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Direct Intermolecular Aniline *Ortho*-Arylation via Benzyne Intermediates

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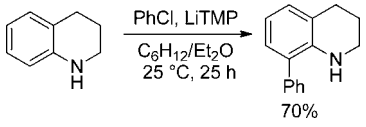
ABSTRACT



A method for direct, transition-metal-free *ortho*-arylation of anilines by aryl chlorides, bromides, fluorides, and triflates has been developed. This methodology provides the most direct approach to 2-arylanilines since no protecting or directing groups on nitrogen are required. The arylation is functional-group tolerant, with alkene, ether, trifluoromethyl, dimethylamino, carbonyl, chloro, and cyano functionalities tolerated. Phenylation of enantiopure binaphthyldiamine affords a product with >99% ee.

The most efficient routes to many structures involve direct functionalization of carbon−hydrogen bonds. The past few years have witnessed spectacular progress in developing C−H bond functionalization methodologies.[1] However, some issues are still unresolved. For example, direct arylation of aniline derivatives in most cases requires either a protecting or directing group on nitrogen.[2] Palladium-catalyzed *ortho*-arylation of anilides offers a short pathway to 2-aminobiphenyls or terphenyls; however, installation followed by removal of a directing group adds two steps to the synthetic sequence.[2a−c] Additionally, directing group removal requires harsh conditions. Gevorgyan has recently reported a method for intramolecular palladium-catalyzed arylation of anilines by employing a temporary silyl tether.[2d] The silyl group removal can be performed under mild conditions. However, several extra steps are required to install and remove the tether. A recent paper by Greaney describes *o*-arylation of *N*-tritylanilines by benzynes generated from silyl aryl triflates. The reaction proceeds by an ene mechanism.[2f] However, the reaction is not applicable for arylation of *N*- and *o*-substituted anilines. Additionally, only a few silyl aryl triflates are commercially available thus limiting the practical applications of this procedure. Only a few articles describe direct arylation of free anilines.[3] Aminobiphenyls have been synthesized by Ti-catalyzed arylation of free anilines by diazonium salts.[3a] Isomer mixtures were obtained in many cases. A selective transition-metal-free *para* arylation of *N*-substituted anilines has been recently reported by employing diaryliodonium salt electrophiles.[3b] Selective, direct *o*-arylation of unprotected anilines has not yet been disclosed. We report here a method for direct aniline *o*-arylation by aryl halides that proceeds via aryne intermediates.

We have recently reported direct *C*-arylation of heterocycles, arenes, alkynes, and phenols proceeding via benzyne

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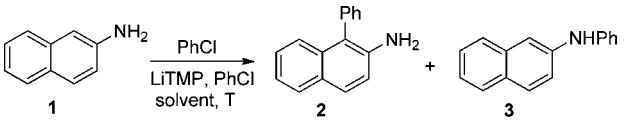
intermediates. It was observed that the amount of *C*-arylation is dependent on the solvent.[4] It is well-known that *N*-arylation of NH-anilines can be accomplished by benzynes[5a,b] and that the *N*-arylation products are sometimes accompanied by minor amounts of *C*-arylation.[5c,d] Since, as described above, the ratio of *C*- vs *O*- or *N*-arylation can be tuned by changing the reaction solvent, we decided to explore aniline *o*-arylation. Arynes can be generated from silyl aryl triflates under nearly neutral conditions at room temperature.[6] Unfortunately, these starting materials are expensive, and only a few of them are commercially available. To increase the applicability of the arylation, we decided to use readily accessible and cheap aryl chlorides as aryne sources. Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) base was used to retard the reaction of arynes with base.[7a]

The optimization of reaction conditions was carried out for the 2-naphthylamine **1** arylation by chlorobenzene (Table 1). The ratio of *C*-arylation vs *N*-arylation was found to be dependent on solvent, base, and **1**/base ratio. Reactions in THF afforded *N*-arylation with only minor amounts of *C*-arylation product formed (entries 1 and 2). Arylation in Et_2O also gave predominately *N*-arylation (entry 3). If LDA was used instead of LiTMP, clean formation of *N*-phenyl-2-naphthylamine was observed (entry 4). Lowering the reaction temperature to −20 °C resulted in good *C*-arylation selectivity in diethyl ether (entry 5). Reactions in pentane at 40 °C gave substantial amount of *C*-arylation (entries 6−7). However, competitive formation of PhTMP was observed. Use of pentane/Et_2O mixtures increased the *C*/*N*-arylation ratio (entries 8−10). The best results were obtained in cyclohexane/diethyl ether mixed solvent at 25−50 °C (entries 11, 13, 14) by using **1**/LiTMP ratio of 1/1.8. Sensitive substrates can be arylated at low temperature in diethyl ether.

