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Regioselective Copper-Catalyzed Amination of Chlorobenzoic Acids: Synthesis and Solid-State Structures of *N*-Aryl Anthranilic Acid Derivatives

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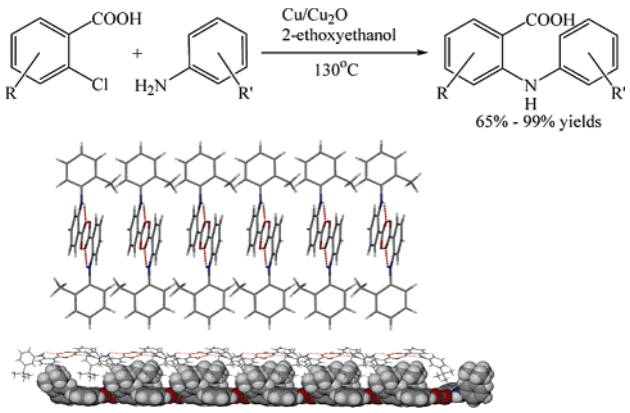

A chemo- and regioselective copper-catalyzed cross-coupling reaction for effective amination of 2-chlorobenzoic acids with aniline derivatives has been developed. The method eliminates the need for acid protection and produces a wide range of *N*-aryl anthranilic acid derivatives in up to 99% yield. The amination was found to proceed with both electron-rich and electron-deficient aryl chlorides and anilines and also utilizes sterically hindered anilines such as 2,6-dimethylaniline and 2-*tert*-butylaniline. The conformational isomerism of appropriately substituted *N*-aryl anthranilic acids has been investigated in the solid state. Crystallographic analysis of seven anthranilic acid derivatives showed formation of two distinct supramolecular architectures exhibiting trans−anti and unprecedented trans−syn dimeric structures.

Introduction

Cross-coupling reactions resulting in carbon−heteroatom bond formation have received increasing attention in recent years.[1] Significant progress has been reported for Pd-catalyzed amination reactions proceeding with aryl halides under mild conditions.[2] Alternatively, copper-mediated cross-coupling reactions utilizing anilines,[3] amides,[4] imidazoles,[5] and other heterocycles,[6] β-amino alcohols,[7] and aliphatic amines have also been developed.[8]

Copper-mediated amination of 2-chlorobenzoic acid was first accomplished by Ullmann.[9] Since then, various efforts to improve the efficiency of this reaction involving the use of ultrasound-assisted methods have been reported.[10] We have

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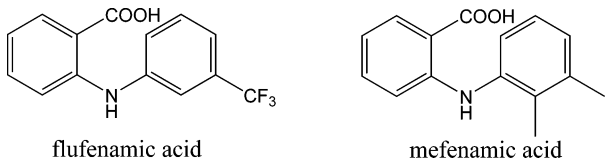
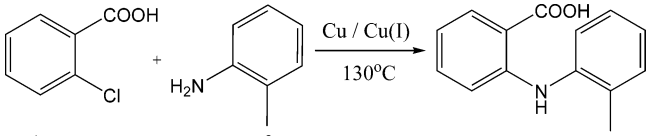


FIGURE 1. Structures of anthranilic acid derivatives used as NSAIDs and for the treatment of amyloidogenic diseases.

recently described a copper-catalyzed amination protocol for the synthesis of substituted *N*-aryl anthranilic acids, which were further utilized as precursors for ring construction of 9-chloro- and 9-bromoacridines.[11] *N*-Aryl anthranilic acids, such as flufenamic and mefenamic acid, are important nonsteroidal antiinflammatory drugs (NSAIDs) and promising candidates for the therapy of neurodegenerative and amyloid diseases (Figure 1).[12] They are also important precursors for the synthesis of substituted acridines which have been used as antimalarial and anticancer drugs.[13] Buchwald et al. developed an effective Pd-catalyzed amination procedure that is applicable to aryl chlorides with free carboxylic acid groups in the meta or para position.[14] A complementary copper-catalyzed amination reaction that proceeds with *ortho*-chlorobenzoic acid, albeit with only moderate yields, has been reported.[15] As a result, *N*-aryl anthranilic acid derivatives are usually prepared through the Ullmann−Jourdan reaction or the Buchwald−Hartwig amination with alkyl 2-iodobenzoates and subsequent hydrolysis.[16] We wish to report a general synthetic procedure providing substituted *N*-aryl anthranilic acids in high to excellent yields via Cu-catalyzed amination of *ortho*-chlorobenzoic acids. Through isothermal evaporation, we were able to obtain single crystals of a series of *N*-aryl anthranilic acid derivatives. Crystallographic analysis revealed two distinctive packing motifs exhibiting either a syn or an anti arrangement of anthranilic acid dimers which are stabilized by two centrosymmetric C═O···H−O hydrogen bonds. The unprecedented interdependence of the dimeric arrangement and crystal structure of substituted anthranilic acids is closely related to supramolecular conformational isomerism.

TABLE 1. Copper-Catalyzed Amination of 2-Chlorobenzoic Acid[a]



1 2 3

entry	catalyst (mol %)	reaction time (h)	yield (%)[b]
1	CuI (4)	24	55
2	Cu_2O (4)	24	56
3	Cu (9)	24	55
4	Cu (9), CuI (4)	24	51
5	Cu (9), Cu_2O (4)	24	76
6	Cu (12), Cu_2O (4)	5	66
7	Cu (9), Cu_2O (4)	5	71
8	Cu (6), Cu_2O (4)	5	51
9	Cu (4), Cu_2O (4)	5	51

[a] Reaction conditions: 2-chlorobenzoic acid (1.38 g, 8.83 mmol), 1.05 equiv of 2-methylaniline, and 2.0 equiv of potassium carbonate in 3 mL of 2-ethoxyethanol at 130°C. [b] Isolated yields.

