Direct Amination

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Directed Amination of Non-Acidic Arene C–H Bonds by a Copper–Silver Catalytic System**

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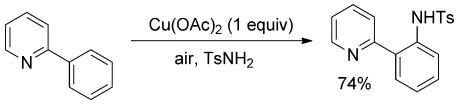
New methods for direct arylation, alkylation, and oxygenation of C(sp^2)–H bonds in directing-group-containing benzenes have resulted in efficient synthetic routes to functionalized arenes.[1] In contrast, direct amination reactions that do not proceed through nitrenoid intermediates[2] are relatively rare. In most cases, palladium catalysis is used for aminations.[3a–p] Furthermore, the majority of publications describe intramolecular C–N bond formation.[3a–i] Typically, protected amines or hydroxylamine derivatives are used to install the nitrogen moiety; simple amine coupling partners are employed only rarely. Several deprotonative, copper-catalyzed thiazole and oxazole aminations have been reported.[4b,c,e] Yu et al. have reported a method for palladium-catalyzed benzamide amination by employing a removable auxiliary.[3k] Herein, we disclose a method for the auxiliary-assisted amination of non-acidic benzamide β-C–H bonds and benzylamine derivative γ-C–H bonds, which is catalyzed by copper(II) acetate.

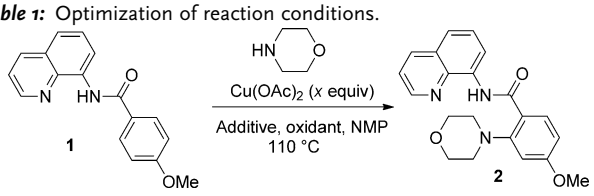
Notably, the first copper-catalyzed directed amination of arene C–H bonds was reported by Yu et al. in 2006 [Eq. (1)].[5a] Subsequently, several other groups have shown that 2-phenylpyridine derivatives can be *ortho* aminated by employing copper salts.[5]



(1)

However, the scope of these reactions is limited by the presence of a non-removable pyridine moiety. We hypothesized that 8-aminoquinoline and picolinic acid auxiliaries[3g,6] would effect *ortho*-amination of C(sp^2)–H bonds based on the following considerations: 1) copper promotes amination and sulfenylation of 2-phenylpyridine derivatives,[5] and 2) sulfenylation can be directed by 8-aminoquinoline and picolinic acid moieties.[6c] The reaction of 8-aminoquinoline *p*-methoxybenzamide and morpholine was investigated with respect to oxidant, additives, and amount of copper(II) acetate (Table 1). Use of $Cu(OAc)_2$ (1 equiv) gave 39% conversion into the product (entry 1). Higher conversion was obtained by employing of $Cu(OAc)_2$ (0.5 equiv) in the presence of oxygen

Table 1: Optimization of reaction conditions.



Entry	*x* equiv	Oxidant	Additive	Yield [%]
1	1	none	none	39[a]
2	0.5	O_2	none	51[a]
3	0.25	NMO	K_2CO_3	44[a]
4	0.25	NMO	Ag_2CO_3 0.25 equiv	74[b]
5	0.1	NMO	Ag_2CO_3 0.13 equiv	87[b]
6	0.05	NMO	Ag_2CO_3 0.075 equiv	80[a]
7	0	NMO	Ag_2CO_3 0.125 equiv	<2[a]

[a] Yield determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Yield of isolated product. NMO = *N*-methylmorpholine oxide.

(entry 2). If *N*-methylmorpholine oxide (NMO) oxidant was used in the presence of a catalytic amount of Ag_2CO_3 additive, 74% conversion into the product was observed (entry 4). It was possible to decrease the catalyst loading to 10 mol% (entry 5). A control experiment showed that $Cu(OAc)_2$ is essential for the amination reaction (entry 7).

