

Copper-catalyzed *ortho*-C–H amination of protected anilines with secondary amines†

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A practical Cu-catalyzed picolinamide-directed *o*-amination of anilines showing excellent mono-substitution selectivity and high functional group tolerance has been developed.

The ubiquity of arylamines¹ among pharmaceuticals, natural products and materials continues to inspire the development of efficient and sustainable methods for the construction of aryl C–N bonds. The direct cross-dehydrogenative coupling between arenes and R₂NH represents an appealing approach² that complements standard procedures for *N*-aryl bond formation relying on pre-activated substrates such as the Ullmann–Goldberg, Buchwald–Hartwig and Chan–Lam aminations.³ In this context, the Pd-catalyzed intermolecular amination of arenes with R₂NH is emerging as an increasingly viable tool.^{4,5}

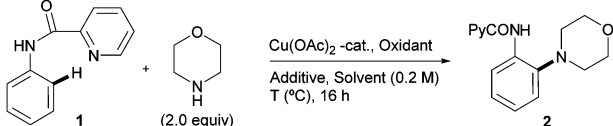
Cu-catalyzed C–H amination represents a distinct challenge that has stimulated substantial research effort since the pioneering reaction of 2-phenylpyridine with tosylamide reported by Yu *et al.* in 2006.⁶ However, most of the reports have focused on intramolecular processes⁷ or base-promoted reactions at acidic C–H bonds.^{8,9} In contrast, Cu-catalyzed intermolecular amination of “inert” aryl C–H bonds has been mainly limited to arenes with the non-removable 2-pyridyl directing group.^{10,11} Daugulis’s group has recently overcome this limitation and developed a removable directing group strategy for the Cu-catalyzed amination of non-acidic benzamide derivatives assisted by 8-aminoquinoline and 2-picolinic acid auxiliaries.¹² Despite this progress, the Cu-catalyzed intermolecular amination of arenes is in its infancy in terms of scope and practicality.

Recently, we have introduced the 2-pyridylsulfonyl group (SO₂Py) as an effective *N*-protecting/directing group for the Cu-catalyzed *o*-C–H halogenation of anilines.¹³ Herein we disclose the Cu-catalyzed *o*-C–H amination of aniline derivatives with

secondary amines using a readily removable 2-picolinic acid directing group.^{4g–j,12}

Based on our earlier results,^{13,14} we initially envisioned that the *N*-(SO₂Py) protecting group could assist the Cu-catalyzed intermolecular *o*-C–H amination of anilines. Nonetheless, we observed much higher reactivity when using the closely related *N*-COPy directing group.¹⁵ The model reaction of picolinamide **1** with morpholine gave traces of the *o*-amination product **2** under conditions similar to those reported by Daugulis:¹² Cu(OAc)₂–Ag₂CO₃ (25 mol%) and NMO (2.0 equiv.) as an oxidant in NMP or DMSO at 130 °C for 16 hours (Table 1, entry 1). Just switching the oxidant to O₂ led to an encouraging yield of 27% (entry 2). At this point, some control experiments showed that Cu(OAc)₂ was essential (entry 3), whereas Ag₂CO₃ could be absent (entry 4). A brief screening of solvents (entries 5–7) revealed that the use of

Table 1 Evaluation of the reaction conditions

					
	Oxidant	Additive	Solvent	T [°C]	Yield ^a [%]
1	NMO	Ag ₂ CO ₃	NMP	130	Traces
2	O ₂ (1 atm)	Ag ₂ CO ₃	NMP	130	27
3 ^b	O ₂ (1 atm)	Ag ₂ CO ₃	NMP	130	—
4	O ₂ (1 atm)	—	NMP	130	23
5	O ₂ (1 atm)	—	DMSO	130	21
6	O ₂ (1 atm)	—	DMPU	130	30
7	O ₂ (1 atm)	—	<i>p</i> -Xylene	130	48 ^c
8 ^d	O ₂ (1 atm)	—	<i>p</i> -Xylene	130	62 (60) ^e
9	PhI(OAc) ₂	—	<i>p</i> -Xylene	130	85 (84) ^e
10 ^f	PhI(OAc) ₂	—	<i>p</i> -Xylene	130	85 (83) ^e
11 ^f	PhI(OAc) ₂	—	<i>p</i> -Xylene	60	75 (74) ^e

Conditions: aniline **1** (0.20 mmol), morpholine (0.40 mmol), Cu(OAc)₂ (25 mol%), oxidant (2.0 equiv.), additive (25 mol%), solvent (0.2 M), 16 h and N₂.^a GC yields (*n*-C₁₆H₃₄ as internal standard).^b In the absence of Cu(OAc)₂.^c 60% GC yield after 48 h. ^d Reaction under microwave: 130 °C/150 W/3 h. ^e Isolated yield. ^f Cu(OAc)₂ (15 mol%) and PhI(OAc)₂ (1.20 equiv.).

