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Synthesis of Anthranilic Acid Derivatives through Iron-Catalyzed Ortho Amination of Aromatic Carboxamides with *N*-Chloroamines

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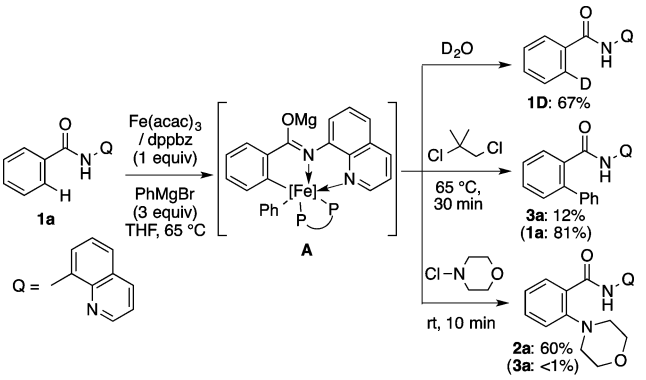
Supporting Information

ABSTRACT: Arenes possessing an 8-quinolinylamide group as a directing group are ortho aminated with *N*-chloroamines and *N*-benzoyloxyamines in the presence of an iron/diphosphine catalyst and an organometallic base to produce anthranilic acid derivatives in high yield. The reaction proceeds via iron-catalyzed C−H activation, followed by the reaction of the resulting iron intermediate with *N*-chloroamine. The choice of the directing group and diphosphine ligand is crucial for obtaining the anthranilic acid derivative with high yield and product selectivity.

The direct conversion of a C−H bond of an arene[1] to the corresponding C−N bond[2] is an attractive synthetic approach to substituted anilines[3]—important compounds in industry, medicinal chemistry, and materials science. The most straightforward method is the oxidative coupling of an amine with an arene; this has been achieved with copper[4] or palladium[5] catalysts[6] under high-temperature conditions. An alternative ortho-amination method using a more reactive electrophilic aminating or amidating reagent employs late transition metal catalysts (rhodium,[7−9] ruthenium,[10] palladium,[11] or iridium[12]) under milder conditions.[13] We report here that reactive first-row iron[14] can effect catalytic ortho-amination[15] of aromatic carboxamides with *N*-chloroamines at 65 °C to produce anthranilic acid derivatives[16] in up to 100% yield. Iron has become a popular catalyst for C−H activation chemistry because of its high reactivity, abundance, and low toxicity.[14,17]

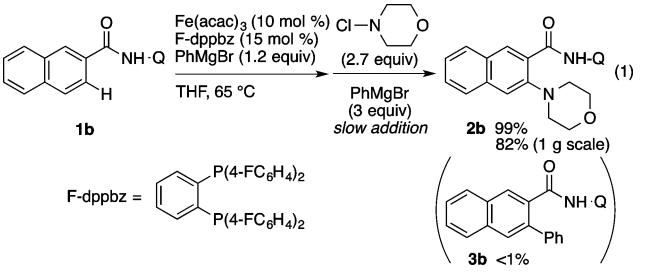
We developed the catalytic ortho-amination reaction on the basis of the stoichiometric formation and amination of a putative iron intermediate **A**[18] from *N*-(quinolin-8-yl)-benzamide (**1a**) that we optimized first (Scheme 1). Treatment of a mixture of **1a** and 1 equiv each of $Fe(acac)_3$ and dppbz with 3 equiv of PhMgBr in THF at 65 °C gave the intermediate **A**. In agreement with the catalytic oxidative C−C bond formation via a similar intermediate,[19] oxidation of **A** with 1,2-dichloroisobutane slowly produced a phenylated product **3a** in 12% yield. Quenching **A** with D_2O resulted in 67% deuterium incorporation at the ortho position of the benzamide (product **1D**) without the formation of **3a**. Thus, **A** is stable and does not undergo thermal reductive elimination. The reaction of **A** with *N*-chloromorpholine occurs much faster than the oxidative C−C bond formation and gave the desired ortho-aminated product **2a** in 60% yield with <1% of **3a**. Note that the reaction of a Grignard reagent (PhMgBr) with a chloroamine also gives a

