Alkyl-Substituted Diarylamines Prepared by Palladium-Catalyzed Cross-Couplings of Aryl Bromides and Arylamines



Ar-NH-Ar'		X	Y	R/R'	Yield[a]
	**39**	CH	CH	Bu	95
	40	N	CH	C_6H_{13}	88
	41	N	N	C_7H_{15}	83
	42	N	CH	H	94 b
	43	N	N	H	82 b
	**44**	N	CH	Bu	73
	45	N	N	Bu	62
	**46**	CH	CH	C_8H_{17}	86 b
	47	N	CH	C_6H_{13}/Bu	62
	48	N	N	C_6H_{13}/Bu	84
	**49**	CH	CH	C_6H_{13}	85
	50	N	CH	C_6H_{13}/C_7H_{15}	71
	51	N	N	C_7H_{15}	81
	52	CH	CH	H	89 b
	53	N	N	H	77 b

[a]Conditions: ArBr (1.0 mmol), $ArNH_2$ (1.1 mmol), Pd (2 mol %), XPhos (4 mol %), NaO^tBu (1.4 mmol) in degassed toluene (2 mL) heated to 90 °C. [b]Reactions done using $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$ (**65**).

To round out the series, a set of alkoxy-substituted compounds were prepared that should have reactivities/stabilities in between the dialkylamino and alkyl compounds (Table 4). In the case of alkoxy-substituted compounds, the reaction becomes more complicated because the alkoxide represents a reasonable leaving group and when in the electrophilic 2-position of a pyridine or pyrimidine ring and in the presence of a nucleophilic amine coupling partner a competing S_NAr reaction can occur. This is reflected in some of the isolated yields, although we found the use of bulkier alkyl groups helped to minimize the undesired substitution reaction.

Unfortunately, the symmetrical 2-alkoxypyrimidine compound (**64**) could not be prepared by the C−N coupling approach as the amines always underwent nucleophilic substitution at the 2-position prior to the desired coupling. Because products were obtained for **56**, **61** and **63**, compounds which also feature 2-alkoxypyrimidine rings, we suspect the desired coupling reaction is sluggish due to the arylamine coupling partner not readily participating in the catalytic cycle. We attempted to decrease the rate of nucleophilic substitution relative to that of amine ligation to palladium by using relatively bulky alkyl substituents (−OCy, −OMeCy, −OBn, −OEtPh, etc.), keeping in mind that the substituent must be small enough to allow conjugation of the oxygen p-orbital (lone pair) with the pyrimidine ring to be effective as an antioxidant. However, none of these compounds gave the desired result.

It should be pointed out that upon preparation of each series of diarylamines, we could readily see that with increasing nitrogen incorporation into the aromatic rings, the diarylamines were much more stable to oxidation. For example, on comparing the series of symmetrically substituted diarylamines in Table 2, compounds **33** and **34** became intensely colored (because of formation of the corresponding radical cation, vide supra) almost immediately upon exposure to air in solution, while compounds **35**, **36**, **37**, and **38** were bench stable.

Although the $Pd_2(dba)_3$/XPhos catalyst system was effective for the preparation of the bulk of the diarylamines shown in Tables 2−4, we found that the little used $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$ precatalyst (**65**)[26,27] afforded higher isolated yields in essentially all cases where a direct comparison was made. We suggest that the increased yields from the **65**/XPhos system can be attributed to the rapid and *irreversible* formation of the active PdL_2 catalyst[27] compared to when $Pd_2(dba)_3$ is used, which remains in *equilibrium* with PdL_2. Although a detailed quantitative comparison of the performance of these two Pd precatalysts in Buchwald−Hartwig amination chemistry is well beyond the objectives of our work, we did monitor the reaction progress of three representative reactions under otherwise identical conditions to provide some insight into their differing performance. The first two reactions (Figure 1A,B) were randomly chosen from the many examples given above, and the third was selected because it was a particularly problematic

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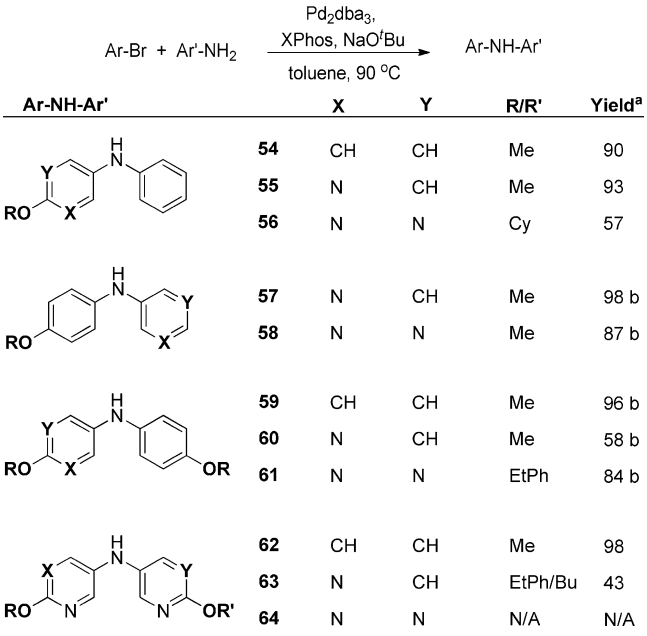
Table 4. Alkoxy-Substituted Diarylamines Prepared by Palladium-Catalyzed Cross-Couplings of Aryl Bromides and Arylamines



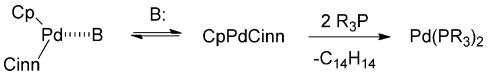
Ar-NH-Ar'		X	Y	R/R'	Yield[a]
	54	CH	CH	Me	90
	55	N	CH	Me	93
	56	N	N	Cy	57
	57	N	CH	Me	98 b
	58	N	N	Me	87 b
	59	CH	CH	Me	96 b
	60	N	CH	Me	58 b
	61	N	N	EtPh	84 b
	62	CH	CH	Me	98
	63	N	CH	EtPh/Bu	43
	64	N	N	N/A	N/A

[a]Conditions: ArBr (1.0 mmol), $ArNH_2$ (1.1 mmol), Pd (2 mol %), XPhos (4 mol %), NaO^tBu (1.4 mmol) in degassed toluene (2 mL) heated to 90 °C. [b]Reactions done using Pd(η^3-1-PhC_3H_4)(η^5-C_5H_5) (**65**).

literature reaction (Figure 1C); the diarylamine product could be obtained in a modest 56% yield but required high precatalyst loading ($Pd(OAc)_2$, 15 mol %), large amounts of ligand (XantPhos, 30 mol %), and long reaction time (48 h) and utilized 3-iodo-2-chloropyridine as a more reactive coupling partner than the corresponding 3-bromo-2-chloropyridine (which we used below).[28] In each case, we monitored reaction progress under typical preparative conditions at regular time intervals by gas chromatography using hexadecane as an internal standard. The results are shown in Figure 1.