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Table 2 Evaluation of the *N*-directing/protecting group

Entry	PG/R (Substrate)	Product	Yield ^a [%]
1	C(O)(2-Py)/H (1)	2	71 (74) ^b
2	C(O)(Ph)/H (3)	—	— ^c
3	Ac/H (4)	—	— ^c
4	SO ₂ (2-Py)/Me (5)	9 + 10 ^d (1 : 1)	30
5	H/H (7)	—	— ^e
6	Ts/H (6)	—	— ^c
7	C(O)(2-Py)/Me (8)	—	— ^c

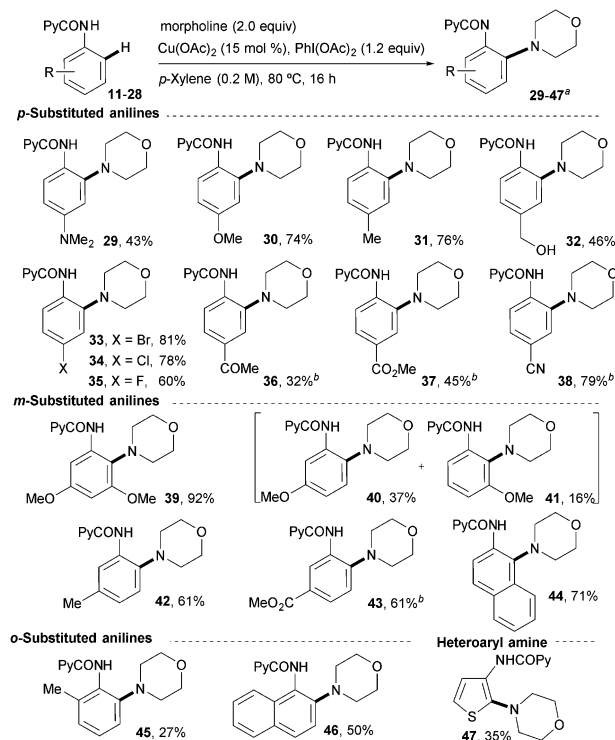
^a GC yields (*n*-C₁₆H₃₄ as internal standard). ^b Isolated yield. ^c Starting aniline recovered. ^d 10 = *N,N*-diphenylpyridine-2-sulfonamide. ^e Complex mixture.

p-xylene, a non-polar solvent, could increase the yield up to 48% (entry 7, 60% upon prolonging the reaction time to 48 hours).

The decisive factor in making the transformation effective was the choice of $\text{PhI}(\text{OAc})_2$ as the oxidant (see the ESI† for further studies).¹⁶ Full conversion in 16 hours was observed with 2 equivalents of $\text{PhI}(\text{OAc})_2$, allowing the desired product 2 to be isolated in 84% yield (entry 9). The loading of both the Cu catalyst (15 mol%) and $\text{PhI}(\text{OAc})_2$ (1.2 equiv.) could be significantly reduced without an appreciable impact (83%, entry 10). Moreover, the temperature could be lowered to 60 °C while maintaining a synthetically useful yield (74%, entry 11). It is remarkable that no diamination products were detected in the crude mixtures.

A screening of protecting groups confirmed the superiority of the COPy group, emphasizing the cooperative directing role of both CO and 2-Py moieties (Table 2). The lack of reactivity of benzanilide 3 and acetanilide 4 revealed the importance of the 2-Py unit (entries 2 and 3). However, the coordinating $\text{NH}(\text{SO}_2\text{Py})$ substrate 5 afforded, with low conversion, the desired *o*-aminated product 9 accompanied by the *N*-arylated product 10 (1 : 1 mixture), the latter arising from the reaction of 5 with the iodobenzene generated as a byproduct (entry 4). The reaction of the free aniline or its *N*-tosyl derivative was totally unproductive (entries 5 and 6). Finally, *N*-alkylation was not tolerated, the *N*(Me)(COPy)-aniline 8 being recovered unaltered (entry 7).