Results and Discussion

For the initial screening of suitable reaction conditions, we decided to study the formation of *N*-(2-methylphenyl)anthranilic acid, **3**, from 2-chlorobenzoic acid, **1**, and 2-methylaniline, **2**, through copper-catalyzed amination using potassium carbonate as the base and 2-ethoxyethanol as solvent. The desired anthranilic acid **3** was obtained in moderate yields with catalytic amounts of CuI, Cu_2O, or Cu (Table 1, entries 1−3). However, results improved significantly in the presence of both Cu and Cu_2O, and **3** was produced in 71% and 76% yields after 5 and 24 h, respectively (Table 1, entries 5 and 7). Variation of the Cu/Cu_2O ratio and replacement of Cu_2O by CuI did not further increase the yields (Table 1, entries 4 and 6−9).

We then decided to study the effect of solvent and base on the amination reaction. Anthranilic acid **3** was obtained in 75% and 76% yields, respectively, using Cu/Cu_2O as the catalyst in *n*-butanol or 2-ethoxyethanol in the presence of two equivalents of potassium carbonate, whereas only poor yields were obtained in water and ethylene glycol (Table 2, entries 1−4). We were pleased to find that yields of **3** could be enhanced to 90% when diethylene glycol or 2-ethoxyethanol was used as the solvent (Table 2, entries 5 and 12). The Cu/Cu_2O-catalyzed amination of 2-chlorobenzoic acid proved to depend significantly on the base employed. Comparison of the results obtained with Na_2CO_3, Cs_2CO_3, K_3PO_4, NaOAc, *tert*-BuOK, and 2,2,6,6-tetramethylpiperidine (TMP) shows that yields of **3** obtained in diethylene glycol vary from 5 to 90% (Table 2, entries 5−11). We found that anthranilic acid **3** was produced in only 5−30% yields in the presence of cesium carbonate, 2,2,6,6-tetramethylpiperidine, and *tert*-BuOK (Table 2, entries 6, 8, and 11). By contrast, anthranilic acid **3** was formed in 90% and 82% yields through Cu/Cu_2O-catalyzed amination of **1** with **2** using

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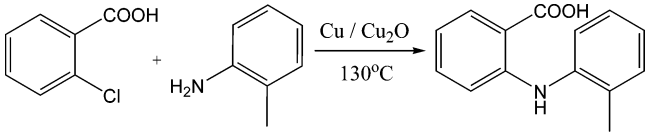
TABLE 2. Screening of Solvents and Bases[a]



1 **2** **3**

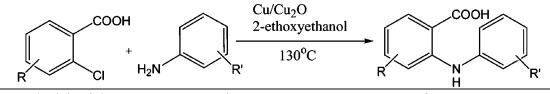
entry	base	solvent	T (°C)	yield (%)[b]
1	K_2CO_3	*n*-butanol	117	75
2	K_2CO_3	water	100	35
3	K_2CO_3	ethylene glycol	130	40
4	K_2CO_3	2-ethoxyethanol	130	76
5	K_2CO_3	diethylene glycol	130	90
6	Cs_2CO_3	diethylene glycol	130	5
7	Na_2CO_3	diethylene glycol	130	82
8	*t*-BuOK	diethylene glycol	130	11
9	K_3PO_4	diethylene glycol	130	70
10	NaOAc	diethylene glycol	130	66
11	TMP	diethylene glycol	130	30
12	Na_2CO_3	2-ethoxyethanol	130	92[d]
13	K_2CO_3	2-ethoxyethanol	130	75[c]
14	K_2CO_3	2-ethoxyethanol	130	83[c,d]

[a] Reaction conditions: 2-chlorobenzoic acid (1.38 g, 8.83 mmol), 1.05 equiv of 2-methylaniline, 9 mol % of Cu, 4 mol % of Cu_2O, 2.0 equiv of base, and 3 mL of solvents, at 130°C for 24 h. [b] Isolated yields. [c] Aniline was used. [d] 1.0 equiv of base was used.

K_2CO_3 or Na_2CO_3 in diethylene glycol (Table 2, entries 5 and 7). We also observed that the amination proceeds with excellent yields with one equivalent of sodium or potassium carbonate in 2-ethoxyethanol (Table 2, entries 12−14).

The copper-catalyzed C−N bond formation procedure was then applied to a variety of aryl amines and chlorobenzoic acids to produce a series of *N*-arylanthranilic acids (Table 3). We found that the presence of one bulky ortho substituent does not impede effective amination (Table 3, entries 2−5). For example, 2-*tert*-butylaniline, **8**, and 2-phenylaniline, **10**, gave *N*-(2-*tert*-butylphenyl)anthranilic acid, **9**, in 86% yield and *N*-(2-biphenyl)-anthranilic acid, **11**, in 85% yield (Table 3, entries 4 and 5). Incorporation of two ortho substituents to aniline, however, was found to decrease yields; e.g., *N*-(2,6-dimethylphenyl)anthranilic acid, **13**, was obtained in only 65% yield (Table 3, entry 6). Coupling of 1-aminonaphthalene or 1-aminopyrene gave the corresponding products **21** and **23** in 96% and 73% yields (Table 3, entries 10 and 11). Importantly, no significant electronic effects were observed in the reaction of substituted anilines and chlorobenzoic acids. For example, amination of **1** with 4-methoxyaniline, **24**, and 4-nitroaniline, **26**, proceeded with 84% and 87% yields, respectively, and electron-deficient chlorobenzoic acid **32** gave anthranilic acid **33** in 99% yield (Table 3, entries 12, 13, and 16). The copper-catalyzed amination was found to proceed with high regio- and chemoselectivity. Amination only occurs when the halide is located in ortho position to the carboxylic acid moiety. For example, coupling of 2,4-dichlorobenzoic acid, **34**, with 4-methoxyaniline, **24**, gave anthranilic acid **35** in 86% yield and amination of 5-bromo-2-chlorobenzoic acid, **36**, produced **37** in 85% yield (Table 3, entries 17 and 18). Aryl halide bonds located in the aniline moiety are also not affected. The coupling reaction between 2-chlorobenzoic acid and 3-chloroaniline, **28**, gave **29** in 99% yield (Table 3, entry 14). The ortho carboxylate group has been known to effectively accelerate homogeneous copper-catalyzed exchange reactions.[17] Accordingly, our amination procedure affords high regioselectivity and tolerates various functionalities thus complementing other methods that allow effective amination of *meta*- and *para*-chlorobenzoic acids.