The reaction progress data clearly show higher rates of catalyst turnover when **65** is used in place of $Pd_2(dba)_3$ as the precatalyst. Since the catalyst in both cases is likely the same [$Pd(XPhos)_2$], the different rates must arise from different concentrations of the catalyst available to turnover. This is consistent with the observed rapid *irreversible* formation of PdL_2 from **65** and phosphine ligands.[27] It is interesting to note that the initial rates of the reactions utilizing **65** are slowed due to the presence of an induction period. We ascribe this induction period to the undesired formation of coordination complexes between the Lewis basic pyridines and **65** in competition with reductive elimination to form the active PdL_2 species (Scheme 3). A recent report comparing **65** with other Pd precatalysts for

Scheme 3. Proposed Origin of the Induction Periods Observed in Reactions Shown in Figure 1



the Suzuki–Miyaura coupling of bromoanisole and phenylboronic acid did not display induction periods, presumably because of the lack of competitively coordinating substrates.[29]

Unlike with **65**, the formation of inactive coordination complexes with $Pd_2(dba)_3$ remains in continuous equilibrium with formation of PdL_2; each intermediate (e.g., $(dba)PdL_2$)[30] can form new complexes with Lewis bases. This equilibrium may explain why the product yields are much lower than reactions using **65** for A–C in Figure 1; the concentration of active catalyst never reaches a sustained level suitable for catalysis to occur. The relative Lewis basicities of the substrates support this explanation, as the yields obtained with $Pd_2(dba)_3$ as the precatalyst are lower for the reactions with 3-aminopyridine as a substrate (Figure 1A,C) than for 2-hexynylpyridine (Figure 1B).

■ CONCLUSIONS

We have presented a simple, modular approach for the preparation of substituted pyridine- and pyrimidine-based

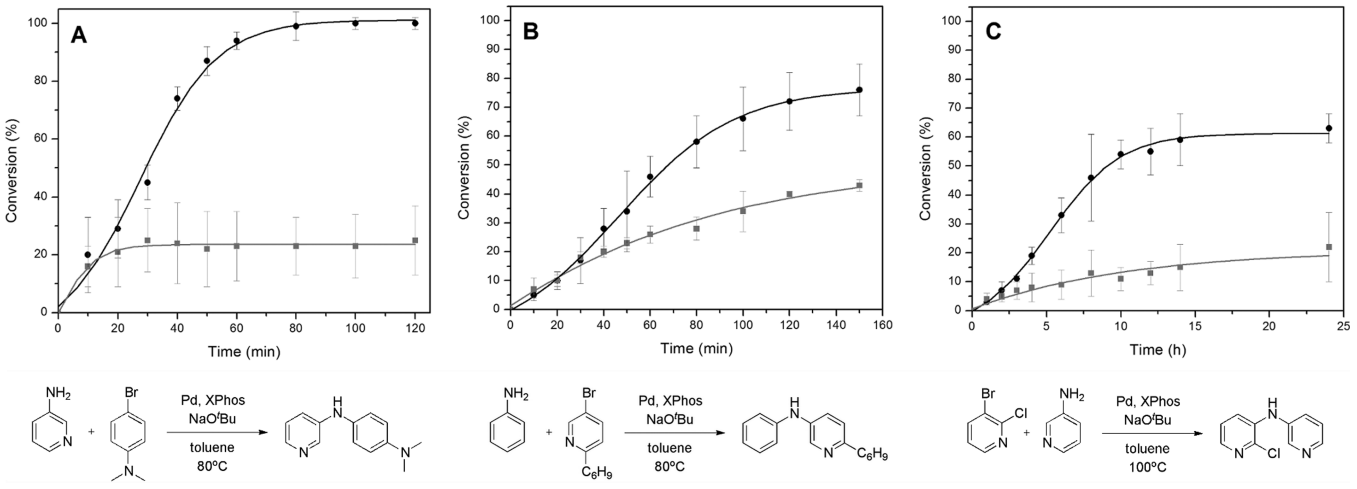


Figure 1. Comparative reaction profiles for a series of cross-coupling reactions where either **65** (●) or $Pd_2(dba)_3$ (■, grey) was used as a precatalyst. Reactions A and B: Pd (1 mol %), XPhos (2 mol %), ArBr (1 mmol), $ArNH_2$ (1.1 mmol), NaO^tBu (1.4 mmol) in toluene (2 mL) at 80 °C. Reaction C: Pd (3 mol %), XPhos (6 mol %), ArBr (1 mmol), $ArNH_2$ (1.3 mmol), NaO^tBu (1.4 mmol) in toluene (3 mL) at 100 °C. All reactions were done with 0.1 mmol hexadecane as an internal standard. Data were fit to sigmoidal functions; no attempt was made to analyze the kinetics of these reactions.