The reaction scope with respect to aryl halides is presented in Table 2. Fluoro-, chloro-, and bromobenzene can be used in the arylation of 2-naphthylamine (entries 1−3). Interestingly, the arylations are selective for 1-position of 2-naphthylamine. 2-Chlorostyrene affords the arylation product in a good yield (entry 4). As expected, substitution occurs mainly at 3-position of the vinylphenyl group, with less than 3% of 1-(2-vinylphenyl)-2-naphthylamine formed.[7b−e] 2-Chloroanisole, 2-chlorobenzotrifluoride, and 2-bromobiphenyl

Table 1. Optimization of Reaction Conditions[a]



entry	**1**/PhCl/base	*T*, °C	solvent	**2**/**3**[b]
1	1/2/3.6	25	THF	1/8 (10)
2	2/1/3.6	25	THF	1/3 (12)
3	1/2/3.6	25	Et_2O	1/5 (16)
4[c]	1/2/3.6	25	Et_2O	1/50 (<2)
5	2/1/3.6	−20	Et_2O	11/1 (27)
6	1/2/3.6	40	C_5H_{12}	1/2 (29)
7	2/1/3.6	40	C_5H_{12}	2/1 (35)
8	1/2/3.6	25	C_5H_{12}/Et_2O 20:1	1.3/1 (43)
9	2/1/3.6	25	C_5H_{12}/Et_2O 20:1	12/1 (27)
10	2/1/3.6	25	C_5H_{12}/Et_2O 1:1	9/1 (64)
11	2/1/3.6	25	C_6H_{12}/Et_2O 1:1	18/1 (74)
12	1/2/3.6	25	C_5H_{12}/Et_2O 1:1	1/2.2 (25)
13	3/1/4.8	50	C_5H_{12}/Et_2O 14:1	50/1 (78)
14	3/1/4.8	50	C_5H_{12}/Et_2O 1:1	5/1 (50)

[a] Total volume of solvent 0.9 mL, 0.25 mmol scale, 24 h; 12 h for entry 5. See the Supporting Information for details. [b] Ratio **2**/**3**; GC yield of **2** (%) in parentheses. [c] LDA base.

are reactive, and the corresponding arylation products were obtained in good yields (entries 5−7). Arylation can also be achieved by employing polycyclic aromatic chlorides (entries 8 and 9). 2-Chlorodimethylaniline affords arylation product in moderate yield (entry 10). If introduction of a chloro-substituted aryl moiety is required, 3-chlorophenyl triflate at low temperature can be employed (entry 11). Arylation by 3-bromobenzoate ester results in substitution at 2-position of aryne, presumably by initial formation of 2-naphthylamide of 3-bromobenzoic acid (entry 12). 4-Chlorotoluene gave nearly equal mixture of isomeric products (entry 13).

The 2-naphthylamine arylation occurs selectively at the 1-position. In that context, observations by Pierini and Rossi may be informative.[8] They have reported the photostimulated reaction of unactivated aryl bromides and iodides with 2-naphthylamide. Substitution occurred at *N*- and 1-positions of 2-naphthylamine. The authors explain the arylation selectivity by the relative basicities of sites in an ambident naphthylamide anion.

Groups that can coordinate a lithium cation afford reduced *C*/*N* selectivities. Lower reaction temperatures have to be used to obtain better yields and arylation selectivities. For example, presence of the dimethylamino substituent reduces *C*/*N* arylation selectivity from >50/1 (entry 2, Table 2) to about 11/1 (entry 10, Table 2) even if the temperature is lowered to −30 °C.