TABLE 3. Arylation of Aryl Chlorides with Aryl Amines[a]



entry	aryl chloride	amine	product	yield (%)[b]
1	**1**	**4**	**5**	83
2	**1**	**2**	**3**	92[c]
3	**1**	**6**	**7**	73
4	**1**	**8**	**9**	86
5	**1**	**10**	**11**	85
6	**1**	**12**	**13**	65
7	**1**	**14**	**15**	80
8	**1**	**16**	**17**	85
9	**1**	**18**	**19**	99
10	**1**	**20**	**21**	96
11	**1**	**22**	**23**	73
12	**1**	**24**	**25**	84
13	**1**	**26**	**27**	87
14	**1**	**28**	**29**	99
15	**1**	**30**	**31**	98[d]
16	**32**	**24**	**33**	99
17	**34**	**24**	**35**	86
18	**36**	**24**	**37**	85

[a] Reaction conditions: 2-chlorobenzoic acid (1.38 g, 8.83 mmol), 1.05 equiv of amine, 1.0 equiv of K_2CO_3, 9 mol % of Cu, 4 mol % of Cu_2O, and 3 mL of 2-ethoxyethanol at 130°C for 24 h. [b] Isolated yields. [c] Na_2CO_3 was used as base. [d] 2.0 equiv of base were used.

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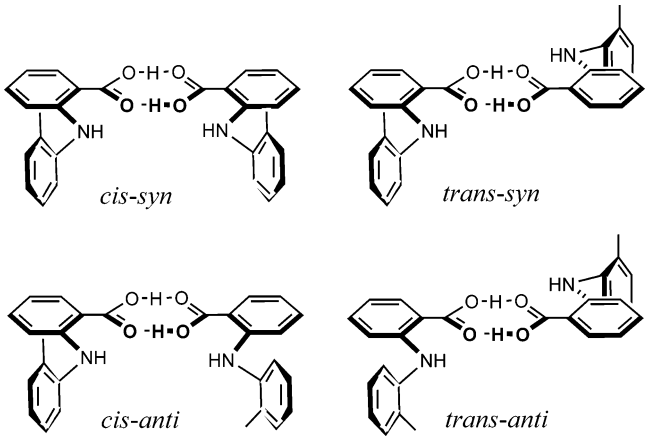

FIGURE 2. Possible arrangements of dimers of **3**.

Carboxylic acids are known to form centrosymmetric dimers in solution and in the solid state to minimize the overall dipole moment.[18] In the case of substituted *N*-aryl anthranilic acids, dimer formation could lead to two geometrical arrangements isolable in the solid state, namely cis and probably favored trans isomers exhibiting the *N*-aryl substituents on the same or opposite sides. In addition, both trans and cis isomers could exhibit either syn or anti orientation having substituted *N*-aryl groups either pointing up or down relative to the anthranilic plane, as shown for *N*-(2-methylphenyl)anthranilic acid, **3** (Figure 2).

Supramolecular isomerism has been defined as the existence of different types of crystal architectures produced from the same molecular building blocks and is closely related to molecular isomerism and polymorphism.[19] The desire to understand and rationally design solid-state structures has resulted in remarkable advances in crystal engineering and supramolecular synthesis.[20] The possibility of four isomeric dimeric structures of anthranilic acids has led us to the study of solid-state conformational isomerism. We therefore employed appropriately substituted anthranilic acids **3**, **7**, **9**, **11**, **15**, **17**, **19**, **21**, and **29** in crystallization experiments. Through isothermal evaporation from methylene chloride solutions, we were able to grow single crystals of seven anthranilic acids (Figure 3). Anthranilic acids **3** and **11** formed monoclinic systems, and the others gave triclinic crystals (Table 4). As expected, dimeric *N*-arylanthranilic acid structures were obtained in all cases. The dimeric arrangements of **3**, **7**, **9**, **11**, and **15** are of the centrosymmetric trans−anti type. A pair of C═O···H−O hydrogen bonds and C═O···H−N hydrogen forces both anthranilic rings into the same plane. The unit cell of the single crystal of **3** contains eight molecules forming four centrosymmetric dimers (Figure 4). Through a Cambridge Structural Database (CSD) search, we found five additional *N*-phenylanthranilic acid derivatives showing acid dimers with the same trans−anti arrangement in the solid state.[21]

The dihedral angle, α, between the 2-methylphenyl moiety and the anthranilic ring of **3** was determined as 49.1° (Figure 5). Changing the ortho substituent from methyl to *iso*-propyl, *tert*-butyl, and phenyl did not affect the supramolecular architecture and molecular isomerism. However, the dihedral angle, α, was found to change from 49.1° (**3**) to 62.5° (**7**), 62.8° (**9**), and 77.1° (**11**) (Figure 5). Although the dihedral angle increases with the bulkiness of the ortho substituent, the almost perpendicular arrangement of the phenyl group is stabilized by additional $\pi-\pi$ interactions between adjacent dimers (Supporting Information).

