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Palladium- and Copper-Catalyzed Site Selective Monoamination of Dibromobenzoic Acid

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Abstract: The carboxylate anion has been used as a directing group in the aromatic amination of electronically equivalent aryl bromides to afford selective *ortho*-substituted derivatives (>99:1 selectivity; 60–80% yield) in the case of copper(I) catalysis. The solvent, base and equivalents of base were important factors in the success of this reaction. Complementary selectivity was achieved with palladium catalysis where the *para*-substituted derivatives were produced selectively (>99% selectivity, 70–80% yield).

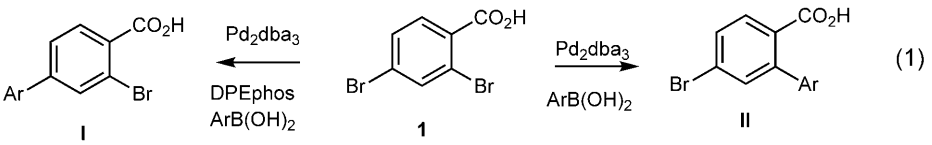
Keywords: carboxylate directed aminations; copper; 2,4-dibromobenzoic acid; palladium; selective aromatic aminations

Selective transformations and in particular directed processes have been in the focus of synthetic chemists for many decades. Such processes include directed *ortho*-metallation reactions, directed C–H activations and directed hydrogenations, to name a few.

The carboxylate anion has not featured as prominently as, for example, amide and carbamate functionalities in such directed processes due to its low "directing" power.[1] However, several research groups have shown recently the directing effect of the carboxylate anion in C–H activation processes, followed by further functionalizations,[2] while we have demonstrated the selective Kumada and Suzuki coupling of electronically similar halides (such as **1**).[3]

In the Suzuki coupling, we have shown that 2,4-dibromobenzoic acid (**1**) can be selectively coupled at the 2- or 4-positions depending on the choice of ligands [Scheme 1, Eq. (1)]. Thus in the presence of Pd_2dba_3 (0.5 mol%), in the absence of phosphine ligands, the 2-substituted product (**II**) can be obtained with >99:1 selectivity while addition of DPEphos (**8**) afforded the 4-substituted analogue (**I**) in >10:1 selectivity (Scheme 1).

In our attempt to extend the scope of the directing effect of the carboxylate in Pd-catalyzed amination reactions, we examined the amination of benzoic acid derivatives bearing reactive halides in the electronically comparable *ortho* and *para* positions.[4] In this preliminary report we describe the reactions of 2,4-dibromobenzoic acid **1** with electronically and stericaly diverse amines. Other dihalide derivatives are being examined and will be reported in due course. In this work complementary regioselectivity could not be achieved by varying the palladium ligand (dibenzylidineacetone *vs.* phopshine) however, complementary reactivity could be obtained by employing Cu for *ortho* substitution[5] while Pd afforded *para* substitution with the appropriate choice of ligands.



Scheme 1. Carboxylate-directed Suzuki coupling.