The reaction of morpholine with 8-aminoquinoline benzamides is presented in Table 2. The amination is successful for both electron-rich (entries 1, 3, 5, 7, 8) and electron-poor amides (entries 2, 4, 6). In contrast with copper-promoted sulfenylation, amination selectively delivers monofunctionalization products at the less sterically demanding position (entries 5, 6, 8). Diamination products were not detected in crude reaction mixtures. The reaction shows good functional group tolerance. Ethers (entries 1 and 5), fluoride (entry 2), and ester substituents (entry 4) are tolerated. Moreover, the reaction is successful for five- and six-membered ring heterocycles. Pyridine (entry 9) and furan (entry 10) derivatives are aminated in good yields. Substrates possessing electron-withdrawing groups require higher catalyst loading. Reactions can be scaled up at least tenfold without significant loss of yield (entry 3).

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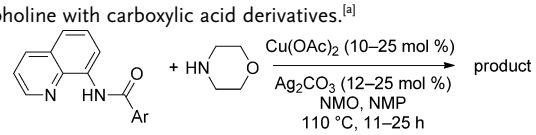
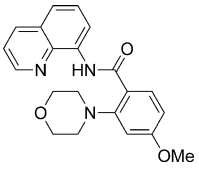
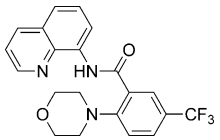
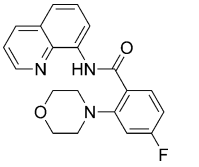
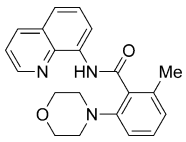
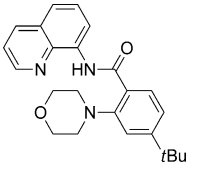
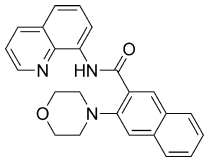
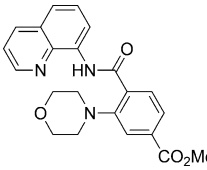
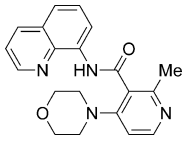
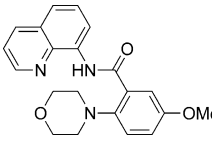
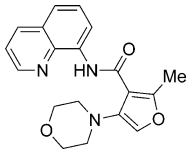
Table 2: Copper-catalyzed reaction of morpholine with carboxylic acid derivatives.[a]



Entry	Ar	Product	Yield [%]	Entry	Ar	Product	Yield [%]
1	4-$MeOC_6H_4$		87	6	3-$CF_3C_6H_4$		67
2	4-FC_6H_4		70	7	2-MeC_6H_4		70
3	4-*t*BuC_6H_4		81 80[b]	8	2-naphthyl		66
4	4-$MeO_2CC_6H_4$		68	9	3-(2-Me-pyridyl)		56
5	3-$MeOC_6H_4$		82	10	3-(2-Me-furyl)		57

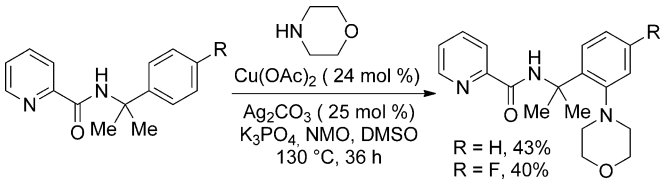
[a] 0.5 mmol scale, NMP (2 mL), NMO (2 equiv), morpholine (2 equiv), $Cu(OAc)_2$ (10–25 mol%), Ag_2CO_3 (12–25 mol%), 110°C, 14–25 h. Yields shown are of isolated products (please see the Supporting Information for details). [b] 5 mmol scale.

α,α-Disubstituted benzylamine picolinamides can also be aminated, albeit in moderate yields (Scheme 1). Thus, α,α-dimethylbenzylamine picolinamide and its *p*-fluoroderivative were reacted with morpholine, and the amination products were isolated in moderate yields. Benzylamine picolinamide amination reactions require relatively high temperatures to achieve reasonable conversions.