The reaction of variously substituted aniline derivatives with morpholine is presented in Scheme 1. Substrates with electron-rich (Me and OMe) and moderately electron-deficient (F, Cl and Br) substituents at the *p*-position reacted particularly well (typically 60–81% yield). Even the strongly coordinating NMe_2 (29, 43%) and the unprotected hydroxymethyl (32, 46%) groups were tolerated. The complete *o*-selectivity was particularly noteworthy in the *p*(OMe)- and *p*(NMe_2)-aniline derivatives, with two *o*-directing groups. Strongly electron-withdrawing groups, such as CO_2Me , CF_3 , CN or the base-sensitive COMe group, were compatible but resulted generally in lower yields and required higher loadings of Cu (25 mol%) and $\text{PhI}(\text{OAc})_2$ (2 equiv.). *m*-Substituted substrates reacted generally with complete regio-control at the sterically less hindered site (42 and 43). As an exception, the aniline with a *m*-OMe group led to a 2 : 1 mixture



Scheme 1 Cu-catalyzed *o*-amination of aniline substrates with morpholine. ^a Isolated yields for products 29–47. ^b $\text{Cu}(\text{OAc})_2$ (25 mol%) and $\text{PhI}(\text{OAc})_2$ (2.0 equiv.).

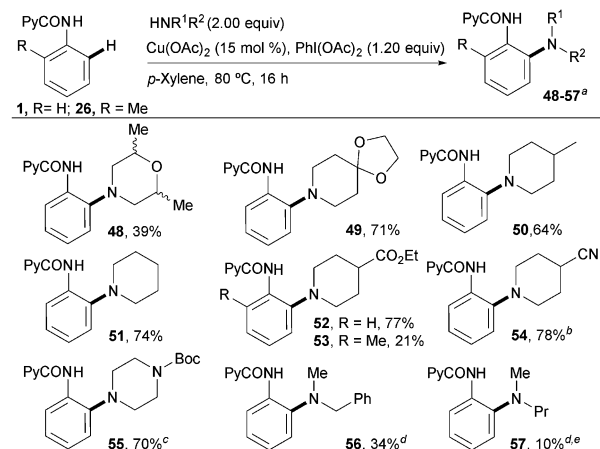
of the two mono-*o*-aminated products (40 and 41). *o*-Substitution led to reduced reactivity (45, 27% yield), presumably because of its increased steric requirements, while the 1-naphthyl derivative was aminated at C2 (46, 50% yield). A heteroaromatic amine was also amenable to the reaction, albeit in lower yield (47, 35%).

Several morpholine, piperidine and piperazine derivatives bearing common functionalities including ethers, esters and nitriles performed well in this reaction (Scheme 2). Unfortunately, simple secondary amines proved to be much less effective (products 56 and 57).

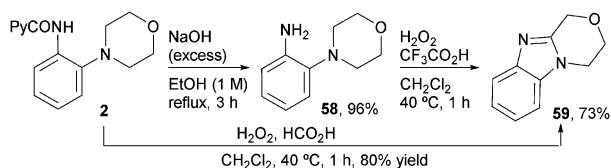
Finally, we demonstrated both the scale-up of the reaction up to 1 gram-scale without loss of yield (see the ESI† for details) and the efficient directing group removal under basic conditions (Scheme 3, product 58, 96% yield). The resulting 2-morpholinoaniline was next derivatized into the corresponding benzimidazol 59 *via* an oxidative cyclization reaction.¹⁷ Although the mechanism is unclear at this point, the lack of reactivity of 1 in the presence of radical scavengers such as TEMPO or Galvinoxyl suggests that a SET pathway might operate¹⁸ (see the ESI† for intramolecular kinetic isotope effect and competition studies).

In summary, we have developed a regioselective Cu-catalyzed *ortho*-C–H amination process assisted by a removable *N*-COPy group that provides a straightforward means for the preparation of *o*-aminoaniline derivatives.

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Scheme 2 Scope of the amine counterpart. ^a Isolated yields for products **48–57**. ^b *p*-Xylene : NMP (1 : 1) (0.2 M). ^c Cu(OAc)₂ (25 mol %) and PhI(OAc)₂ (2.0 equiv.). ^d Using O₂ (1 atm) instead of Cu(OAc)₂. ^e GC-yield (n_{C₁₆H₃₄} as the internal standard).



Scheme 3 Deprotection of **2** and synthesis of the benzimidazole **59**.

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