The reaction scope with respect to anilines is presented in Table 3. *N*-Alkyl- and arylanilines are reactive (entries 1−5). Specifically, anilines possessing *N*-methyl-, phenyl,

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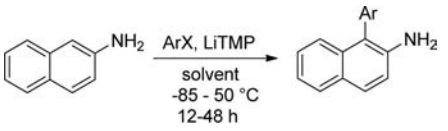
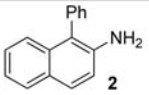
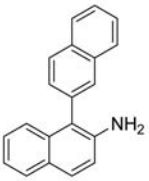
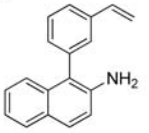
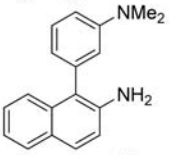
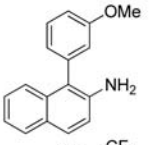
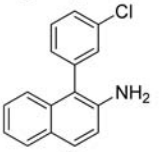
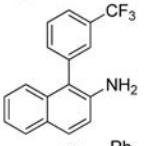
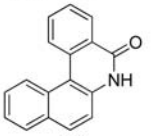
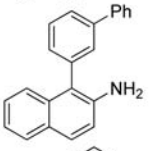
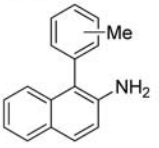
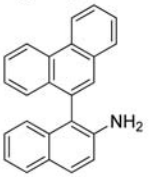
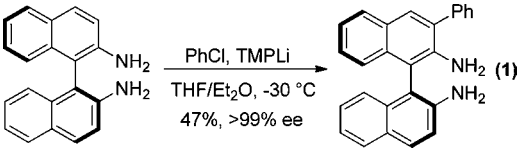
Table 2. Arylation of 2-Naphthylamine[a]



entry	ArX	product	yield (%)	entry	ArX	product	yield (%)
1[b]	PhF	 **2**	68	9[e]	2-chloro-naphthalene		82
2[b]	PhCl	**2**	72				
3[b]	PhBr	**2**	70				
4[c]	2-chlorostyrene		70	10[f]	2-chloro-*N*,*N*-di-methylaniline		61
5[c]	2-chloroanisole		67	11[g]	3-chlorophenyl triflate		50
6[c]	2-chlorobenzo-trifluoride		65	12[h]	*t*-butyl-3-bromo-benzoate		70
7[d]	2-bromobiphenyl		70	13[d]	4-chlorotoluene		78
8[d]	9-chloro-phenanthrene		71				

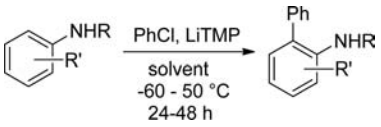
[a] 2-Naphthylamine (1−2 mmol), ArX (0.5 mmol), LiTMP (1.8−3.4 mmol), solvent (1.4−3 mL), −85 to +50 °C, 12−48 h. Yields are isolated yields. [b] Cyclohexane/Et_2O (14/1), 25 °C, < 5% *N*-arylation product observed in crude reaction mixture. [c] Et_2O, −25 °C, ca. 10% *N*-arylation. [d] Cyclohexane/Et_2O (14/1), 50 °C, < 10% *N*-arylation. [e] Cyclohexane/Et_2O (1/1), 25 °C, < 5% *N*-arylation. [f] Et_2O, −30 °C, 8% *N*-arylation. [g] THF, −85 °C, 7% *N*-arylation. [h] Cyclohexane/Et_2O (1/1), −35 °C, LDA base.