The reaction scope with respect to amines is presented in Table 3. Simple secondary amines, such as methylbenzyl- and methylpropylamine, are reactive and the products are obtained in good yields (entries 1 and 2). The reaction tolerates many functional groups on the amine coupling component. Ethyl isonipecotate (entry 3), 4-cyanopiperidine (entry 4), the ethylene ketal of 4-ketopiperidine (entry 5), and Boc-protected 4-aminopiperidine (entry 6) afforded products in good yields. Selective coupling with amine NH in the presence of an amide NH was observed (entry 6). Reactions with primary amines were also successful, albeit with somewhat reduced yields. Thus, coupling with cyclohexyl- (entry 7), cyclooctyl- (entry 8), and neopentylamine (entry 9) afforded products in moderate yields. Straight-chain primary amines afford low yields (entry 10).

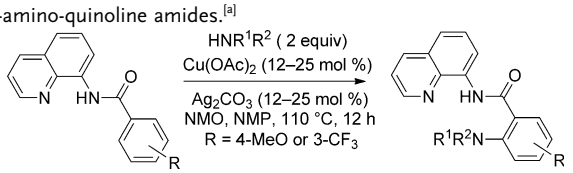
The aminoquinoline directing group can be efficiently removed by base hydrolysis. Thus, **4** was heated with NaOH in ethanol for 72 h to afford 4-*tert*-butyl-2-morpholinobenzoic acid in high yield (Scheme 2).

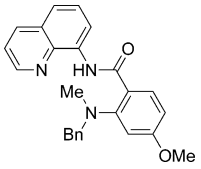
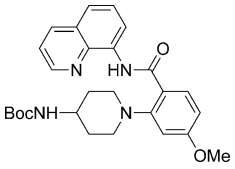
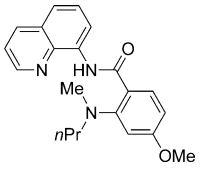
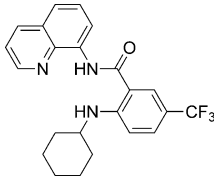
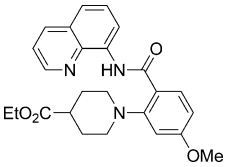
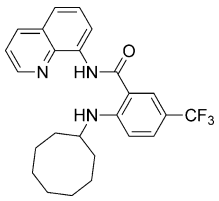
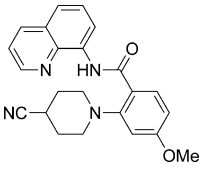
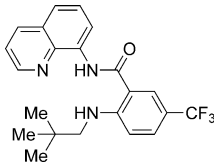
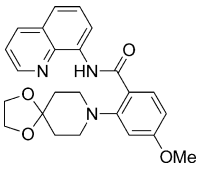
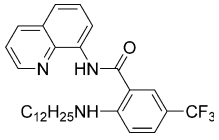
The amination mechanism is unclear at this point. However, activation of an aryl C–H bond by a Cu^{II} complex to form aryl–Cu^{III} species has been reported in a highly geometrically constrained system.[7] Additionally, well-defined Cu^{III} complexes react with N-nucleophiles to form carbon–nitrogen bonds.[8] Furthermore, an early report by Reinaud showed that copper(II) mediates aromatic hydroxylation by trimethylamine *N*-oxide.[9] The reaction presumably proceeds via a Cu^{III} intermediate.



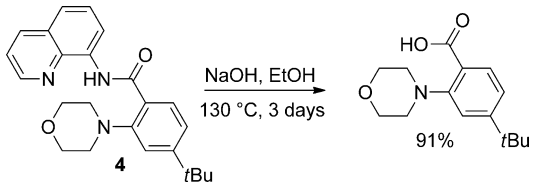
Scheme 1. Benzylamine picolinamide amination.

Table 3: Copper-catalyzed amination of 8-amino-quinoline amides.[a]



Entry	Amine	Product	Yield [%]	Entry	Amine	Product	Yield [%]
1	HNMeBn		82	6	4-BocNH-piperidine		83
2	HNMePr		74	7	cyclohexylamine		40
3	4-EtO_2C-piperidine		69	8	cyclooctylamine		52
4	4-NC-piperidine		71	9	neopentylamine		32
5	ethylene ketal of 4-keto-piperidine		82	10[b]	$nC_{12}H_{25}NH_2$		20

[a] 0.5 mmol scale, NMP (2 mL), NMO (2 equiv), amine (2 equiv), $Cu(OAc)_2$ (12–25 mol%), Ag_2CO_3 (12–25 mol%), 110°C, 12 h. Yields shown are of isolated products (please see the Supporting Information for details). [b] Pyridine solvent. Boc = *tert*-butyloxycarbonyl.