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diarylamine radical-trapping antioxidants. General conditions for Cu-catalyzed amination of pyridyl and pyrimidyl bromides have been described that are best carried out by choosing an appropriate nitrogen nucleophile to match the electronics of the aryl bromide. We have also described general conditions for Pd-catalyzed Buchwald–Hartwig aminations that are effective for electronically diverse aryl bromides and arylamines and that are greatly enabled by the use of the unconventional Pd(η^3-1-PhC_3H_4)(η^5-C_5H_5) precatalyst. These synthetic efforts have permitted extensive quantitative measurements of the effects of nitrogen incorporation on the oxidative stability of diarylamines as well as kinetic and thermodynamic measurements to determine their reactivity with alkyl and peroxyl radicals, which are detailed in the accompanying manuscript (DOI: 10.1021/jo301012x).[13]

EXPERIMENTAL SECTION

General Methods. Reagents were purchased from commercial suppliers and used without further purification, unless otherwise indicated. Pd(η^3-1-PhC_3H_4)(η^5-C_5H_5) (**65**) was synthesized from [Pd(η^3-1-PhC_3H_4)Cl]$_2$ and sodium cyclopentadienide as described by Fraser et al.[29] Column chromatography was carried out using flash silica gel (60 Å, 40–63 μm, 500 m^2/g). ^{1}H and ^{13}C NMR were recorded at 25 °C on a spectrometer operating at 400 and 100 MHz, respectively, unless otherwise indicated. High-resolution mass spectra were obtained by electron-impact ionization in combination with a single quadrupole mass analyzer.

Cu-Catalyzed Benzylamination of Pyri(mi)dyl Bromides. To a Schlenk flask were added ArBr (1.0 mmol), CuI (0.2 mmol), L-proline (0.4 mmol), and K_2CO_3 (1.5 mmol). The flask was evacuated and backfilled with argon before degassed DMSO (1.5 mL) was added. After a few minutes of stirring, $BnNH_2$ (1.2 mmol) was added and the reaction heated to 80 °C until completion, as determined by TLC. The reaction was cooled, quenched with water, and extracted with Et_2O. The combined organics were washed twice with water, washed with brine, and dried over $MgSO_4$. Column chromatography (EtOAc/hexanes eluent) afforded pure products.

***N*^{5}-Benzyl-*N*^{2},*N*^{2}-dimethylpyridine-2,5-diamine (12):** yield 168 mg, 74%; yellow solid; mp 69–70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.74 (d, J = 2.9 Hz, 1H), 7.38–7.31 (m, 4H), 7.28–7.25 (m, 1H), 6.95 (dd, J = 8.9, 2.9 Hz, 1H), 6.48 (dd, J = 8.9, 0.6 Hz, 1H), 4.27 (s, 2H), 3.56 (brs, 1H), 2.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 154.2, 139.5, 135.6, 133.4, 128.6, 127.5, 127.2, 124.8, 107.0, 49.6, 38.9; HRMS (EI) m/z calcd for $C_{14}H_{17}N_3$ 227.1422, found 227.1419.

***N*^{5}-Benzyl-*N*^{2},*N*^{2}-dipentylpyridine-2,5-diamine (13):** yield 294 mg, 87%; yellow needles; mp 32–33 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.71 (d, J = 2.8 Hz, 1H), 7.38–7.28 (m, 5H), 6.92 (dd, J = 9.0, 2.8 Hz, 1H), 6.36 (d, J = 9.0 Hz, 1H), 4.25 (s, 2H), 3.45 (brs, 1H), 3.34 (t, J = 7.6 Hz, 4H), 1.55 (qt, J = 7.6 Hz, 4H), 1.37–1.24 (m, 9H), 0.89 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 152.5, 139.6, 134.7, 133.5, 128.3, 127.6, 126.9, 124.8, 106.1, 49.6, 48.8, 29.2, 27.4, 22.5, 14.0; HRMS (EI) m/z calcd for $C_{22}H_{33}N_3$ 339.2518, found 339.2519.

***N*-Benzyl-6-methoxypyridin-3-amine (14):** yield 133 mg, 62%; white solid; mp 62–64 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.59 (d, J = 2.8 Hz, 1H), 7.38–7.32 (m, 4H), 7.30–7.28 (m, 1H), 6.99 (dd, J = 8.8, 2.8 Hz, 1H), 6.61 (dd, J = 8.8, 0.6 Hz, 1H), 4.29 (s, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 157.4, 139.1, 139.0, 130.4, 128.7, 127.5, 127.4, 125.8, 110.8, 53.3, 49.1; HRMS (EI) m/z calcd for $C_{13}H_{14}N_2O$ 214.1106, found 214.1104.

***N*-Benzyl-6-butoxypyridin-3-amine (15):** yield 194 mg, 80%; reddish solid; mp 51–52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.60 (d, J = 2.8 Hz, 1H), 7.38–7.28 (m, 5H), 6.99 (dd, J = 8.8, 2.8 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H), 4.29 (s, 2H), 4.17 (t, J = 6.8 Hz, 2H), 3.79 (brs, 1H), 1.78 (qt, J = 7.2 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 157.3, 139.0, 138.8, 130.5, 128.6, 127.4, 127.3, 125.6, 110.8, 67.4, 49.0, 22.4, 10.5; HRMS (EI) m/z calcd for $C_{16}H_{20}N_2O$ 242.1419, found 242.1419.

***N*^{5}-Benzyl-*N*^{2},*N*^{2}-dimethylpyrimidine-2,5-diamine (19):** yield 187 mg, 82%; yellow solid; mp 89–90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.93 (s, 2H), 7.36–7.24 (m, 5H), 4.25 (s, 2H), 3.11 (s, 6H); ^{13}C NMR ($CDCl_3$,100 MHz) δ ppm 144.5, 144.5, 138.5, 132.5, 128.7, 127.6, 127.5, 49.7, 37.6; HRMS (EI) m/z calculated for $C_{13}H_{16}N_4$ 228.1375, found 228.1373.

***N*^{5}-Benzyl-*N*^{2},*N*^{2}-diethylpyrimidine-2,5-diamine (20):** yield 184 mg, 72%; yellow solid; mp 89–90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.93 (s, 2H), 7.37–7.27 (m, 5H), 4.24 (s, 2H), 3.55 (q, J = 7.0 Hz, 4H), 3.41 (brs, 1H), 1.15 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.6, 145.0, 139.0, 132.5, 128.7, 127.5, 127.4, 49.9, 41.9, 13.2; HRMS (EI) m/z calcd for $C_{15}H_{20}N_4$ 256.1688, found 256.1668.