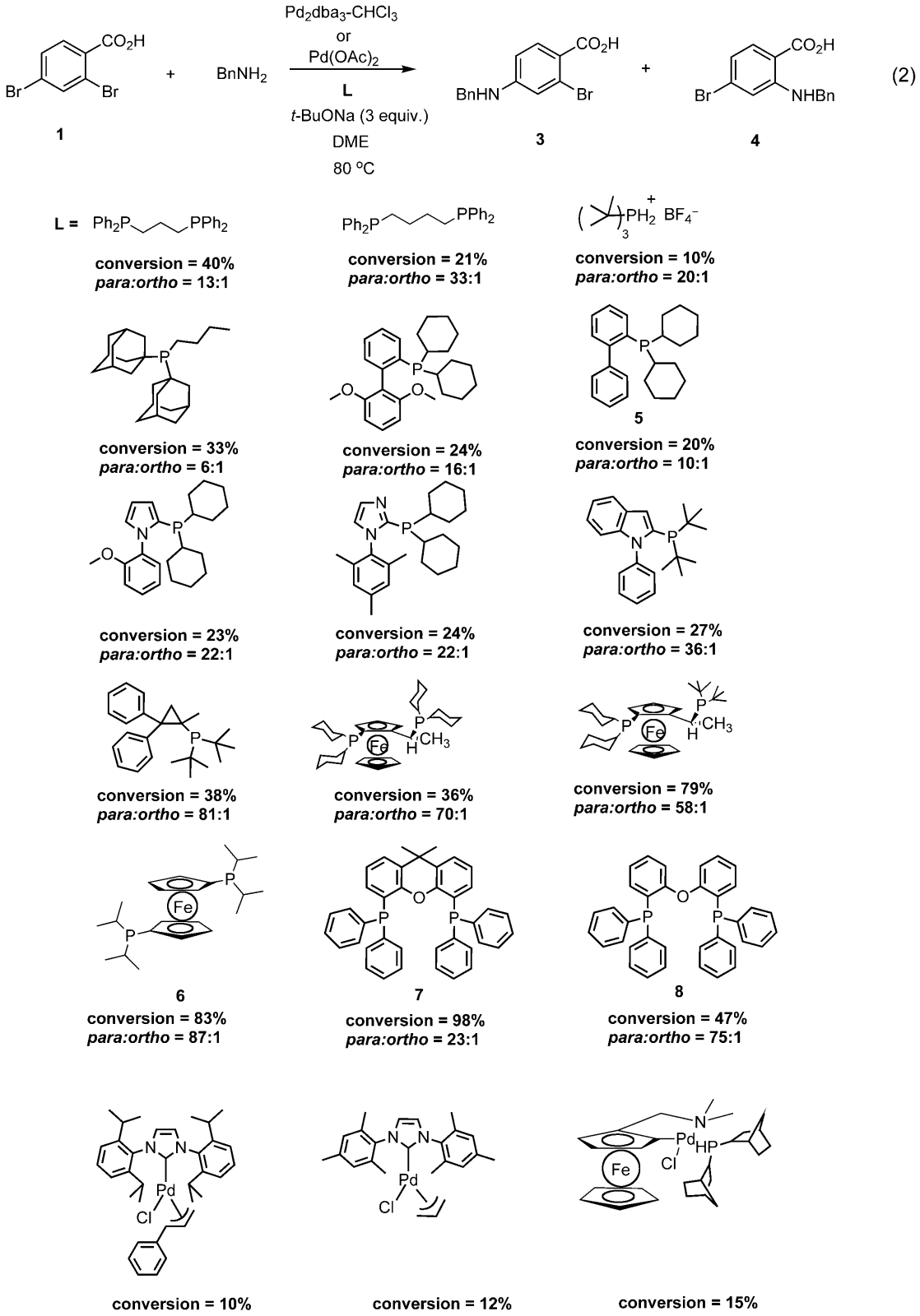


Figure 1. Ligand screen in the Pd-catalyzed amination of **1** with benzylamine.

As in our previous work, we began by reacting **1** with benzylamine (**2**) in the presence of Pd_2dba_3,[3b] under a variety of combinations of solvent and base [Figure 1, Eq. (2)], however no reaction was observed. In an attempt to effect this transformation, we initiated a screening exercise in two phases. A pre-

Table 1. Initial base and solvent screening for the coupling of **l** with benzylamine.

Entry	L[a]	Base	Solvent[b]	Conversion [%]	Ratio[c] **3**:**4**
1	BINAP	*t*-BuONa	DME	51	7:1
2	**7**	*t*-BuONa	DME	98	20:1
3	dppf	*t*-BuONa	DME	38	n.d.
4	**7**	*t*-BuOK	DME	34	n.d.
5	**5**	*t*-BuONa	DME	20	10:1
6	**7**	Cs_2CO_3	DME	0	n.d.
7	**7**	LiHMDS	DME	0	n.d.
8	$(t\text{-Bu})_3P$	*t*-BuONa	DME	0	n.d.
9	**8**	*t*-BuONa	DME	50	30:1
10	**8**	LiOH	DME	3	n.d.

[a] $Pd(OAc)_2$ (3 mol%) was used as the Pd source (Pd:L = 1:2 for monedentate, 1:1 for bidentate ligands).
[b] Toluene, THF and Me-THF gave inferior results.
[c] The ratio was determined by NMR integration.