The trans−anti dimers of **3**, **7**, **11**, and **15** show one-dimensional $\pi-\pi$ interactions between the anthranilic aromatic rings (Figure 6). Anthranilic acid **3** formed π-stacking rods with a closest-contact distance of 3.46 Å. Anthranilic acids **7**, **11**, and **15** have a similar packing arrangement, and the corresponding closest-contact distance was determined as 3.50, 3.40, and 3.46 Å, respectively. However, the bulky *tert*-butyl group of anthranilic **9** impedes effective π-stacking which is replaced by van der Waals interactions (Supporting Information).

Surprisingly, anthranilic acids **17** and **19** crystallized as noncentrosymmetric trans−syn dimers (Figure 5). The conformational isomerism is accompanied by a quite distinct crystal architecture. In contrast to the formation of π-stacking rods observed with anthranilic acids **3**, **7**, **11**, and **15**, the crystals of **17** and **19** show one-dimensional chains stabilized by $\pi-\pi$ interactions between the *tert*-butylphenyl and 3,5-dimethylbiphenyl rings, respectively. For example, the solid-state structure of anthranilic acid **17** has a closest-contact distance between the *tert*-butylphenyl rings of 3.48 Å (Figure 7). The π-stacking of the trans−syn dimers results in infinite chains along the *b*-axis. Empty space within one chain is filled with a complementary chain, thus providing one-dimensional intertwined rods. The unexpected solid-state structures of the anthranilic acids studied resemble supramolecular conformational isomerism. Although the crystal structures of acids **3**, **7**, **9**, **11**, and **15** show a previously reported packing motif exhibiting trans−anti dimers, anthranilic acids **17** and **19** crystallized as dimeric

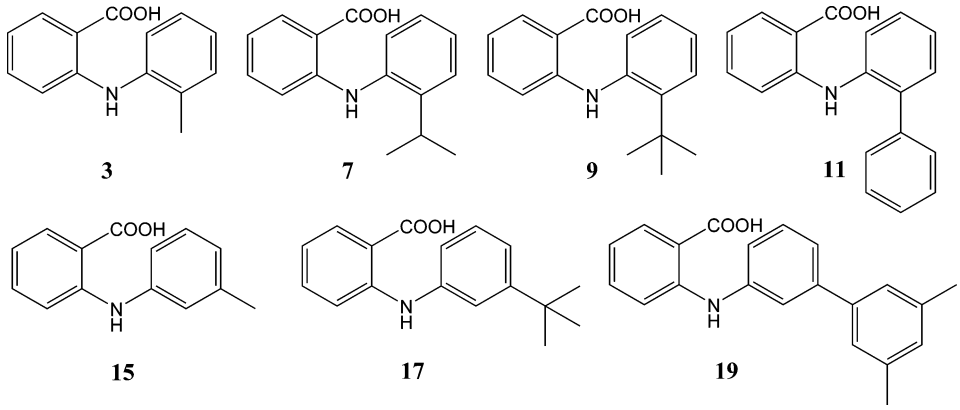

FIGURE 3. Structures of *N*-phenylanthranilic acid derivatives employed in single-crystal analysis.

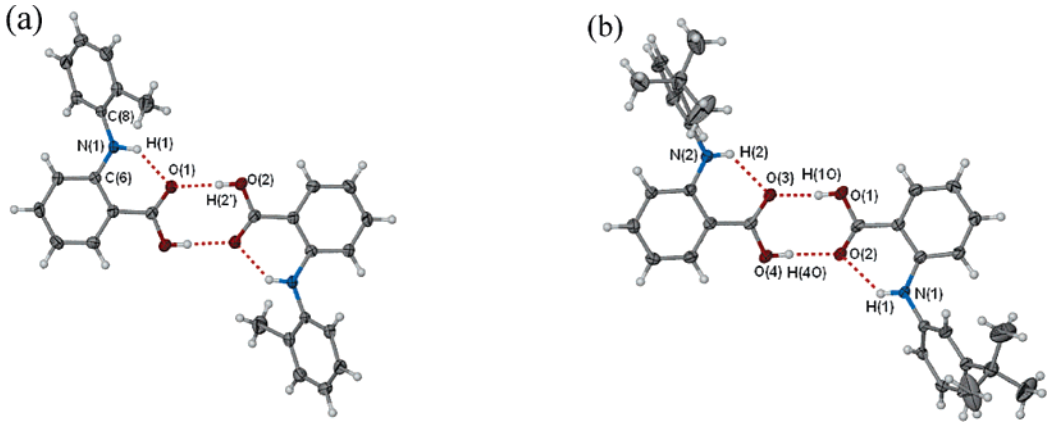

FIGURE 4. ORTEP perspectives of anthranilic acid derivatives (a) *N*-(2-methylphenyl)anthranilic acid **3** and (b) *N*-(3-*tert*-butylphenyl)anthranilic acid **17**. Selected interatomic distances (Å) and angles (deg): (a) O(1)···O(2) = 2.224, N(1)···O(1) = 2.636, O(2)−H(2′)···O(1) = 172.79, N(1)−H(1)···O(1) = 138.32 and (b) O(1)···O(3) = 2.643, O(2)···O(4) = 2.707, N(1)···O(2) = 2.733, N(2)···O(3) = 2.692, O(4)−H(4O)···O(2) = 164.42, N(1)−H(1)···O(2) = 132.77.