Direct Amination of Pyri(mi)dyl Bromides. To a tube equipped with a threaded Teflon screw-cap were added ArBr (1.0 mmol), CuI (0.2 mmol), L-proline (0.4 mmol), and K_2CO_3 (1.5 mmol). The vessel was evacuated and backfilled with argon before DMSO (1 mL) was added. After the mixture was stirred a few minutes, NH_4OH (28%, 1.5 mmol) was added, the tube was sealed and the reaction heated to 90 °C for 12 h. After cooling, the reaction was quenched with water and extracted with Et_2O. The organics were washed with brine and dried over $MgSO_4$. Column chromatography (EtOAc/hexanes/Et_3N eluent) afforded pure products.

6-(Hex-1-ynyl)pyridin-3-amine (16): yield 165 mg, 95%; yellow semisolid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 8.02 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 6.88 (dd, J = 2.1, 8.3 Hz, 1H), 3.80 (s, 2H), 2.41 (t, J = 6.6 Hz, 2H), 1.44–1.64 (m, 4H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 141.4, 137.2, 133.6, 127.1, 121.3, 88.5, 30.6, 22.0, 19.0, 13.6; HRMS (EI) m/z calcd for $C_{11}H_{14}N_2$ 174.1157, found 174.1150.

6-Hexylpyridin-3-amine (17): yield 158 mg, 89%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.95 (t, J = 1.6 Hz, 1H), 6.86–6.85 (m, 2H), 3.56 (bs, 2H), 2.60 (t, J = 8.0 Hz, 2H), 1.63–1.55 (m, 2H), 1.28–1.19 (m, 6H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 152.3, 140.1, 136.5, 122.4, 122.4, 37.2, 31.6, 30.0, 28.9, 22.4, 13.9; HRMS (EI) m/z calcd for $C_{11}H_{18}N_2$ 178.1470, found 178.1475.

3-Aminopyridine (18): yield 265 mg, 93%; peach-colored solid. Spectral data are consistent with those of commercially obtained material.

2-(Phenethoxy)pyrimidin-5-amine (21): yield 109 mg, 51%; white solid; mp 78–79 °C; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ ppm 8.03 (s, 2H), 7.34–7.27 (m, 4H), 7.22–7.18 (m, 1H), 4.54 (brs, 1H), 4.40 (t, J = 7.1 Hz, 2H), 3.04 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ ppm 146.8, 140.7, 130.9, 130.1, 128.0, 69.1, 37.1; HRMS (EI) m/z calcd for $C_{12}H_{13}N_3O$ 215.1059, found 215.1060.

2-(Cyclohexyloxy)pyrimidin-5-amine (22): yield 133 mg, 69%; white solid; mp 94–96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.02 (s, 2H), 4.87–4.80 (m, 1H), 3.35 (brs, 2H), 2.01–1.97 (m, 2H), 1.81–1.76 (m, 2H), 1.58–1.49 (m, 3H), 1.43–1.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 159.2, 146.3, 134.7, 74.7, 31.7, 25.6, 23.8; HRMS (EI) m/z calcd for $C_{10}H_{15}N_3O$ 193.1215, found 193.1206.

2-(Hex-1-ynyl)pyrimidin-5-amine (23): yield 150 mg, 84%; yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.12 (s, 2H), 3.94 (brs, 2H), 2.39 (t, J = 7.0 Hz, 2H), 1.58 (qt, J = 7.0 Hz, 2H), 1.45 (qt, J = 7.2 Hz, 2H), 0.89 (t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 143.6, 142.7, 139.0, 87.4, 30.2, 22.0, 18.8, 13.5; HRMS (EI) m/z calcd for $C_{10}H_{13}N_3$ 175.1109, found 175.1108.

6-Hexylpyrimidin-5-amine (24): yield 104 mg, 58%; off-white solid; mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.13 (s, 2H), 6.34 (brs, 2H), 2.81 (t, J = 7.7 Hz, 2H), 1.73 (qt, J = 7.7 Hz, 2H), 1.33–1.27 (m, 6H), 0.84 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 161.9, 143.4, 137.7, 38.4, 31.6, 29.0, 28.9, 22.5, 14.0; HRMS (EI) m/z calcd for $C_{10}H_{17}N_3$ 179.1423, found 179.1407.

5-Aminopyrimidine (25): yield 63 mg, 66%; pale-yellow solid. Spectral data are consistent with those of commercially obtained material.

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Deprotection of *N*-benzylamines. To a solution of benzyl-protected amine (1.0 mmol) in EtOH (5 mL) degassed with argon were added 10% Pd/C (10 wt %) and ammonium formate (5.0 mmol). The solution was heated to reflux until completion, as determined by TLC. When complete, the solution was cooled, diluted with EtOAc, and filtered through a pad of silica. No further purification was attempted because of oxidative instability and difficulty associated with chromatographing these compounds.

General Procedure for Synthesis of Diarylamines. To a Schlenk flask were added **59** (or Pd_2dba_3, 0.005−0.02 mmol) and XPhos (Pd/L = 1:2). The flask was evacuated and backfilled with argon before degassed toluene (2 mL) was added and the solution heated to 60 °C. After 10 min, ArBr (1.0 mmol), $ArNH_2$ (1.1 mmol), and NaO^{t}Bu (1.4 mmol) were added, and the reaction was heated to the desired temperature. Once complete, the mixture was cooled and quenched by filtering through Celite. Column chromatography (EtOAc/hexanes eluent with 1−5% Et_3N added depending on substrate) afforded pure products.

***N*^{1},*N*^{1}-Dimethyl-*N*^{4}-phenylbenzene-1,4-diamine (26):** yield 197 mg, 93%; off-white needles. Spectral data are consistent with those in the literature.[31]

***N*^{1},*N*^{1}-Dimethyl-*N*^{4}-(pyridin-3-yl)benzene-1,4-diamine (27):** yield 158 mg, 74%; yellow needles; mp 145−147 °C; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ ppm 8.23 (d, J = 2.6 Hz, 1H), 7.91 (dd, J = 4.5, 1.2 Hz, 1H), 7.20 (ddd, J = 8.3, 2.6, 1.2 Hz, 1H), 7.13 (brs, 1H), 7.10−7.06 (m, 3H), 6.79−6.75 (m, 2H), 2.89 (s, 6H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ ppm 149.3, 144.9, 140.9, 139.4, 133.4, 125.3, 124.6, 124.5, 121.1, 115.6, 42.1; HRMS (EI) m/z calcd for $C_{13}H_{15}N_3$ 213.1266, found 213.1257.