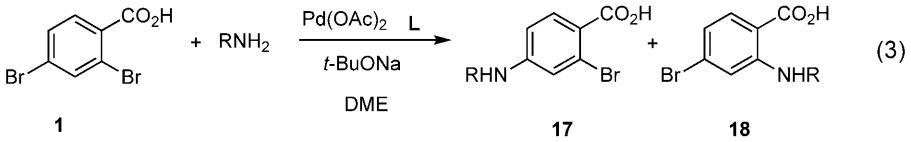
liminary screening of ligands, base and solvent was initiated to identify reasonable base and solvent combinations (Table 1) followed by a more thorough screen of ligands in a 96-well plate, using the best solvent and base combination identified in the preliminary screening, and finally the results from this screening were confirmed by scaling up the most promising reactions (Figure 1). The results exhibit some interesting trends.

First, all the catalyst systems that were investigated preferentially give the *para*-product **3**, which is consistent with our previous results.[3b] Second, popular ligands for aromatic amination reactions failed to give any product, and the same is true of imidazolinium carbene-based catalysts.[6,7]

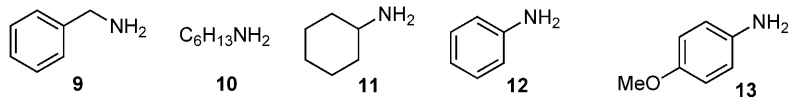
Third, the best results were obtained with ferrocenyl ligands (e.g., **6**, Figure 1)[8] while XantPhos[9] **7** also gave promising results as expected from our preliminary screen (Figure 1 and entry 2, Table 1). Last, the optimal base was *t*-BuO^- (Table 1) with the counterion playing a significant role (entries 2 and 4, Table 1). Thus, we decided to optimize the reaction, using the conditions shown in Eq. (3) (Table 2), with ligands **6** and **7** and examine its scope.

We confirmed that DME was the preferred solvent for both Xant-Phos (**7**), as shown before, and the ferrocenyl ligand **6** and that *t*-BuONa was the optimal

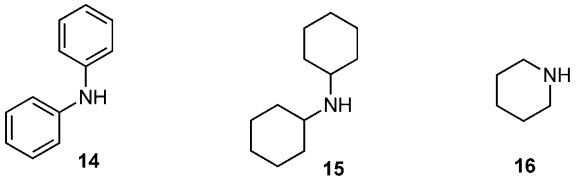
Table 2. Optimization and scope of the Pd-catalyzed amination of **1** with various amines.



1 17 18



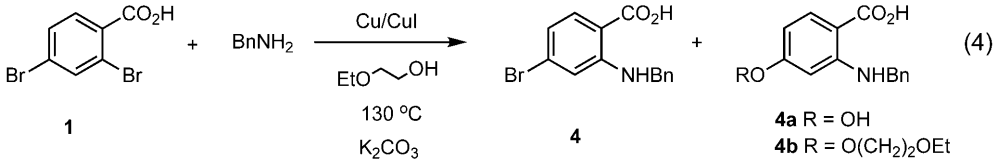
9 10 11 12 13



14 15 16

Entry	Amine	Base [equiv.]	Temperature [°C]	L (% Pd)	Conversion [%]	**17/18**	Yield [%]
1	**9**	2	80	**6** (5)	62	5	–
2	**9**	3	60	**6** (5)	95	100	79
3	**9**	2	80	**7** (3)	95	20	58
4	**10**	3	60	**6** (5)	95	100	82
5	**10**	3	80	**7** (3)	60	7	–
6	**10**	3	60	**6** (1)	95	100	78
7	**11**	3	60	**6** (5)	70	100	–
8	**11**	3	80	**7** (5)	100	100	59
9	**12**	3	60	**6** (5)	50	100	15
10	**13**	3	60	**6** (5)	50	100	27
11	**12**	3	80	**7** (5)	90	30	75
12	**14–16**	3	60	**6** (5)	0	–	–

Table 3. Optimization of the Cu-catalyzed cross coupling of **1** with $BuNH_2$ in DMA.