TABLE 4. Crystallographic Parameters of Anthranilic Acid Derivatives

compound name	**3**	**7**	**9**	**11**	**15**	**17**	**19**
formula	$C_{14}H_{13}NO_2$	$C_{16}H_{17}NO_2$	$C_{17}H_{19}NO_2$	$C_{19}H_{15}NO_2$	$C_{14}H_{13}NO_2$	$C_{17}H_{19}NO_2$	$C_{21}H_{19}NO_2$
mol wt	227.25	255.31	269.33	289.32	227.25	269.33	317.37
temp (K)	173	183	173	183	173	163	173
system	monoclinic	triclinic	triclinic	monoclinic	triclinic	triclinic	triclinic
space group	*C*2/*c*	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	11.7804(16)	7.4585(10)	7.4748(12)	5.7231(8)	4.6299(14)	10.9634(7)	10.5769(16)
b (Å)	7.4503(10)	7.5891(10)	9.3856(15)	17.929(2)	8.332(2)	11.7048(7)	11.4108(17)
c (Å)	26.627(3)	13.6653(19)	11.0319(17)	14.4300(19)	15.336(4)	22.9688(14)	14.162(2)
α (deg)	90	79.998(2)	106.582(3).	90	98.466(4)	88.8990(10)	80.856(3)
β (deg)	100.168(2)	85.875(2)	91.207(3)	101.064(2)	92.198(4)	89.0970(10)	82.334(3)
γ (deg)	90	62.141(2)	99.212(3)	90	101.337(4)	82.0050(10)	84.982(3)
V (Å^3)	2300.3(5)	673.42(16)	730.4(2)	1453.2(3)	572.3(3)	2918.0(3)	1668.5(4)
Z	8	2	2	4	2	8	4
ρ (g/cm^3)	1.312	1.259	1.225	1.322	1.319	1.226	1.263
θ range (deg)	1.55−27.99	1.51−27.99	1.93−28.00	1.83−27.99	2.52−28.00	1.76−28.00	1.95−27.99
index ranges	$-15 \le h \le 15$	$-9 \le h \le 9$	$-9 \le h \le 9$	$-7 \le h \le 7$	$-76 \le h \le 6$	$-14 \le h \le 14$	$-13 \le h \le 13$
	$-9 \le k \le 9$	$-9 \le k \le 10$	$-12 \le k \le 12$	$-23 \le k \le 22$	$-10 \le k \le 11$	$-15 \le k \le 15$	$-14 \le k \le 14$
	$-35 \le l \le 34$	$-17 \le l \le 18$	$-14 \le l \le 14$	$-18 \le l \le 19$	$-20 \le l \le 19$	$-30 \le l \le 29$	$-18 \le l \le 18$
reflns collected	9959	6018	6614	12467	4861	25329	14927
unique reflns	2714	3054	3338	3401	2552	13122	7547
R(int)	0.0410	0.0282	0.0231	0.0430	0.0211	0.0345	0.0309
refined params	155	174	192	199	155	733	445
GOF on F^2	1.020	0.914	1.060	1.027	0.980	1.045	1.032
R_1 [$I > 2\sigma(I)$]	0.0483	0.0462	0.0414	0.0463	0.0442	0.0618	0.0460
wR2 (all data)	0.1409	0.1228	0.1073	0.1127	0.1140	0.2060	0.1154

trans−syn conformers providing an unprecedented supramolecular architecture.

Conclusion

We have developed a highly regioselective Cu/Cu_2O-catalyzed cross-coupling reaction for effective C−N bond formation with 2-chlorobenzoic acids and aniline derivatives. The reaction complements existing methods, tolerates a variety of functional groups, and gives high to excellent yields with both electron-deficient and electron-rich reagents. Crystallographic analysis of seven substituted *N*-aryl anthranilic acids showed two distinct supramolecular structures due to formation of trans−anti and trans−syn dimers in the solid state.

Experimental Section

General Procedure for the Cu-Catalyzed Amination of Aryl Halides. A mixture of aniline (9.30 mmol), aryl halide (8.83 mmol), K_2CO_3 (8.83 mmol), Cu powder (0.78 mmol), and Cu_2O (0.35 mmol) in 3 mL of 2-ethoxyethanol was refluxed at 130°C under inert atmosphere for 24 h. The cooled reaction mixture was poured into 30 mL of water. Charcoal was then added, and the solution was filtered through Celite. The crude product was obtained by precipitation upon acidification of the filtrate with diluted HCl. The residue was dissolved in 100 mL of 5% aqueous Na_2CO_3 solution and filtered through Celite, and the final product was isolated by precipitation upon careful pH adjustment.

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(21) *N*-(2-Methoxyphenyl)anthranilic acid, *N*-(2-carboxyphenyl)anthranilic acid, *N*-(2′-carboxy-5′-chlorophenyl)-4-chloroanthranilic acid, *N*-(2-methyl-3-chlorophenyl)anthranilic acid, and *N*-(3-methyl-2,6-dichlorophenyl)-anthranilic acid.