Scheme 1. Stoichiometric C−H Activation of *N*-(Quinolin-8-yl)benzamide (1a) and Amination with *N*-Chloromorpholine



chlorinated product, sometimes even predominantly, instead of an aminated product,[20] suggesting that **A** is an organoiron species rather than a Grignard species. As discussed later, the quinolin-8-yl group (Q) and the diphosphine ligand are important factors that effectively retard the undesired C−C bond formation. We note that PhMgBr is the best among the other Grignard reagents investigated (Supporting Information (SI)), and organozinc reagents were completely ineffective and mainly produced the phenylated product such as **3a**.

The reaction was rendered catalytic by careful tuning of the reaction conditions (eq 1). To a mixture of naphthalene-



carboxamide **1b** (60 mg, 0.2 mmol), $Fe(acac)_3$ (10 mol %), and 1,2-bis[bis(4-fluorophenyl)phosphino]benzene (F-dppbz, 15 mol %) was added 1.2 equiv of PhMgBr, and the mixture was heated at 65 °C. This operation results in deprotonation of the amide (with 1.0 equiv of PhMgBr) and the formation of a small amount of **A** (0.2 equiv). A solution of PhMgBr in THF

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(0.67 mL, 0.89 mol/L, 0.60 mmol) and a solution of freshly distilled *N*-chloromorpholine in THF (0.54 mmol in 0.72 mL) were added simultaneously using a dual syringe pump at 65 °C over 60 min. The reaction was quenched just after the addition finished and gave **2b** in 99% yield after isolation. The procedure was amenable to scaling up, and we obtained **2b** in 89% yield on a 1 mmol scale and 82% yield on a gram scale (with 20 mol % catalyst). We note that the purity of the chloroamine was crucial for the large scale reaction, because a trace impurity due to decomposition of the *N*-chloroamine impedes the catalytic cycle.

The synchronization of the formation of **A** (addition of PhMgBr) with the slow addition of the aminating reagent is necessary to prevent the direct reaction between PhMgBr and *N*-chloroamine[20] that prevents catalytic turnover. As with the stoichiometric reaction (Scheme 1), formation of the ortho-phenylated **3b** was mostly suppressed (<1%). Note that 1 equiv of PhMgBr takes up the ortho hydrogen of **1b**, and the rest was consumed for biphenyl formation through iron-catalyzed homocoupling.[19]

The directing group and the ligand are crucial for the success of this reaction (Figure 1). The bidentate 8-quinolinylcarboxamide directing group[21] was uniquely effective (Figure 1a). A monodentate carboxamide such as *N*-phenyl- or *N*-methylcarboxamide resulted in recovery of the amide, as did 2-phenylpyridine or *N*-phenylpyrazole (SI). Increasing the flexibility of the directing group, as with picolinylcarboxamide, resulted in increased phenylation. 2-Methylquinolin-8-yl amide entirely failed to participate in the reaction, suggesting the sensitivity of the chelation formation to steric hindrance. An *N*-methylated amide also did not react at all.

