Rapid Amination of Methoxy Pyridines with Aliphatic Amines

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ABSTRACT:

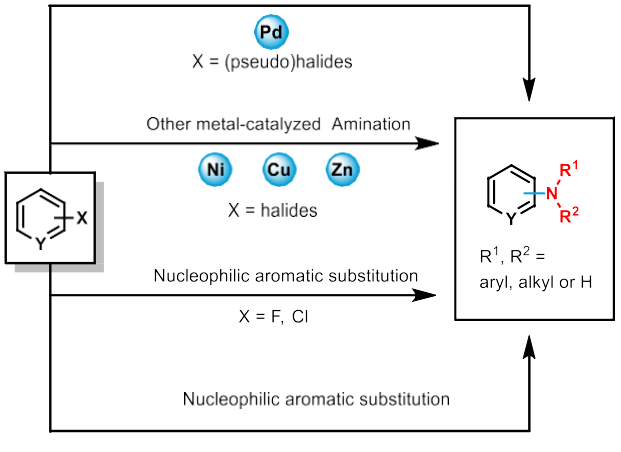
A *n*-BuLi triggered practical amination protocol of methoxy pyridine derivatives with aliphatic amines was developed. The reaction could finish in 30 min for primary amines and 10 min for secondary amines. The amination is further highlighted by its excellent reactivity and substrate scope.

KEYWORDS: *amination, methoxy pyridines, n-BuLi, transition-metal-free*

Introduction:

The transition-metal-catalyzed synthesis of heteroaryl amines (Scheme 1) had been one of the most challenging research

Scheme 1. Approaches for the Synthesis of Heteroaryl Amines



topics in the C−N bond formation research area because the coordinating ability of the heteroatom can

cause catalyst deactivation.[1] In the past few decades, extensive efforts have been dedicated to the development of efficient catalytic systems to couple a wide range of heteroaryl halides with amines.[2] Buchwald−Hartwig amination, the Pd-catalyzed C− N cross-coupling of aryl (pseudo)halides with amines, has become a principal technique for production of heteroaromatic amines. For instance, Buchwald and co-workers developed a

Verkade's,[5] Nolan's,[6] Beller's,[7] Zhang's,[8] Yin's,[9] Dommisse's,[10] Cao's,[11] and Tu's,[12] also made their great efforts on the amination of heteroaryl halides. Except Pd-catalysis, Ni, Cu, and Zn were also utilized as catalysts to prepare heteroaryl amines.[13] Notably, these methods often use heteroaryl halides as starting material; the aminations of heteroaryl alkyl ethers with amines have gained much less attention, which could be rationalized by the high dissociation energy of the C−O bond.[14]

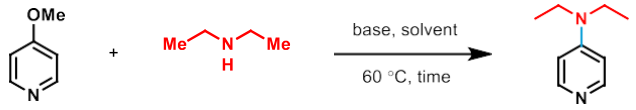
Apart from transition-metal-catalysis, the transition-metal- free amination of heteroaryl halides is a powerful alternative to provide heteroaryl amines.[15] In particular, the amination via the nucleophilic aromatic substitution pathway could serve as an attractive supplement to the ones that need transition-metal catalysts.[16] However, this transformation is largely limited to highly activated substrates, for instance heteroaryl fluorides or nitro substituted aryl halides. Our and Zhao's groups recently developed a base triggered amination of nitrile substituted aryl alkyl thioethers with weak nucleophilic aromatic amines.[17] The preliminary mechanistic studies showed that this trans- formation might undergo thorough nucleophilic aromatic substitution. Promoted by this protocol, we envisioned that the amination of methoxy pyridines with aliphatic amines would occur owing to the electron-deficient nature of the heteroarenes and the strong nucleophilicity of aliphatic amines.