***N*^{1},*N*^{1}-Dipropyl-*N*^{4}-(pyrimidin-5-yl)benzene-1,4-diamine (28):** yield 251 mg, 93%; greenish solid; mp 79−80 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 8.45 (s, 1H), 8.27 (s, 2H), 8.00 (brs, 1H), 7.02−6.98 (m, 2H), 6.66−6.61 (m, 2H), 3.19 (t, J = 7.4 Hz, 4H), 1.51 (sextet, J = 7.5 Hz, 4H), 0.88 (t, J = 7.4 Hz, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 147.5, 144.5, 141.1, 140.8, 128.3, 122.7, 112.5, 52.2, 19.9, 11.2; HRMS (EI) m/z calcd for $C_{16}H_{22}N_4$ 270.1845, found 270.1837.

***N*^{1},*N*^{1}-Dimethyl-*N*^{4}-(pyridin-2-yl)benzene-1,4-diamine (29):** yield 170 mg, 80%; green solid; mp 129−130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.13 (ddd, J = 5.0, 1.9, 0.9 Hz, 1H), 7.39 (ddd, J = 8.7, 7.2, 1.9 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 8.6 Hz, 1H), 6.65−6.55 (m, 3H), 2.94 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 158.0, 148.3, 148.1, 137.5, 129.6, 124.9, 113.7, 113.6, 106.7, 50.0; HRMS (EI) m/z calcd for $C_{13}H_{15}N_3$ 213.1266, found 213.1260.

***N*^{1},*N*^{1}-Dipropyl-*N*^{4}-(pyrimidin-2-yl)benzene-1,4-diamine (30):** yield 121 mg, 45%; dark green solid; mp 84−86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.33 (d, J = 4.8 Hz, 2H), 7.34−7.30 (m, 2H), 6.97 (brs, 1H), 6.62−6.22 (m, 2H), 6.59 (t, J = 4.8 Hz, 1H), 3.21 (t, J = 7.6 Hz, 4H), 1.65−1.55 (m, 4H), 0.92 (t, J = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 161.2, 158.1, 145.4, 127.2, 123.4, 112.3, 111.4, 53.2, 20.4, 11.4; HRMS (EI) m/z calcd for $C_{16}H_{22}N_4$ 270.1844, found 270.1864.

***N*^{2},*N*^{2}-Dimethyl-*N*^{5}-phenylpyridine-2,5-diamine (31):** yield 200 mg, 94%; yellow solid; mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.07 (d, J = 2.6 Hz, 1H), 7.36 (dd, J = 8.9, 2.7 Hz, 1H), 7.20−7.16 (m, 2H), 6.80−6.76 (m, 3H), 6.54 (d, J = 9.3 Hz, 1H), 5.35 (brs, 1H), 3.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.7, 146.5, 143.6, 133.9, 129.3, 127.5, 118.8, 114.3, 106.1, 38.5; HRMS (EI) m/z calcd for $C_{13}H_{15}N_3$ 213.1266, found 213.1275.

***N*^{2},*N*^{2}-Dimethyl-*N*^{5}-phenylpyrimidine-2,5-diamine (32):** yield 199 mg, 93%; yellow solid; mp 111−112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.26 (s, 2H), 7.21−7.16 (m, 2H), 6.80 (tt, J = 7.3, 1.0 Hz, 1H), 6.73−6.70 (m, 2H), 5.23 (brs, 1H), 3.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 159.9, 155.0, 146.4, 129.4, 125.3, 119.1, 113.9, 37.4; HRMS (EI) m/z calcd for $C_{12}H_{14}N_4$ 214.1218, found 214.1197.

***N*^{1}-(4-(Dimethylamino)phenyl)-*N*^{4},*N*^{4}-dimethylbenzene-1,4-diamine (33):** yield 226 mg, 89%; beige solid. Spectral data are consistent with those in the literature.[32]

***N*^{5}-(4-(Dimethylamino)phenyl)-*N*^{2},*N*^{2}-dimethylpyridine-2,5-diamine (34):** yield 159 mg, 62%; dark green solid; mp 111−112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.94 (d, J = 2.8 Hz, 1H), 7.28 (dd, J = 8.9, 2.8 Hz, 1H), 6.86−6.82 (m, 2H), 6.72−6.68 (m, 2H), 6.57 (dd, J = 8.9, 0.5 Hz, 1H), 6.39 (brs, 1H), 2.99 (s, 6H), 2.82 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 157.2, 147.4, 141.2, 138.8, 133.5, 131.2, 119.7, 116.5, 107.8, 42.7, 39.6; HRMS (EI) m/z calcd for $C_{15}H_{20}N_4$ 256.1688, found 256.1674.

***N*^{5}-(4-(Dimethylamino)phenyl)-*N*^{2},*N*^{2}-dimethylpyrimidine-2,5-diamine (35):** yield 223 mg, 87%; yellow needles; mp 116−117 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 8.15 (s, 2H), 7.15 (brs, 1H), 6.74 (dd, J = 2.4, 6.8 Hz, 2H), 6.65 (dd, J = 2.4, 6.8 Hz, 2H), 3.07 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (DMSO-d_6,100 MHz) δ ppm 158.0, 149.6, 144.7, 136.2, 128.8, 116.5, 114.5, 41.1, 37.0; HRMS (EI) m/z calcd for $C_{14}H_{19}N_5$ 257.1640, found 257.1632.

***N*^{5}-(6-(Dimethylamino)pyridin-3-yl)-*N*^{2},*N*^{2}-dimethylpyridine-2,5-diamine (36):** yield 185 mg, 72%; pale-green plates; mp 113−114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.91 (d, J = 2.4 Hz, 2H), 7.15 (dd, J = 2.8, 8.8 Hz, 2H), 6.46 (d, J = 8.8 Hz, 2H), 4.96 (brs, 1H), 3.02 (s, 12H); ^{13}C NMR ($CDCl_3$,100 MHz) δ ppm 155.7, 139.1, 131.3, 121.4, 106.4, 38.7; HRMS (EI) m/z calcd for $C_{14}H_{19}N_5$ 257.1640, found 257.1646.