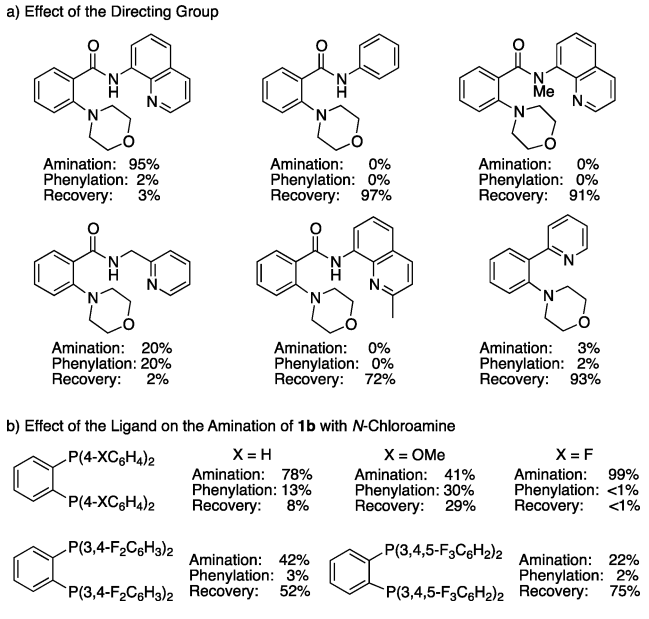
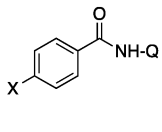
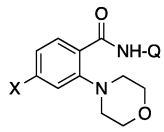
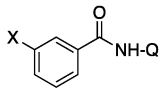
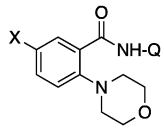
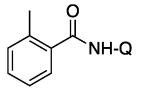
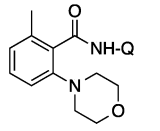
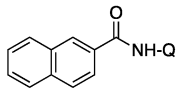
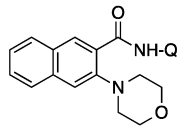
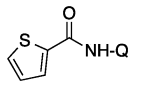
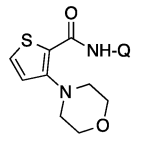
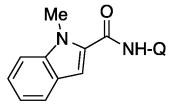
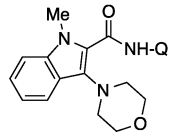


Figure 1. Effect of the directing group and ligand on the amination of arenes with *N*-chloromorpholine.

The electronic property of the diphosphine ligand strongly affects the product selectivity (Figure 1b).[22] Thus, a more electron-rich ligand favors the phenylated product, and a less electron-rich ligand favors the desired amination product.

With the optimized conditions in hand, we next investigated the scope of the carboxamide substrate (Table 1). Most of the substrates we examined reacted with high yield (>90%). These

Table 1. Iron-Catalyzed Reaction of Various Carboxamides with *N*-Chloromorpholine[a]

entry	substrate[b]	product[b]	yield (%)[c]
1			X = H 91
2			X = Me 96
3			X = OMe 92
4			X = CF_3 97
5			X = F 92
6			X = Cl 100
7			X = Br 54[d]
8			X = Me 99
9			X = OMe 95
10[e]			X = NMe_2 94
11[e]			X = F 81
12[e]			0
13			99
14			75
15[e]			60

[a]Reaction conditions: PhMgBr in THF (1.2−1.4 equiv) was added to a THF solution of carboxamide (1.0 equiv), $Fe(acac)_3$ (10 mol %), and F-dppbz (15 mol %), and then PhMgBr in THF (3.0 equiv) and *N*-chloromorpholine in THF (2.7 equiv) were added slowly at 65 °C. See the Supporting Information for details. [b]Q = 8-quinolinyl. [c]Determined by isolation. [d]Debrominated compound was obtained in 9%. [e]20 mol % of catalyst was used.

quinolyn-8-yl amide products can be readily hydrolyzed to the corresponding carboxylic acid.[4e] In all cases, only the monoaminated product was obtained selectively without diamination. In agreement with this observation, an ortho substituent was found to completely shut off the reaction (entry 12), while para- and meta-substituted carboxamides reacted well. We speculate that steric interactions disturb the formation of the ferracycle intermediate **A**.[19d] For meta-substituted carboxamides (entries 8−11), the reaction proceeded exclusively at the less hindered ortho position. Electron-rich substrates reacted quickly (over 20−60 min), while electron-deficient ones reacted more slowly (over 60−120 min; see the SI for details). Halides such as chloride and bromide were tolerated under the reaction conditions (entries 6 and 7, debromination product was obtained in 9% at entry 7). 2-Naphthalenecarboxamide also reacted well (entry 13). Heteroaromatic substrates such as thiophene- and indole-carboxamide (entries 14 and 15) also reacted, albeit in lower yield, to give heteroaromatic amino acid derivatives. For these substrates, the phenylation product accounted for a significant