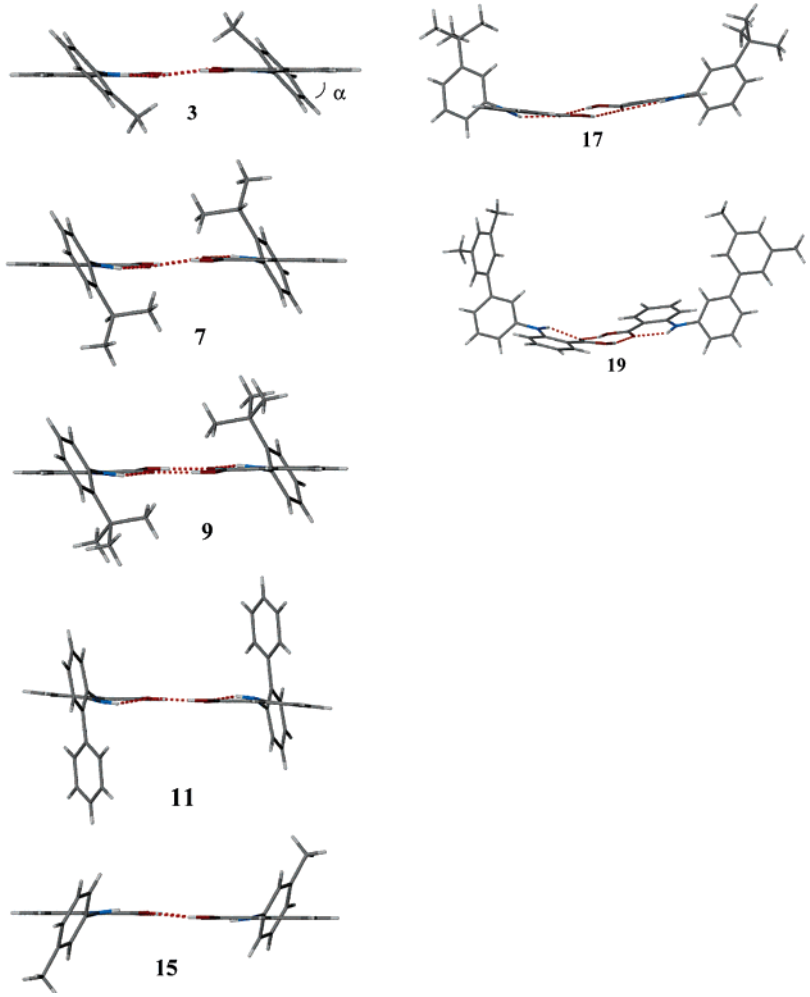

FIGURE 5. X-ray crystal structures of anthranilic acids **3**, **7**, **9**, **11**, **15**, **17**, and **19** exhibiting trans−anti (left) and trans−syn (right) dimeric conformations.

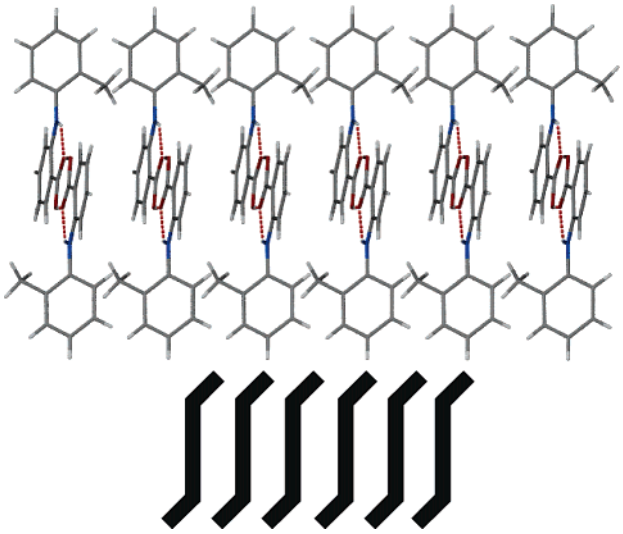

FIGURE 6. One-dimensional π-stacking of anthranilic acid **3** (top) and schematic illustration of the trans−anti dimers and packing motif (bottom).

***N*-(2-Methylphenyl)anthranilic Acid (3).**[12a] Compound **3** was obtained from 2-chlorobenzoic acid, **1**, and 2-methylaniline, **2**, as an off-white powder in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.29 (s, 3H), 6.72 (bs, 1H), 6.85 (d, J = 8.2 Hz, 1H), 7.12 (dd, J = 7.2 Hz, 7.4 Hz, 1H), 7.20−7.34 (m, 5H), 8.05 (d, J = 7.2 Hz, 1H), 9.18 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 17.6, 113.4, 116.9, 122.6, 124.0, 126.6, 130.9, 131.3, 134.0, 138.7, 148.6.

***N*-Phenylanthranilic Acid (5).**[22] Anthranilic acid **5** was obtained from 2-chlorobenzoic acid, **1**, and aniline, **4**, as a white solid in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.75 (dd, J = 7.9 Hz, 8.3 Hz, 1H), 7.13 (dd, J = 7.3 Hz, 8.6 Hz, 1H), 7.20−7.50 (m, 5H), 8.05 (d, J = 7.6 Hz, 1H), 9.33 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 111.0, 114.7, 117.8, 123.8, 124.7, 130.0, 133.2, 135.8, 140.9, 149.5, 174.3.

***N*-(2-Isopropylphenyl)anthranilic Acid (7).**[12a] Amination of 2-chlorobenzoic acid, **1**, and 2-isopropylaniline, **6**, gave anthranilic acid **7** as a white powder in 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.22 (d, J = 6.9 Hz, 6H), 3.21 (sept, J = 6.9 Hz, 1H), 4.68 (bs, 1H), 6.68 (dd, J = 7.2 Hz, 7.4 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 7.22−7.40 (m, 4H), 8.1 (dd, J = 1.7 Hz, 8.2 Hz, 1H), 9.18 (bs, 1H).^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.6, 28.4, 112.0, 113.6, 117.0, 125.7, 126.1, 127.1, 127.3, 132.5. 135.0, 137.9, 143.6, 149.8, 171.0.