***N*^{5}-(6-(Dimethylamino)pyridin-3-yl)-*N*^{2},*N*^{2}-diethylpyrimidine-2,5-diamine (37):** yield 260 mg, 91%; metallic green solid; mp 102−103 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.11 (s, 2H), 7.87 (d, J = 2.8 Hz, 1H), 7.10 (dd, J = 2.8, 8.8 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 4.74 (brs, 1H), 3.58 (q, J = 7.0 Hz, 4H), 3.03 (s, 3H), 1.18 (t, J = 7.0 Hz, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) δ ppm 159.5, 157.1, 152.0, 139.5, 134.2, 131.2, 129.5, 108.0, 43.5, 39.6, 14.5; HRMS (EI) m/z calcd for $C_{15}H_{22}N_6$ 286.1906, found 286.1907.

***N*^{5}-(2-(Diethylamino)pyrimidin-5-yl)-*N*^{2},*N*^{2}-diethylpyrimidine-2,5-diamine (38):** yield 246 mg, 78%; yellow needles; mp 72−73 °C; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ ppm 8.11 (s, 4H), 6.24 (brs, 1H), 3.62 (q, 7.0 Hz, 8H), 1.14 (t, 7.0 Hz, 12H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ ppm 159.5, 151.3, 131.5, 43.5, 14.5; HRMS (EI) m/z calcd for $C_{16}H_{25}N_7$ 315.2171, found 315.2150.

4-Butyl-*N*-phenylaniline (39): yield 213 mg, 95%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.27−7.23 (m, 2H), 7.10 (d, J = 6.0 Hz, 2H), 7.04−7.02 (m, 4H), 6.89 (t, J = 7.2 Hz, 1H), 5.68 (brs, 1H), 2.57 (t, J = 6.7 Hz, 2H), 1.63−1.57 (m, 2H), 1.37 (sextet, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 143.8, 140.4, 136.0, 129.3, 129.2, 120.3, 118.7, 116.9, 34.9, 33.8, 22.3, 14.0; HRMS (EI) m/z calcd for $C_{16}H_{19}N$ 225.1517, found 225.1495.

6-Hexyl-*N*-phenylpyridin-3-amine (40): yield 223 mg, 88%; off-white semisolid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.31 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 8.4, 2.5 Hz, 1H), 7.28−7.23 (m, 2H), 7.04−7.00 (m, 3H), 6.93 (tt, J = 7.4, 1.0 Hz, 1H), 5.92 (brs, 1H), 2.73 (t, J = 7.8 Hz, 2H), 1.70 (qt, J = 7.4 Hz, 2H), 1.37−1.26 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 155.0, 142.9, 140.1, 137.1, 129.4, 125.4, 122.5, 121.0, 117.1, 37.5, 31.7, 30.0, 29.0, 22.5, 14.0; HRMS (EI) m/z calcd for $C_{17}H_{22}N_2$ 254.1783, found 254.1796.

2-Heptyl-*N*-phenylpyrimidin-5-amine (41): yield 223 mg, 83%; off-white solid; mp 71−72 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.49 (s, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.04 (d, J = 7.5 Hz, 2H), 7.01 (t, J = 7.4 Hz, 1H), 5.61 (brs, 1H), 2.90 (t, J = 7.7 Hz, 2H), 1.80 (qt, J = 7.6 Hz, 2H), 1.41−1.27 (m, 8H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 164.0, 146.4, 141.6, 135.3, 129.7, 122.3, 117.8, 38.6, 31.8, 29.4, 29.1, 28.9, 22.6, 14.1; HRMS (EI) m/z calcd for $C_{17}H_{23}N_3$ 269.1892, found 269.1873.

***N*-Phenylpyridin-5-amine (42):** yield 160 mg, 94%; peachy solid; mp 139−140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.38 (d, J = 2.8 Hz, 1H), 8.16 (dd, J = 4.6, 1.2 Hz, 1H), 7.41 (ddd, J = 8.3, 2.8, 1.2 Hz, 1H), 7.33−7.28 (m, 2H), 7.16 (ddd, J = 8.3, 4.6, 0.4 Hz, 1H), 7.10−7.07 (m, 2H), 6.99 (tt, J = 7.4, 1.1 Hz, 1H), 5.88 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 141.9, 141.8, 140.1, 139.8, 129.5, 123.7, 123.4, 122.0, 118.3; HRMS (EI) m/z calcd for $C_{11}H_{10}N_2$ 170.0844, found 170.0820.

***N*-Phenylpyrimidin-5-amine (43):** yield 140 mg, 82%; white solid; mp 214−215 °C; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ ppm 8.61 (s, 1H), 8.55 (d, J = 1.6 Hz, 2H), 7.72 (brs, 1H), 7.35−7.30 (m, 2H),

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7.20−7.18 (m, 2H), 6.99 (tt, J = 7.4, 1.0 Hz, 1H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ ppm 152.0, 146.1, 143.6, 140.8, 131.4, 123.9, 120.1; HRMS (EI) m/z calcd for $C_{10}H_9N_3$ 171.0796, found 171.0789.

***N*-(4-Butylphenyl)pyridin-3-amine (44):** yield 165 mg, 73%; pale yellow solid; mp 78−79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.33 (d, J = 2.8 Hz, 1H), 8.11 (dd, J = 4.6, 1.2 Hz, 1H), 7.35 (ddd, J = 8.2, 2.8, 1.2 Hz, 1H), 7.16−7.11 (m, 3H), 7.02 (dt, J = 8.4, 2.2 Hz, 2H), 5.67 (brs, 1H), 2.58 (t, J = 7.8 Hz, 2H), 1.63−1.55 (m, 2H), 1.36 (sextet, J = 7.4 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 140.9, 140.6, 139.1, 137.3, 129.4, 123.7, 122.6, 119.3, 100.0, 34.9, 33.8, 22.3, 14.0; HRMS (EI) m/z calcd for $C_{15}H_{18}N_2$ 226.1470, found 226.1469.