Scheme 2. Directing group removal.

In conclusion, we have developed a method for direct, auxiliary-assisted amination of β-C(sp^2)–H bonds of benzoic acid derivatives and γ-C(sp^2)–H bonds of benzylamine derivatives. The reaction employs $Cu(OAc)_2$ as catalyst in conjunction with a Ag_2CO_3 cocatalyst, an amine coupling partner, NMP or dimethylsulfoxide solvent, and NMO as an oxidant. The utilization of an inexpensive copper acetate catalyst and removable directing group are advantages that allow for a favorable comparison with previous direct amination reactions. The reaction shows high generality and functional group tolerance, as well as providing a straightforward means for the preparation of *ortho*-aminobenzoic acid derivatives. Attempts to isolate and characterize reaction intermediates are in progress.

Experimental Section

N-(2-Morpholino-4-*tert*-butylbenzoyl)-8-aminoquinoline (Table 2, entry 3): *N*-4-*tert*-butylbenzoyl-8-aminoquinoline (152 mg, 0.5 mmol), $Cu(OAc)_2$ (11 mg, 0.06 mmol), and Ag_2CO_3 (17 mg, 0.06 mmol) were added to a 1-dram vial equipped with a stir bar. Inside a glove box, NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box, NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped with aluminum foil and stirred at 110°C for 11 h and 15 min. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (4:1) gave 158 mg (81%) of product as a tan solid. $R_f = 0.40$ (SiO_2, hexanes/EtOAc, 3:1), mp 142–144°C (from hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): $\delta =$

12.75–12.67 (*s*, 1H) 9.13 (*dd*, $J = 7.8$ Hz, $J = 1.4$ Hz, 1H) 8.87 (*dd*, $J = 4.1$ Hz, $J = 1.8$ Hz, 1H) 8.19 (*dd*, $J = 8.2$ Hz, $J = 1.4$ Hz, 1H) 8.13 (*d*, $J = 8.2$ Hz, 1H) 7.63–7.51 (*m*, 2H) 7.48 (*dd*, $J = 8.2$ Hz, $J = 4.1$ Hz, 1H) 7.31–7.26 (*m*, 2H) 4.03–3.93 (*m*, 4H) 3.21–3.15 (*m*, 4H) 1.37 ppm (*s*, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.0$, 156.3, 151.2, 148.4, 139.2, 136.7, 136.1, 132.3, 128.7, 127.9, 126.3, 121.9, 121.8, 118.0, 116.4, 66.5, 54.3, 35.6, 31.3 ppm. The signal for one carbon could not be located. FT-IR (neat): $\tilde{\nu}$ =2961, 1660, 1526, 1486, 1112 cm^{-1}. HRMS (ESI+): Calculated for $C_{24}H_{27}N_3O_2$ $[M+H]^+$ 390.2182, Found 390.2184.

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Keywords: amination · arenes · C–H activation · copper

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Communications

Direct Amination

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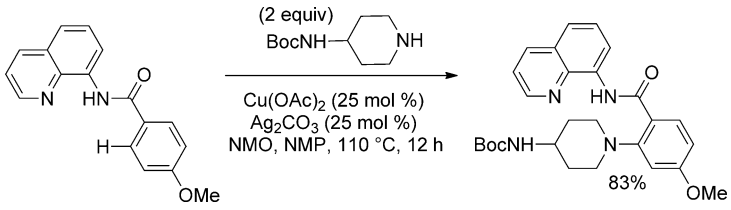
Directed Amination of Non-Acidic Arene C–H Bonds by a Copper–Silver Catalytic System



Amine meets arene: A method for direct amination of β-C(sp^2)–H bonds of benzoic acid derivatives and γ-C(sp^2)–H bonds of benzylamine derivatives has been developed. The reaction is catalyzed by $Cu(OAc)_2$ and a Ag_2CO_3 cocatalyst, and shows high generality and functional-group tolerance, as well as providing a straightforward means for the preparation of *ortho*-aminobenzoic acid derivatives.