***N*-(2-*tert*-Butylphenyl)anthranilic Acid (9).**[23] Anthranilic acid **9** was produced from 2-chlorobenzoic acid, **1**, and 2-*tert*-butylaniline, **8**, as white crystals in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.41 (s, 9H), 6.65 (dd, J = 7.0 Hz, 7.9 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.17−7.28 (m, 4H), 7.47−7.50 (m, 1H), 8.02 (d, J = 8.1 Hz, 1H), 9.21 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ

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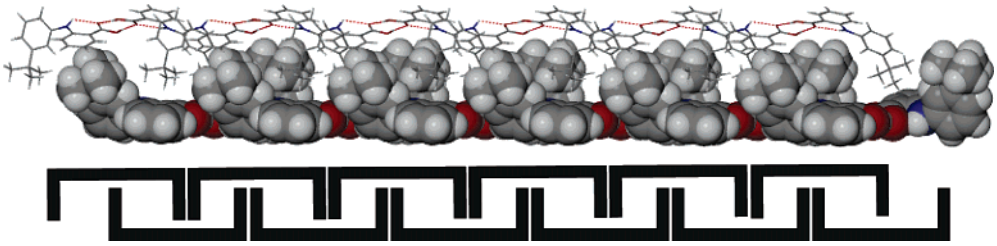

FIGURE 7. Formation of intertwined rods in the crystal structure of anthranilic acid **17** (top) and schematic illustration of the packing of the trans−syn dimers (bottom).

= 31.3, 35.7, 110.0, 114.8, 116.7, 126.6, 127.6, 128.1, 129.8, 133.1, 135.9, 139.4, 147.1, 151.4, 173.7.

***N*-(2-Biphenyl)anthranilic Acid (11).**[24] Acid **11** was obtained from 2-chlorobenzoic acid, **1**, and 2-aminobiphenyl, **10**, as a white solid in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.74 (bs, 1H), 6.72 (dd, J = 7.2 Hz, 7.7 Hz, 1H), 7.20−7.52 (m, 11H), 7.94 (d, J = 8.3 Hz, 1H), 9.18 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 111.4, 114.7, 117.7, 123.7, 124.8, 128.0, 128.6, 129.0, 129.7, 131.7, 133.1, 135.6, 136.9, 138.2, 139.5, 149.3, 174.2.

***N*-(2,6-Dimethylphenyl)anthranilic Acid (13).**[25] Amination of 2-chlorobenzoic acid, **1**, and 2,6-dimethylaniline, **12**, afforded acid **13** as a white powder in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.21 (s, 6H), 6.22 (d, J = 8.5 Hz, 1H), 6.66 (dd, J = 7.1 Hz, 7.1 Hz, 1H), 7.10−7.20 (m, 3H), 7.24 (dd, J = 7.6 Hz, 7.8 Hz, 1H), 8.04 (d, J = 7.6 Hz, 1H), 8.88 (bs, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ = 18.5, 112.0, 115.7, 126.3, 128.3, 132.8, 134.1, 135.6, 135.9, 137.0, 149.9, 173.8.

***N*-(3-Methylphenyl)anthranilic Acid (15).**[25] Compound **15** was obtained from 2-chlorobenzoic acid, **1**, and 3-methylaniline, **14**, as a white solid in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 6.79 (bs, 1H), 6.97 (d, J = 7.31 Hz, 1H), 7.00−7.15 (m, 2H), 7.25−7.30 (m, 2H), 7.38 (m, 1H), 8.10 (m, 1H), 9.25 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 21.0, 113.9, 117.3, 118.3, 122.0, 123.8, 129.2, 132.5, 134.0, 138.9, 140.5, 147.5.

***N*-(3-*tert*-Butylphenyl)anthranilic Acid (17).** Acid **17** was produced by amination of 2-chlorobenzoic acid, **1**, and 3-*tert*-butylaniline, **16**, as a white solid in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ =1.34 (s, 9H), 6.74 (dd, J = 0.7 Hz, 7.4 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 7.16−7.37 (m, 5H), 8.05 (dd, J = 1.5 Hz, 8.1 Hz, 1H), 9.29 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 31.0, 34.4, 112.4, 113.5, 117.2, 118.7, 118.9, 120.3, 129.0, 132.0, 134.1, 140.1, 147.4, 152.2, 170.1. Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58. Found: C, 67.27; H, 7.16; N, 4.93. (The HCl salt was formed by addition of hydrogen chloride (diethyl ether, 2.0 M) for elemental analysis.)

***N*-[3-(3′,5′-Dimethylbiphenyl)]anthranilic Acid (19).**[26] Anthranilic acid **19** was obtained from 2-chlorobenzoic acid, **1**, and 3-amino-3′,5′-dimethylbiphenyl, **18**, as an off-white solid in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.39 (s, 6H), 4.43 (s, 2H), 6.77 (dd, J = 7.1 Hz, 7.6 Hz, 1H), 7.02 (s, 1H), 7.22−7.50 (m, 8H), 8.06 (d, J = 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.7, 113.7, 114.4, 115.9, 117.5, 121.9, 122.1, 123.1, 125.2, 128.7, 129.3, 129.8, 133.9, 135.3, 138.5, 140.9, 143.0, 149.1. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.50; H, 5.99; N, 4.42. Found: C, 79.10; H, 6.23; N, 4.32.

***N*-(1-Naphthyl)anthranilic Acid (21).**[27] Anthranilic acid **21** was obtained from 2-chlorobenzoic acid, **1**, and 1-aminonaphthalene, **20**, as an off-white solid in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.73 (dd, J = 7.3 Hz, 7.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 7.23−7.29 (m, 1H), 7.46−7.51 (m, 4H), 7.75 (d, J = 7.6 Hz, 1H), 7.89−7.92 (m, 1H), 8.08 (m, 2H), 9.60 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ =110.5, 114.2, 117.5, 122.8, 123.5, 126.5, 126.5, 127.1, 129.1, 130.8, 133.1, 135.5, 136.0, 136.9, 151.2, 174.2.