RESULTS AND DISCUSSION

To test our hypothesis, we chose 4-methoxy pyridine (1a) as modeling substrate to study its amination with diethyl amine (2a). We first examined different bases, potassium carbonate, lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*- butoxide, and even potassium hexamethyldisilazane did not give any desired amination product (Table 1, entries 1−5). These results can be explained by the fact that the bases we

series of bulky monodentate phosphine ligands, applied them in the Pd-catalyzed amination of heteroaryl halides, and achieved marvelous outcomes.[3] Hartwig's research group also developed highly efficient catalytic protocols to access the desired heteroaryl amines, significantly promoting the develop- ment of this research field.[4] Many other groups, such as

Table 1. Reaction Condition Optimization of Amination



1a 2a 3a

entry	base	solvent	time (h)	yield (%)
1	K_2CO_3	THF	16	0
2	LiO*t*-Bu	THF	16	0
3	NaO*t*-Bu	THF	16	0
4	KO*t*-Bu	THF	16	0
5	KHMDS	THF	16	0
6	*n*-BuLi	THF	16	99
7	*n*-BuLi	THF	16	94[b]
8	*n*-BuLi	THF	16	59[c]
9	*n*-BuLi	Et_2O	16	98
10	*n*-BuLi	DME	16	trace
11	*n*-BuLi	1,4-dioxane	16	trace
12	*n*-BuLi	THF	8	99
13	*n*-BuLi	THF	1	99
14	*n*-BuLi	THF	30 min	99

15	*n*-BuLi	THF	10 min	96

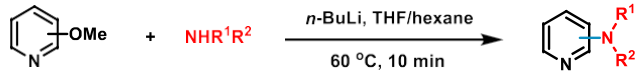
[a]Reaction conditions: 1a (1.0 equiv, 0.5 mmol), 2a (2.0 equiv, 1.0 mmol), base (2.0 equiv), THF (0.5 mL), 60 °C, 16 h. [b]1a (1.0 equiv, 0.5 mmol), 2a (1.4 equiv, 0.7 mmol), *n*-BuLi (1.54 equiv, 0.77 mmol, 0.3 mL, 2.5 M in hexane), THF (0.5 mL), 60 °C, 16 h. [c]1a (1.0 equiv, 0.5 mmol), 2a (1.2 equiv, 0.6 mmol), *n*-BuLi (1.32 equiv, 0.66 mmol, 0.26 mL, 2.5 M in hexane), THF (0.5 mL), 60 °C, 16 h.

applied are not basic enough to deprotonate the proton of 2a to generate a more nucleophilic lithium diethylamide. Next, we moved our attention to *n*-BuLi that is commonly used to prepare lithium diisopropylamide (LDA) through the depro- tonation of diisopropylamine process. To our delight, the aimed heteroaryl amine 3a was observed in 99% NMR yield while the reaction was conducted in the presence of 2 equivalents of *n*-BuLi in THF at 60 °C for 16 h (entry 6).[18] Increasing or decreasing the amount of *n*-BuLi led to inferior yields (entries 7 and 8). We also found that this transformation was sensitive to solvent; while the use of diethyl ether gave comparable yield, 1,2-dimethoxyethane and 1,4-dioxane delivered trace amount of targeted amine 3a (entries 9−11). The optimization of reaction time allowed us to identify the optimal reaction time for this reaction, the reaction was completed in 30 min for the secondary amines, and almost quantitative yield was obtained (entries 12−14). The yield slightly decreased to 96% while the reaction time was shortened to 10 min (entry 15).

After establishing the optimized reaction conditions, we then decided to investigate the representative examples of our newly developed rapid amination protocol. As shown in Table 2, other acyclic secondary amines such as dibutyl amine, dibenzyl amine, and *N*-methyl-1-phenylmethanamine were suited to this amination, delivering the corresponding products in excellent yields (Table 2, 3b, 3c, 3d). Moreover, we found that cyclic secondary amines could also participate in this transformation. The use of (*R*)-2-methylpyrrolidine gave the

final product in 99% yield. This technique could also be extended to piperazine derivatives; the products 3f, and 3g were respectively produced in 99%, and 96% yield. Furthermore, we chose dibutyl amine as the amino source to exame the generality of *N*-heteroarenes of our newly developed amination protocol. To our surprise,