***N*-(4-Butylphenyl)pyrimidin-5-amine (45):** yield 140 mg, 62%; off-white solid; mp 161−162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.72 (s, 1H), 8.49 (s, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 5.76 (brs, 1H), 2.60 (t, J = 7.7 Hz, 2H), 1.64−1.56 (m, 2H), 1.36 (sextet, J = 7.5 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 149.6, 143.8, 139.2, 138.7, 137.5, 129.7, 120.1, 35.0, 33.7, 22.3, 13.9; HRMS (EI) m/z calcd for $C_{14}H_{17}N_3$ 227.1422, found 227.1421.

Bis(4-octylphenyl)amine (46): yield 350 mg, 86%; beige solid. Spectral data are consistent with those reported in the literature.[33]

***N*-(4-Butylphenyl)-6-hexylpyridin-3-amine (47):** yield 192 mg, 62%; pale yellow solid; mp 39−40 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.28 (d, J = 2.6 Hz, 1H), 7.32 (dd, J = 8.4, 2.8 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 8.4, 2.8 Hz, 2H), 5.60 (brs, 1H), 2.72 (t, J = 7.8 Hz, 2H), 2.56 (d, J = 7.6 Hz, 2H), 1.73−1.68 (m, 2H), 1.62−1.54 (m, 2H), 1.40−1.29 (m, 8H), 0.93 (d, J = 7.3 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 154.4, 140.2, 139.3, 137.8, 136.3, 129.3, 124.6, 122.6, 118.1, 37.4, 34.9, 33.8, 31.7, 30.1, 29.1, 22.6, 22.3, 14.1, 14.0; HRMS (EI) m/z calcd for $C_{21}H_{30}N_2$ 310.2409, found 310.2406.

***N*-(4-Butylphenyl)-2-hexylpyrimidin-5-amine (48):** yield 261 mg, 84%; off white solid; mp 73−74 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.44 (s, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 5.54 (brs, 1H), 2.88 (t, J = 7.8 Hz, 2H), 2.57 (t, J = 7.7 Hz, 2H), 1.79 (qt, J = 7.7 Hz, 2H), 1.62−1.55 (m, 2H), 1.40−1.30 (m, 8H), 0.93 (d, J = 7.3 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 154.3, 140.2, 139.4, 137.8, 136.2, 129.3, 124.5, 122.5, 118.0, 37.5, 34.9, 33.7, 31.7, 30.0, 29.0, 22.5, 22.3, 14.0, 13.9; HRMS (EI) m/z calcd for $C_{20}H_{29}N_3$ 311.2362, found 311.2360.

Bis(6-hexylpyridin-3-yl)amine (49): yield 288 mg, 85%; light red solid; mp 44−45 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.27 (d, J = 2.8 Hz, 2H), 7.29 (dd, J = 8.4, 2.8 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 5.96 (brs, 1H), 2.71 (t, J = 7.8 Hz, 4H), 1.68 (qt, J = 7.8 Hz, 4H), 1.35−1.28 (m, 12H), 0.86 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 155.4, 139.7, 136.9, 124.8, 122.7, 37.5, 31.7, 30.0, 29.0, 22.5, 14.0; HRMS (EI) m/z calcd for $C_{22}H_{33}N_3$ 339.2674, found 339.2685.

2-Heptyl-*N*-(6-hexylpyridin-3-yl)pyrimidin-5-amine (50): yield 250 mg, 71%; white solid; mp 64−65 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.44 (s, 2H), 8.33 (d, J = 2.8 Hz, 1H), 7.35 (d, J = 8.4, 2.8 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 5.69 (brs, 1H), 2.90 (t, J = 7.8 Hz, 2H), 2.75 (d, J = 7.8 Hz, 2H), 1.83−1.67 (m, 4H), 1.39−1.27 (m, 14H), 0.89−0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 164.5, 156.5, 146.0, 140.1, 135.8, 135.0, 125.5, 123.0, 38.7, 37.5, 31.8, 31.7, 29.9, 29.3, 29.1, 29.0, 28.9, 22.63, 22.57, 14.07, 14.06; HRMS (EI) m/z calcd for $C_{22}H_{34}N_4$ 354.2784, found 354.2773.

Bis(2-heptylpyrimidin-5-yl)amine (51): yield 299 mg, 81%; white solid; mp 103−104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.48 (s, 4H), 5.58 (brs, 1H), 2.92 (t, J = 7.6 Hz, 4H), 1.84−1.76 (m, 4H), 1.36−1.28 (m, 16H), 0.87 (t, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 165.5, 146.6, 134.1, 38.7, 31.7, 29.3, 29.1, 28.8, 22.6, 14.1; HRMS (EI) m/z calcd for $C_{22}H_{35}N_5$ 369.2893, found 369.2892.

Dipyridin-3-ylamine (52): yield 152 mg, 89%; off-white solid; mp 129−131 °C; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ ppm 8.56 (brs, 1H), 8.37 (d, J = 2.4 Hz, 2H), 8.08 (dd, J = 4.6, 1.2 Hz, 2H), 7.50 (ddd, J = 8.3, 2.4, 1.2 Hz, 2H), 7.26 (dd, J = 8.3, 4.6 Hz, 2H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ ppm 141.2, 139.4, 139.1, 123.8, 122.7; HRMS (EI) m/z calcd for $C_{10}H_9N_3$ 171.0797, found:171.0787.

Dipyrimidin-5-ylamine (53): yield 133 mg, 77%; off-white solid; mp 226−228 °C; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ ppm 8.88 (brs, 1H), 8.75 (s, 2H), 8.66 (s, 4H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ ppm 150.9, 145.0, 137.0; HRMS (EI) m/z calcd for $C_8H_7N_5$ 173.0702, found 173.0692.