***N*-(1-Pyrenyl)anthranilic Acid (23).** Amination of 2-chlorobenzoic acid, **1**, and 1-aminopyrene, **22**, afforded anthranilic acid **23** as an off-white solid in 73% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 6.94 (dd, J = 7.4 Hz, 7.4 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.43 (dd, J = 8.0 Hz, 7.4 Hz, 1H), 8.09−8.41 (m, 10H), 10.7 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 114.2, 118.1, 122.0, 122.1, 124.8, 124.9, 125.4, 125.7, 125.8, 126.4, 126.7, 127.2, 128.0, 128.2, 131.4, 131.7, 133.6, 134.6, 135.2, 148.8, 172.7. Anal. Calcd for $C_{23}H_{15}NO_2$: C, 81.88; H, 4.48; N, 4.15. Found: C, 81.63; H, 4.74; N, 4.32.

***N*-(4-Methoxyphenyl)anthranilic Acid (25).**[16] Anthranilic acid **25** was obtained from 2-chlorobenzoic acid, **1**, and 4-methoxyaniline, **24**, as a white powder in 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.83 (s, 3H), 6.68 (dd, J = 7.3 Hz, 7.3 Hz, 1H), 6.93 (dd, J = 8.6 Hz, 8.6 Hz, 3H), 7.18 (d, J = 8.6 Hz, 2H), 7.26−7.32 (m, 1H), 8.0 (d, J = 8.6 Hz, 1H), 9.60 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 55.2, 111.4, 112.8, 114.8, 116.3, 125.1, 131.9, 133.0, 134.2, 148.9, 156.1, 170.2.

***N*-(4-Nitrophenyl)anthranilic Acid (27).**[16] Anthranilic acid **27** was produced from 2-chlorobenzoic acid, **1**, and 4-nitroaniline, **26**, as a yellow solid in 87% yield. ^{1}H NMR (300 MHz, CD_3OD) δ = 7.22 (dd, J = 7.1 Hz, 7.8 Hz, 1H), 7.50 (m, 2H), 7.68−7.78 (m, 2H), 8.26 (d, J = 8.1 Hz, 1H), 8.36−8.36 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ = 118.1, 118.2, 118.8, 122.2, 127.1, 133.7, 135.3, 142.6, 145.4, 150.0, 171.5.

***N*-(3-Chlorophenyl)anthranilic Acid (29).**[28] Amination of 2-chlorobenzoic acid, **1**, and 3-chloroaniline, **28**, gave anthranilic acid, **29**, as an off-white solid in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.82 (dd, J = 7.3 Hz, 7.6 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.26−7.30 (m, 3H), 7.40 (dd, J = 7.6 Hz, 7.8 Hz, 1H), 8.06 (d, J = 7.3 Hz, 1H), 9.32 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 114.2, 114.7, 118.5, 118.8, 119.9, 122.1, 130.9, 132.0, 133.9, 134.0, 142.6, 145.8, 169.9.

***N*-(4-Carboxyphenyl)anthranilic Acid (31).**[27] Anthranilic acid **31** was obtained from 2-chlorobenzoic acid, **1**, and 4-aminobenzoic acid, **30**, using two equivalents of K_2CO_3 as a white solid in 98% yield. ^{1}H NMR (300 MHz, CD_3OD) δ = 7.00−7.06 (m, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.56−7.59 (m, 2H), 7.98 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.3 Hz, 1H), 9.91 (bs, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ = 115.3, 116.2, 117.9, 119.6, 123.5, 131.2, 132.0, 134.1, 144.6, 145.6, 167.1, 169.7.

***N*-(4-Methoxyphenyl)-4-nitroanthranilic Acid (33).**[26] Anthranilic acid **33** was obtained from 2-chloro-4-nitrobenzoic acid, **32**, and 4-methoxyaniline, **24**, as a yellow solid in 99% yield. ^{1}H NMR (300 MHz, CD_3OD) δ = 3.98 (s, 3H), 5.07 (bs, 1H), 7.05−7.20 (m, 3H), 7.32 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.8 Hz, 1H), 8.05

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(s, 1H). ^{13}C NMR (75 MHz, CD_3OD/DMSO-d_6 = 10:1) δ = 55.0, 116.1, 116.2, 121.6, 126.7, 126.9, 132.5, 134.4, 135.3, 149.8, 158.6, 170.6.

***N*-(4-Methoxyphenyl)-4-chloroanthranilic Acid (35).**[26] Compound **35** was produced from 2,4-dichlorobenzoic acid, **34**, and 4-methoxyaniline, **24**, as an off-white powder in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.83 (s, 3H), 6.87 (d, J = 9.2 Hz, 1H), 6.92 (d, J = 8.9 Hz, 2H), 7.15 (d, J = 8.9 Hz, 2H), 7.19−7.24 (m, 1H), 7.95 (d, J = 2.5 Hz, 1H), 9.05 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 56.2, 111.52, 115.4, 121.2, 126.9, 132.1, 133.1, 133.5, 135.5, 149.5, 157.7, 173.1.

***N*-(4-Methoxyphenyl)-4-bromoanthranilic Acid (37).** Amination of 4-bromo-2-chlorobenzoic acid, **36**, and 4-methoxyaniline, **24**, afforded anthranilic acid **37** as an off-white solid in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.83 (s, 3H), 6.82 (d, J = 9.0 Hz, 1H), 6.92 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 7.30−7.35 (m, 1H), 8.10 (s, 1H), 9.10 (bs, 1H).^{13}C NMR (75 MHz, DMSO-d_6) δ = 55.8, 113.5, 115.4, 120.1, 125.8, 131.4, 133.3, 133.7, 134.2, 148.3, 157.0, 169.8. Anal. Calcd for $C_{14}H_{12}BrNO_3$: C, 52.20; H, 3.75; N, 4.35. Found: C, 52.08; H, 3.72; N, 4.78.

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Supporting Information Available: Single-crystal structures, NMR spectra, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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