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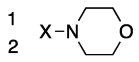
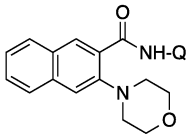
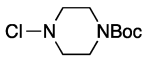
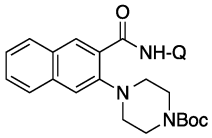
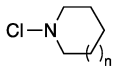
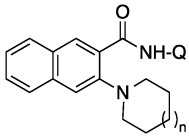
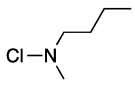
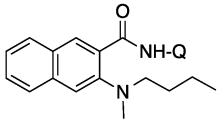
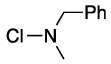
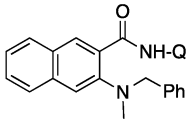
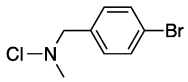
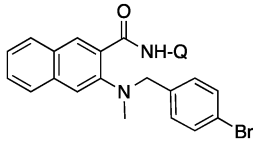
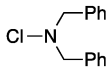
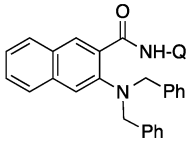
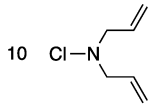
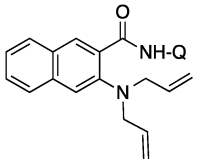
portion of the reaction outcome (thiophene substrate, 6%; indole substrate, 24%).

The reaction proceeded well (>90% yield) with the common *N*-chloroamines (Table 2). We could also use *N*-benzoyloxymorpholine, which gave the corresponding aminated product in 89% yield (entry 2). However, other *N*-benzoyloxyamines reacted in poor yield (SI). Cyclic and acyclic chloroamines reacted equally well. Morpholine (entry 1), protected piperidine (entry 3), and six- and seven-membered amines (entries 4 and 5) could be introduced in high yield. A dialkylamine could also be introduced to produce an unsymmetrical *N*-dialkylaniline derivative (entry 6). Benzylamines (entries 7–9), including sterically demanding dibenzylamine (entry 9), and diallylamine (entry 10) were well tolerated and introduced to the substrate in high yield. A bromide substituent on the benzylic amine (entry 8) was well tolerated.

Table 2. Iron-Catalyzed Reaction of *N*-(Quinolin-8-yl)naphthaleneamide with *N*-Chloro- and *N*-benzoyloxyamines[a]

entry	chloroamine	product[b]	yield (%)[c]
1			X = Cl 99
2			X = OBz 89
3			99
4			n = 1 98
5			n = 2 93
6			94
7			96
8			89
9			96
10			91

[a]Reaction conditions: PhMgBr in THF (1.4 equiv) was added to a THF solution of *N*-(quinolin-8-yl)naphthaleneamide (1.0 equiv), $Fe(acac)_3$ (20 mol %), and F-dppbz (20 mol %), and then PhMgBr in THF (3.0 equiv) and *N*-chloroamine in THF (2.7 equiv) were added slowly over 40 min at 65 °C. [b]Q = 8-quinolinyl. [c]Determined by isolation.

In conclusion, we have developed an iron-catalyzed directed amination of a $C(sp^2)$–H bond with chloroamines to produce anthranilic acid derivatives in up to 100% yield. The structure of the directing group and the control of the electronic properties of the diphosphine ligand allowed selective formation of the aminated product, by balancing the rate of the C–H activation step with the stability of the forming iron intermediate. Further understanding of this balance will lead to efficient iron-catalyzed C–H bond functionalization.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and physical properties of the compounds. 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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