Entry	Cu(I) (mol%)	Base (equiv.)	Temperature/Time	Conversion	**4**	**4a**
1	CuI (10%)	K_2CO_3 (2)	25 °C/16 h	70%	53%	13%
2	CuI (10%)	Cs_2CO_3 (2)	25 °C/16 h	85%	57%	22%
3	CuI (5%)	Cs_2CO_3 (2)	25 °C/16 h	25%	18%	–
4	CuI (20%)	Cs_2CO_3 (2)	25 °C/16 h	98%	70%	25%
5	$Cu(acac)_2$ (10%)	Cs_2CO_3 (2)	25 °C/16 h	7%	–	–
6	CuBr (10%)	Cs_2CO_3 (2)	25 °C/16 h	20%	14%	–
7	CuI (10%)	Cs_2CO_3 (2)	50 °C/16 h	95%	80%	9%
8	CuI (10%)	Cs_2CO_3 (2)	70 °C/16 h	95%	86%	4%
9	Cu_2O (10%)	K_3PO_4 (2)	70 °C/16 h	100%	92%	2%
10	Cu_2O (5%)	K_3PO_4 (2)	70 °C/16 h	100%	94%	<1%

base. Finally, the equivalents of base, catalyst load and amine structure were examined, and the results are shown in Table 2. The data showed that the reaction was almost completely *para*-selective with both ferrocenyl catalyst **6** and Xant-phos **7** albeit the selectivity of the former is higher. The equivalents of base are critical to the success of the reaction, in both reactivity and selectivity. However unlike our previously reported Suzuki coupling reactions, where 2 equivalents of base were optimal, the amination rection required 3 equivalents of base to achieve nearly 100% *para*-selectivity (entries 1 and 2, Table 2).

Catalyst **6** performed well with unhindered alkylamines (entries 2 and 4, Table 2) while **7** was the catalyst of choice for hindered primary amines and aniline derivatives (entries 8 and 11, Table 2), so the two catalytic systems complement each other well. The ferrocenyl catalyst (**6**) is somewhat more reactive, requiring *ca.* 1 hour at 60 °C while Xant-phos (**7**) required overnight heating at 80 °C for complete conversion. The former catalysts can be used at <1% palladium load while *ca.* 3% is required for the latter. It should be noted that no diamination products were identified in any of the reactions.

Unfortunately, we were not successful in effecting the cross-coupling of secondary amines with a variety of substrates (entry 12, Table 2).

Having accomplished *para*-substitution selectively we then turned our attention to devising an *ortho*-selective process. Indeed, one of the earliest carboxylate-directed cross-coupling reactions is the Cu-catalyzed amination of 2-halobenzoic acids where significant rate acceleration is observed by the presence of the carboxylate ion *ortho* to the halogen.

This process, pioneered by Ullmann, was shown to be catalytic by Goldberg and extended to carbon nucleophiles by Hartley.[10] Although several subsequent studies have demonstrated the *ortho*-directing effect of the carboxylate in dihalobenzoic acid derivatives, the examples found in the literature use halides of different reactivity (e.g., F *vs.* Cl) to obtain the desired selectivity. Wolf et al. have studied[5b] the amination of *2,5-dibromobenzoic acid* obtaining the expected *ortho* coupling product. To the best of our knowledge, electronically comparable halides have not been studied to date.

Our investigation started with the reaction of benzylamine with **1** using the Wolf protocol (130 °C; 2-ethoxyethanol)[5b] developed for 2,5-dibromobenzoic acid. The starting material was completely consumed and *ca.* 50% (HPLC area%) of the product **4** was obtained [Table 3, Eq. (4)]. However, under the drastic conditions of the reaction the product reacts with adventitious water, and indeed we observed significant amounts of the aminophenol **4a** (*ca.* 20%) as well as the product originating from solvent attack **4b** [*ca.* 12%; Eq. (4)].

As a consequence we sought to develop conditions that would exclude nucleophilic solvents and, in a brief study, focused on polar aprotic solvents such as *N*-methylpyrrolidinone, *N*,*N*-dimethyl formamide and dimethyl acetamide (DMA).

Since we found no substantial difference between these three solvents, we chose DMA for further optimization, and the most relevant results are outlined in Table 3.