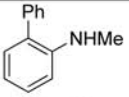
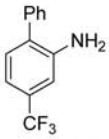
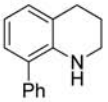
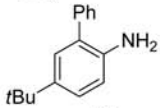
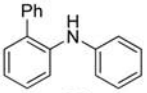
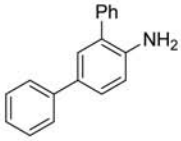
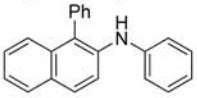
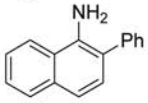
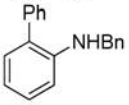
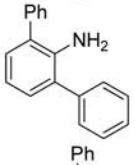
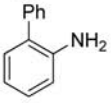
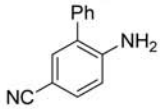
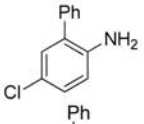
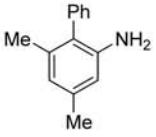
and benzyl substituents all give products in good to excellent yields (entries 1, 3, and 5). 1,2,3,4-Tetrahydroisoquinoline is arylated at the 7-position in good yield (entry 2). Unsubstituted anilines can be selectively and efficiently monoarylated (entries 6−14). Thus, aniline can be *ortho*-phenylated in a moderate yield (entry 6). Arylation of 3-aminobenzotrifluoride affords about 3/1 mixture of isomers. 2-Phenyl-5-trifluoromethylaniline was isolated in 50% yield (entry 9). 3,5-Dimethylaniline is arylated in the *ortho*-position in a good yield (entry 8). Palladium-catalyzed arylation of anilides that possess *meta*-substituents is not efficient and thus structures such as the one generated in entry 8 typically cannot be accessed by using transition-metal catalysis.[2a,b] *p*-Substituted anilines are arylated in good yields (entries 7, 10, and 11). 1-Naphthylamine is arylated at the 2-position (entry 12). 2-Aminobiphenyl can be arylated at 6-position affording 2,6-diphenylaniline (entry 13). 2,6-Diarylanilines are used in the synthesis of ligands for Brookhart-type transition-metal catalyzed olefin polymerization.[9] The reaction tolerates chloro- and cyano substituents (entries 7 and 14). Arylation of enantiopure binaphthyldiamine afforded the monoarylation product in 47% yield and > 99% ee (eq 1).



The reaction is selective (> 50/1) for *ortho*-arylation as opposed to *para*-arylation. For entries 1, 6, and 13, Table 3, the crude reaction mixtures were analyzed by GC for the

Table 3. Arylamine Phenylation[a]



entry	amine	product	yield (%)	entry	amine	product	yield (%)
1[b]	PhNHMe		62	9[d,f]	3-aminobenzotrifluoride		50
2[b]	1,2,3,4-tetrahydroquinoline		70	10[d]	4-*t*-butylaniline		60
3[b]	diphenylamine		78	11[d]	4-aminobiphenyl		67
4[b]	*N*-phenyl-2-naphthylamine		80	12[b]	1-naphthylamine		85
5[c]	*N*-benzylamine		70	13[d]	2-aminobiphenyl		70
6[d]	aniline		55	14[g]	4-cyanoaniline		65
7[e]	*p*-chloroaniline		60				
8[d]	3,5-dimethylaniline		70				

[a] Amine (1−2 mmol), PhCl (0.5 mmol), LiTMP (1.8−3.4 mmol), solvent (1.4−3 mL), −60 to +50 °C, 24−48 h. Yields are isolated yields. See the Supporting Information for C/N ratios. [b] Cyclohexane/Et_2O (1/1), 25 °C. [c] Pentane/THF (36/1), 25 °C. [d] Cyclohexane/Et_2O (14/1), 50 °C. [e] Pentane/Et_2O (1/1), −50 °C, PhOTf. [f] Isomeric 2-phenyl-3-trifluoromethylaniline also isolated (17%). [g] THF/Et_2O (1:1), −60 °C.

presence of *p*-phenyl derivatives (comparison with authentic commercial samples). No products arising from *p*-arylation were observed.

The amount of *N*- vs *C*-arylation is dependent on solvent coordination ability, aniline/LiTMP base ratio, and reaction temperature. These features point to different reactivity of intermediate lithium anilide/LiTMP aggregates as the reason for switch in arylation regioselectivity. Because of the complexity of lithium anilide solution-state structures and insolubility of LiCl additive in reaction mixture, further mechanistic speculations are premature at this point.[10]

In conclusion, we have developed a method for direct, transition-metal-free *ortho*-arylation of anilines by aryl chlorides, bromides, fluorides, and triflates. This methodology provides the most direct approach to 2-arylanilines since no protecting or directing groups on nitrogen are required. Easily available aryl chlorides can be used as the coupling partner. The arylation is functional-group tolerant, with alkene, ether, trifluoromethyl, dimethylamino, carbonyl, chloro, and cyano functionalities tolerated.

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Supporting Information Available. Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.