4-Methoxy-*N*-phenylaniline (54): yield 179 mg, 90%; white solid. Spectral data are consistent with those reported in the literature.[34]

6-Methoxy-*N*-phenylpyridin-3-amine (55): yield 186 mg, 93%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.00 (dd, J = 2.8, 0.4 Hz, 1H), 7.45 (dd, J = 8.8, 2.8 Hz, 1H), 7.25−7.20 (m, 2H), 6.88−6.84 (m, 3H), 6.72 (dd, J = 8.8, 0.4 Hz, 1H), 5.44 (brs, 1H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 160.2, 144.8, 139.7, 133.2, 132.8, 129.4, 120.0, 115.4, 111.0, 53.5; HRMS (EI) m/z calcd for $C_{12}H_{12}N_2O$ 200.0950, found 200.0934.

2-(Cyclohexyloxy)-*N*-phenylpyrimidin-5-amine (56): yield 153 mg, 57%; white needles; mp 164−165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.38 (s, 2H), 7.26−7.22 (m, 2H), 6.92−6.86 (m, 3H), 5.39 (brs, 1H), 4.98−4.91 (m, 1H), 2.07−2.03 (m, 2H), 1.86−1.80 (m, 2H), 1.65−1.57 (m, 5H), 1.47−1.26 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 161.0, 152.7, 144.0, 131.3, 129.6, 120.7, 115.5, 75.4, 31.6, 25.5, 23.9; HRMS (EI) m/z calcd for $C_{16}H_{19}N_3O$ 269.1528, found 269.1520.

***N*-(4-Methoxyphenyl)pyridin-3-amine (57):** yield 196 mg, 98%; pale red solid; mp 123−125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.25 (d, J = 2.4 Hz, 1H), 8.06 (dd, J = 4.7, 1.3 Hz, 1H), 7.20 (ddd, J = 8.3, 2.4, 1.3 Hz, 1H), 7.10 (d, J = 4.7 Hz, 1H), 7.09−7.06 (m, 2H), 6.90−6.86 (m, 2H), 5.58 (brs, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 155.9, 141.7, 140.66, 140.64, 138.4, 134.3, 123.6, 122.7, 121.1, 114.8, 55.5; HRMS (EI) m/z calcd for $C_{12}H_{12}N_2O$ 200.0950, found 200.0932.

***N*-(4-Methoxyphenyl)pyrimidin-5-amine (58):** yield 175 mg, 87%; purple needles; mp 211−212 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.69 (s, 1H), 8.35 (s, 2H), 7.13−7.09 (m, 2H), 6.93−6.89 (m, 2H), 5.47 (brs, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.7, 1450.0, 143.0, 139.9, 132.7, 123.4, 115.1, 55.6; HRMS (EI) m/z calcd for $C_{11}H_{11}N_3O$ 201.0902, found 201.0904.

Bis(4-methoxyphenyl)amine (59): yield 219 mg, 96%; white needles. Spectral data are consistent with those reported in the literature.[35]

6-Methoxy-*N*-(4-methoxyphenyl)pyridin-3-amine (60): yield 133 mg, 58%; reddish oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.89 (d, J = 2.8 Hz, 1H), 7.31 (dd, J = 8.8, 2.8 Hz, 1H), 6.90−6.87 (m, 2H), 6.83−6.80 (m, 2H), 6.67 (d, J = 8.8 Hz, 1H), 5.32 (brs, 1H), 3.90 (s, 3H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 159.1, 154.4, 137.4, 136.6, 134.9, 130.7, 119.2, 114.8, 110.8, 55.6, 53.5; HRMS (EI) m/z calcd for $C_{13}H_{14}N_2O_2$ 230.1055, found 230.1042.

2-Phenethoxy-*N*-(4-phenethoxyphenyl)pyrimidin-5-amine (61): yield 345 mg, 84%; white solid; mp 143−144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.29 (d, J = 1.2 Hz, 2H), 7.35−7.29 (m, 8H), 7.23−7.20 (m, 2H), 7.02−6.98 (m, 2H), 6.90−6.86 (m, 2H), 4.47 (t, J = 7.0 Hz, 2H), 4.17 (t, J = 6.9 Hz, 2H), 3.09−3.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 155.7, 150.2, 141.2, 136.6, 130.9, 130.2, 128.1, 121.0, 117.4, 70.7, 69.5, 37.4, 37.0; HRMS (EI) m/z calcd for $C_{26}H_{25}N_3O_2$ 411.1947, found 411.1931.

Bis(6-methoxypyridin-3-yl)amine (62): yield 226 mg, 98%; pale yellow oil; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ ppm 7.89 (d, J = 2.8 Hz, 2H), 7.41 (dd, J = 8.8, 2.8 Hz, 2H), 6.96 (brs, 1H), 6.69 (d, J = 8.8 Hz, 2H), 3.83 (s, 6H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ ppm 160.8, 137.7, 137.2, 131.6, 112.5, 54.4; HRMS (EI) m/z calcd for $C_{12}H_{13}N_3O_2$ 231.1008, found 231.0996.

***N*-(6-Butoxypyridin-3-yl)-2-phenethoxypyrimidin-5-amine (63):** yield 156 mg, 43%; off-white solid; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ ppm 8.30 (d, J = 1.2 Hz, 2H), 7.92 (d, J = 2.9 Hz, 1H), 7.48 (dd, J = 8.8, 2.9 Hz, 1H), 7.35−7.29 (m, 4H), 7.23−7.19 (m, 1H), 7.05 (brs, 1H), 6.71 (d, J = 8.5 Hz, 1H), 4.48 (t, J = 7.0 Hz, 2H), 4.24 (d, J = 6.6 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H), 1.75−1.68 (m, 2H), 1.47 (st, J = 7.5 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($(CD_3)_2CO$,

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100 MHz) δ ppm 162.0, 161.2, 150.2, 140.6, 138.7, 138.6, 136.4, 136.3, 135.6, 135.9, 132.26, 132.13, 130.9, 130.2, 128.1, 112.8, 69.5, 67.1, 37.0, 33.0, 21.0, 15.1; HRMS (EI) m/z calcd for $C_{21}H_{24}N_4O_2$ 364.1899, found 364.1895.

■ ASSOCIATED CONTENT

Supporting Information

Nuclear magnetic resonance spectra for compounds **12**−**63**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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