Surprisingly, the reaction progressed well even at room temperature, giving up to 85% conversion when Cs_2CO_3 was used as the base (Table 3, entries 1 and 2). Only the *ortho*-product **4** was observed. However, the aminophenol **4a** was still formed in substantial amounts. CuI initially appeared to be the best cata-

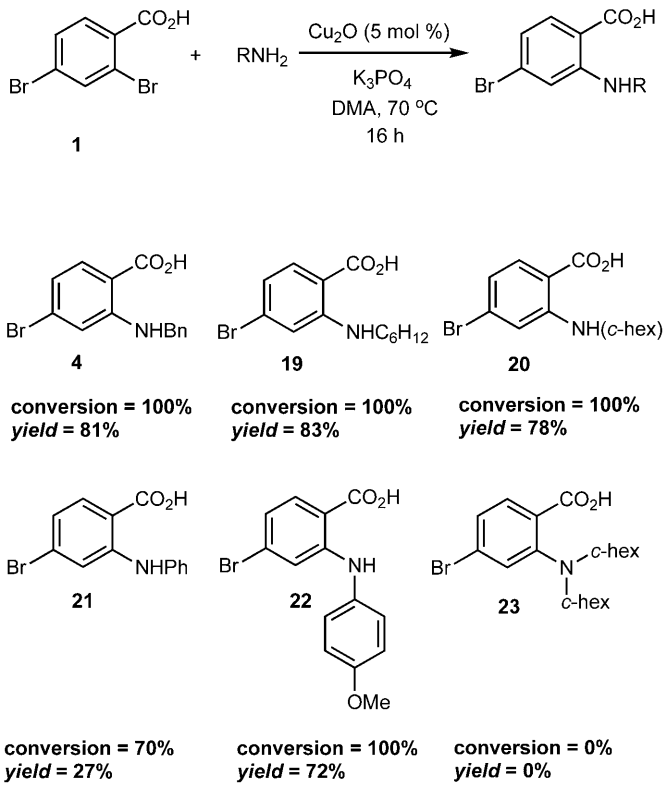


Figure 2. Scope of the Cu-catalyzed *ortho*-amination of **1a**.

lyst, but up to 20% was needed for complete conversion (Table 3, entries 2–4).

Other Cu sources were not useful (Table 3, entries 5 and 6) and, even more surprisingly, commonly used Cu-amine-derived catalysts were also unsuccessful.[11] Finally, when the reaction was performed at a higher temperature (Table 3, entry 7), the reaction proceeded to *ca.* 95% conversion with reasonable catalyst load (10%) while forming only 9% of **4a** as compared to 22% at room temperature (Table 3; entries 7 *versus* 2). Finally, our screen revealed that Cu_2O and K_3PO_4 was the ideal combination of catalyst and base (Table 3, entry 10), giving 94% of the desired product **4** with only traces of the aminophenol **4a**.

We examined the scope of the reaction using these optimized conditions and the results are shown in Figure 2. The reaction appears to be general with primary alkylamines to afford *ortho*-aminated benzoic acids (**4**, **19** and **20)** in good isolated yield. Aniline is not a good substrate, affording the desired adduct (**21**) in low yield, however, electron-rich anilines do give useful yields of the desired *ortho*-product (e.g., **22**). Amines **14**–**16** again fail to react under our reaction conditions as was the case in the Pd-catalyzed reaction. We are actively investigating conditions that will effect the reaction with secondary amines.

In summary, we have demonstrated that the carboxylate ion can have a pronounced effect in aromatic amination of electronically similar aromatic bis-bromides as shown in the case of 2,4-dibromobenzoic acid.[12] We have further shown that this amination reaction can be induced to give selectively the ortho or para product by simply tuning the catalyst system from palladium to copper.