Table 2. Substrate Scope of Secondary Amines and Methoxy Heteroarenes



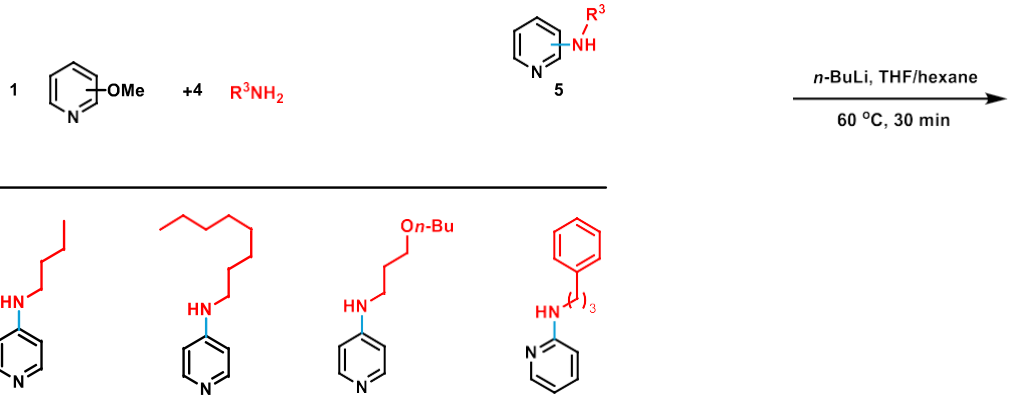
1 2 3

the introduction of a methyl group on the pyridine ring significantly affected the amination efficiency; the yields dramatically decreased to 69% (3j) and 58% (3k). Intriguingly, excellent site-selectivity was observed for the 2,3-dimethoxy substituted pyridine, the amination proceeded exclusively at the *ortho*-position of pyridine, whereas the methoxy group at the *meta*-position of pyridine remained untouched (3l). We also witnessed the difference in terms of reactivity between dimethoxy substituted pyridine and pyrimidine. As pictured, the use of 2,6-dimethoxypyridine offered a monoamination product 3m while double amination took place for dimethoxy
substituted pyrimidine (3n).

We next moved to study the substrate scope of primary
amines (Table 3). Gladly, the amination rate was at the same level as secondary amines; all the reactions that we carried out were finished within 30 min. As presented, the employment of 1-aminobutane gave the final product 5a in 80% isolated yield. 1-Amino hexane could participate in the amination in high efficiency, giving 5b in almost quantitative yield. The presence
of the ether group did not influence reactivity of amine, 5c was
obtained in slightly lower yield of 94%. Unexpectedly, the
utilization of 3-phenylpropan-1-amine resulted in much lowered isolated yield (5d). In

addition, sterically bulky amines such as 2,3-dihydro-1H-inden-1-amine and adamantan- 2-amine could take part in this amination, producing the corresponding products 5e, and 5f in 90% and 56% yield, respectively. A heterocycle such as thiophene was well tolerated as demonstrated by 5g. We also found that chiral

Table 3. Substrate Scope of Primary Amine

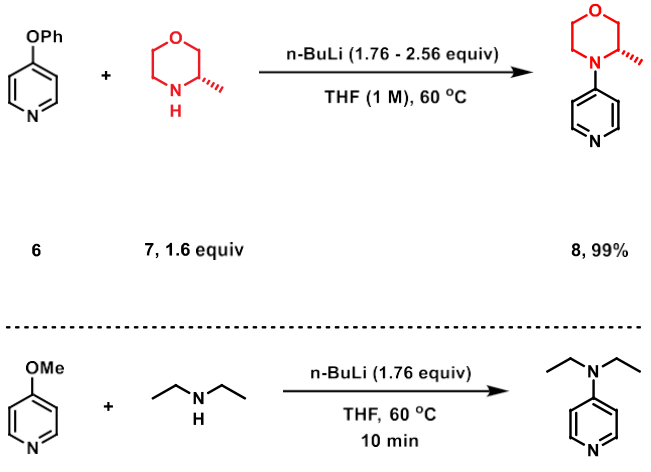


amine (*S*)-1-phenylpropan-1-amine exhibited excellent reac- tivity.