Experimental Section

Representative Experimental Procedures for the Preparation of Compounds 17–9 to 17–13 (RNH_2 = 9–13)

2,4-Dibromobenzoic acid (0.227 g, 1 mmol), $BnNH_2$ (0.161 g, 1.5 mmol) and *t*-BuONa (0.28 g, 3 mmol) were added under nitrogen into a Schleck tube followed by dimethoxyethane (2.0 mL). The mixture was degassed thoroughly by bubbling nitrogen for 30 min. 1,1-Bis(diisopropylphosphino)ferrocene (0.024 g, 0.05 mmol) and $Pd(OAc)_2$ (0.011 g, 0.05 mmol) were added in sequence under nitrogen. The mixture was heated to 60 °C and stirred for 16 h at that temperature until LC-MS showed the complete consumption of 2,4-dibromobenzoic acid. The mixture was cooled to 0 °C and 2NHCl was added to pH 4 ~ 5. The mixture was concentrate to remove solvent and water (10.0 mL) was added followed by EtOAc (20.0 mL × 2). The combined organic layer was washed with brine (20 mL × 2), dried over Na_2SO_4, filtered and concentrated to afford a yellow residue which was purified by chromatography on silica gel using EtOAc/heptane (v/v 1.3/1) as eluent.^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.29 (2H, s, CH_2), 6.52 (1H, dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, Ar), 6.83 (1H, d, J = 2.0 Hz, Ar), 7.17–7.28 (5H, m, Ar), 7.70 (1H, d, J = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 109.9, 116.7, 116.9, 123.6, 126.5, 126.6, 128.0, 133.3, 138.5, 152.4, 167.5; HR-MS: m/z = 306.0116, calcd. for $C_{14}H_{12}BrNO_2$ $[M+H]^+$: 306.1456.

2-Bromo-4-*n*-hexylaminobenzoic acid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.9 (3H, triplet, J = 6.8 Hz, CH_3), 1.23–1.39 (6H, m, CH_2), 1.58–1.62 (2H, m, CH_2), 3.12 (2H, triplet, J = 6.8 Hz, CH_2), 6.46 (1H, dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, Ar), 6.81(1H, d, J = 2.0 Hz, Ar), 7.92(1H, d, J = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.5, 26.6, 29.1, 31.4, 43.2, 110.4, 110.6, 116.2, 117.3, 117.5, 125.3, 134.7, 152.3, 169.9; HR-MS: m/z = 300.0584, calcd. for $C_{13}H_{18}BrNO_2$ $[M+H]^+$: 300.1915.

2-Bromo-4-cyclohexylaminobenzoic acid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16–1.42 (5H, m, CH_2), 1.64–1.78 (3H, m, CH_2), 2.01–2.04 (2H, m, CH_2), 3.27–3.32 (1H, m, CH_2), 6.42 (1H, dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, Ar), 6.80 (1H, s, Ar), 7.91 (1H, d, J = 8.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.7, 25.5, 29.6, 32.9, 51.2, 110.7, 115.8, 117.7, 125.3, 134.8, 151.2, 169.1; HR-MS: m/z = 298.0428, calcd. for $C_{13}H_{16}BrNO_2$ $[M+H]^+$: 298.1756.

2-Bromo-4-phenylaminobenzoic acid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.96 (1H, dd, J1 = 2.4 Hz, J2 = 8.8 Hz, Ar), 7.02 (1H, triplet, J = 7.2 Hz, Ar), 7.16 (2.0H, d, J = 7.6 Hz, Ar), 7.24 (1H, d, J = 2.4 Hz, Ar), 7.31 (2H, dd, J_1 = 7.2 Hz, J_2 = 8.4 Hz, Ar), 7.81 (1H, d, J = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 112.2, 119.3, 119.8, 120.1, 122.6, 123.5, 129.0, 133.3, 140.8, 149.0, 167.4; HR-MS; m/z = 291.9958, calcd. for $C_{13}H_{10}BrNO_2$ $[M+H]^+$: 292.1280.

2-Bromo-4-(4-methoxyphenylamino)-benzoic acid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.77 (3H, s, CH_3), 6.88–6.92 (2H, m, Ar), 7.06–7.11 (3H, m, Ar), 7.77 (2H, d, J = 8.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 54.5, 111.2, 114.2, 118.2, 118.5, 123.6, 123.7, 133.3, 133.5, 150.5, 156.4, 167.5; HR-MS: m/z = 322.0064, calcd. for $C_{14}H_{12}BrNO_3$ $[M+H]^+$: 322.1540.

Representative Experimental Procedures for the Preparation of Compounds 4 and 19–22

Solid 2,4-dibromobenzoic acid (0.455 g, 2 mmmol), $BnNH_2$ (0.321 g, 3 mmol) and K_3PO_4 (0.848 g, 4 mmol) were placed in a Schlenck tube under nitrogen and *N*,*N*-dimethylacetamide was added (4.0 mL). The mixture was degassed by bubbling nitrogen for 30 min. Cu_2O (0.014 g, 0.1 mmol) was added under nitrogen and the mixture was heated to 70 °C and stirred at that temperature for 16 h. Upon completion (LC-MS showed that 2,4-dibromobenzoic acid had been consumed completely) the mixture was cooled to 25 °C and filtered through Celite to remove the solids. Water (20.0 mL) was added to the mixture at 25 °C, the pH was adjusted to 4–5 by addition of 2N HCl and the mixture was extracted with EtOAc (25.0 mL × 2). The combined organic layer was washed with brine (30 mL × 2), dried over Na_2SO_4, filtered and concentrated to afford a solid residue which was purified by chromatography on silica gel using EtOAc/heptane (v/v 1.5/1) as eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.42 (2H, s, CH_2), 6.74 (1H, dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, Ar), 6.81 (1H, d, J = 1.6 Hz, Ar),7.26–7.37 (5H, m, Ar), 7.81 (1H, d, J = 8.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 46.9, 107.8, 114.5, 118.5, 127.0, 127.5, 128.8, 131.0, 133.8, 137.8, 152.1, 172.9; HR-MS: m/z = 306.0116, calcd. for $C_{14}H_{12}BrNO_2$ $[M+H]^+$: 306.1456.

4-Bromo-2-*n*-hexylaminobenzoic acid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.90 (3H, triplet, J = 7.2 Hz,CH_3), 1.31–1.33 (4H, m, CH_2), 1.37–1.42 (2H, m, CH_2), 1.63–1.70 (2H, m, CH_2), 3.15 (2H, triplet, J = 7.2 Hz, CH_2), 6.68 (1H, dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, Ar), 6.81 (1H, d, J = 1.6 Hz, Ar), 7.77 (1H, d, J = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.5, 26.7, 28.8, 31.4, 42.8, 107.1, 114.1, 117.6, 130.9, 133.8, 152.3, 172.8; HR-MS: m/z = 300.0586, calcd. for $C_{13}H_{18}BrNO_2$ $[M+H]^+$: 300.1915.

4-Bromo-2-cyclohexylaminobenzoic acid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22–1.45 (5H, m, CH_2), 1.61–1.64 (1H, m, CH_2), 1.74–1.78 (2H, m, CH_2), 1.97–2.03 (2H, m, CH_2), 3.31–3.36 (1H, m, CH), 6.65 (1H, dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, Ar), 6.82 (1H, d, J = 1.6 Hz, Ar), 7.76(1H, d, J = 8.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.5, 25.6, 32.6, 50.6, 107.0, 114.3, 117.36, 117.37, 130.8, 134.0, 151.4, 172.7; HR-MS: m/z = 298.0429, calcd. for $C_{13}H_{16}BrNO_2$ $[M+H]^+$: 298.1756.

4-Bromo-2-phenylaminobenzoic acid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.78 (1H, dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, Ar), 7.12 (1H, triplet, J = 7.2 Hz Ar), 7.24 (1H, s, Ar), 7.26(1H, s, Ar),7.31 (1H, d, J = 1.6 Hz, Ar), 7.40 (2H, triplet, J1 = 8.0 Hz, J2 = 7.6 Hz, Ar), 7.87 (1H, d, J = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 108.9, 116.3, 120.3, 123.7, 124.9, 129.7, 130.5, 133.7, 139.4, 149.8, 172.3; HR-MS: m/z = 291.9959, calcd. for $C_{13}H_{10}BrNO_2$ $[M+H]^+$: 292.1280.