We additionally examined the possibility of using other pyridyl ether as material. Likewise, 4-phenoxypyridine could be utilized to perform the amination with morpholine derivative 7 to afford the targeted heteroaryl amine in 99% yield. To demonstrate the potential utility in industrial application of our

newly developed amination protocol, we carried out a large- scale reaction of 200 mmol. The reaction was finished in 10 min, generating the desired product in 98% isolated yield (Scheme 2).

Scheme 2. Other Etheric Substrate and Large-Scale Reaction



CONCLUSIONS

In summary, we reported practical amination protocols that are capable of efficiently incorporating both primary and secondary aliphatic amines into pyridine, generating the corresponding amines in good to excellent yields. This strategy is distinguished by its high reactivity; the amination of methoxy methoxypyridine 1a was added by microsyringe. The tube was capped and stirred in a 60 °C oil bath for 10 min. The reaction mixture was then allowed to cool to room temperature, quenched by water (3 mL), and then extracted with DCM (5 mL × 3). The solvent layer was dried with dried Na_2SO_4. The crude mixture was concentrated in vacuo and purified by flash column chromatography eluting with EtOAc (1% Et_3N) to give compound 3b as a yellow oil (102 mg, 99% yield). ^{1}H NMR (400 MHz, $DCCl_3$) δ 8.13 (d, *J* = 5.1 Hz, 2H), 6.39 (d, *J* = 5.1 Hz, 2H), 3.23 (t, *J* = 6 Hz, 4H), 1.57−1.50 (m, 4H), 1.38−1.28 (m, 4H), 0.93 (t, *J* = 8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $DCCl_3$) δ 152.51, 149.85, 106.40, 49.96, 29.16, 20.28, 13.97 ppm.

N,*N*-Dibenzylpyridin-4-amine (3c). Following Typical Procedure I, the reaction of 1a (0.5 mmol, 54.5 mg), 2c (0.8 mmol, 157.6 mg), and *n*-BuLi (0.88 mmol, 0.35 mL, 2.5 M in hexane in THF (0.5 mL) for 10 min at 60 °C afforded 3c (109.6 mg, 80%) as a yellow solid (eluent: EtOAc (1% Et_3N)). Melting point: 85.5 °C. HRMS (ESI) calculated for $C_{19}H_{18}N_2$: [M + H^+]: 275.1543, found: 275.1556. ^{1}H NMR (400 MHz, $DCCl_3$) δ 8.24 (d, *J* = 6.5 Hz, 2H), 7.42−7.38 (m, 4H), 7.36−
7.31 (m, 2H), 7.25 (d, *J* = 4 Hz, 4H), 6.63 (d, *J* = 4 Hz, 2H), 4.72 (s, 4H) ppm. ^{13}C NMR (101 MHz, $DCCl_3$) δ 154.01, 150.27, 136.97, 129.02, 127.53, 126.58, 107.23, 53.32 ppm.

N-Benzyl-*N*-methylpyridin-2-amine (3d). Following Typical Procedure I, the reaction of 1d (0.5 mmol, 54.5 mg), 2d (0.8 mmol, 96.8 mg), and *n*-BuLi (0.88 mmol, 0.35 mL, 2.5 M in hexane in THF (0.5 mL) for 10 min at 60 °C afforded 3d (92.1 mg, 93%) as a yellow oil (eluent: petroleum ether (1% Et_3N)). ^{1}H NMR (400 MHz, $DCCl_3$) δ 8.16 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.29−7.26 (m, 2H), 7.20 (d, *J* =8 Hz, 3H), 6.53 (s, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 4.77 (s, 2H), 3.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $DCCl_3$) δ 158.97,148.06, 138.79, 137.42, 128.62, 127.08, 126.98, 111.91, 105.80, 53.32, 36.29 ppm.

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