4-Bromo-2-(4-methoxyphenylamino)-benzoic acid: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 3.77 (3H, s, CH_3), 6.72 (1H, dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, Ar), 6.87 (2H, d, J = 8.8 Hz, Ar), 6.97 (1H, d, J = 1.6 Hz, Ar), 7.09 (2H, d, J = 9.2 Hz, Ar), 7.76 (1H, d, J = 8.4 Hz, Ar); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 55.5, 114.9, 115.9, 119.5, 126.7, 130.5, 132.0, 133.7, 151.2, 157.5, HR-MS: m/z = 322.0062, calcd. for $C_{14}H_{12}BrNO_3$ $[M+H]^+$: 322.1540.

References

[1] Directed *ortho*-metallation eactions: a) E. J.-G. Anctil, V. Snieckus, *J. Organomet. Chem.* **2002**, *653*, 150; b) E. J.-G. Anctil, V. Snieckus, in: *Metal-Catalyzed Cross Couping Reactions*, 2nd edn., (Eds.: F. Diederich, A. De Meijere), Wiley, New York, **2004**, pp 761–814; c) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206. Directed hydrogenations: d) R. H. Crabtree, M. W. Davies, *J. Org. Chem.* **1986**, *51*, 2655.

[2] Reviews: a) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439; b) J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041.

[3] a) I. N. Houpis, C. Huang, U. Nettekoven, J. G. Chen, R. Liu, M. Canters, *Org. Lett.* **2008**, *10*, 5601; b) I. N. Houpis, J.-P. Van Hoeck, U. Tilstam, *Synlett* **2007**, *14*, 2179; c) I. N. Houpis, R. Liu, Y. Wu, Y. Yuan, Y. Wang, U. Nettekoven, *J. Org. Chem.* **2010**, *75*, 6965.

[4] Selected reports of the carboxylate directing effect see: a) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1159; b) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407; c) D. Tanaka, S. P. Stuart, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323; d) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510; e) T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 5293; *Angew. Chem. Int. Ed.* **2008**, *47*, 5215; f) H. A. Chiong, Q.-N. Pham, O. J. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879; g) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; h) A. V. Kalinin, J. F. Bower, P. Riebel, V. Snieckus, *J. Org. Chem.* **1999**, *64*, 2986; i) review: B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949.

[5] Significant information is available in the literature. Some recent examples: a) X. Liu, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem.* **2009**, *121*, 354; *Angew. Chem. Int. Ed.* **2009**, *48*, 348; b) S. Liu, J.-P. C. Pestano, C. Wolf, *Synthesis* **2007**, 3519; c) M. L. Docampo, R. F. Pellon, A. Estevez-Broen, A. G. Ravelo, *Eur. J. Org. Chem.* **2007**, 4111; d) Review: K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428.

[6] E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2842; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768.

[7] For a thorough review of modern Pd-catalyzed amination reaction of aryl halides and amines and references for the use of biaryl phosphine ligands in several metal catalyzed reactions see: a) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; b) A. R. Mucci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131; c) J. F. Hartwig, in: *Handbook of Organoaplladium Chemistry in Organic Syn-*

thesis, (Ed.: E. Negishi), Wiley-Interscience, New York, **2002**, Vol. 1, p 1051.
[8] Ferrocenyl-based ligands have been successfully used to effect amination reactions: a) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217; b) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 7369.
[9] Y. Guari, D. S. Van Es, J. N. H. Reek, P. C. J. Kamer, P. Van Leeuwen, *Tetrahedron Lett.* **1999**, *40*, 3789.
[10] For a thorough review, see: J. Lindley, *Tetrahedron* **1984**, *40*, 1433.
[11] A number of such ligands were investigated with no success; a) A. Shafir, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 8742 and references cited therein; b) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; c) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428.
[12] A thorough mechanistic investigation has not been undertaken, however we believe that in the case of Cu the selectivity is determined by the formation of the Cu-metallacycle **A**. In the case of Pd, in the absence of phosphine ligands, we have rationalized previously (I. N. Houpis, R. Liu, Y. Wu, Y. Yuan, Y. Wang, U. Nettekoven, *J. Org. Chem.* **2010**, *75*, 6965) that a similar palladacycle **B** is formed in the case of the Suzuki reaction . In the presence of phophines, steric effects direct the oxidative addition to the less hindered *para*-position (**C**).