

Direct Intermolecular Aniline *Ortho*-Arylation via Benzyne Intermediates

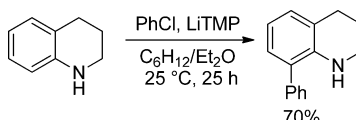
Thanh Truong and Olafs Daugulis*

Department of Chemistry, University of Houston, Houston, Texas 77204-5003,
United States

olafs@uh.edu

Received October 18, 2012

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 binaphthylidiamine 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 benzyne 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

(1) Reviews: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (g) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (h) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 677. (i) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(2) (a) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (b) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720. (c) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (d) Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2009**, *131*, 10844. (e) Phipps, R. J.; Gaunt, M. *Science* **2009**, *323*, 1593. (f) Piralì, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1006. (g) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554. (h) Scarborough, C. C.; McDonald, R. I.; Hartmann, C.; Sazama, G. T.; Bergant, A.; Stahl, S. S. *J. Org. Chem.* **2009**, *74*, 2613. (i) Brasche, G.; Garcia-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207.

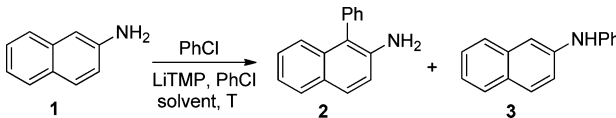
(3) (a) Wetzel, A.; Ehrhardt, V.; Heinrich, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 9130. (b) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458.

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 benzyne^{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 aryne 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 Et₂O 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/Et₂O 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–c} 2-Chloroanisole, 2-chlorobenzotrifluoride, and 2-bromobiphenyl

Table 1. Optimization of Reaction Conditions^a



entry	1 /PhCl/base	<i>T</i> , °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 ₂ O	1/5 (16)
4 ^c	1/2/3.6	25	Et ₂ O	1/50 (<2)
5	2/1/3.6	-20	Et ₂ O	11/1 (27)
6	1/2/3.6	40	C ₅ H ₁₂	1/2 (29)
7	2/1/3.6	40	C ₅ H ₁₂	2/1 (35)
8	1/2/3.6	25	C ₅ H ₁₂ /Et ₂ O 20:1	1.3/1 (43)
9	2/1/3.6	25	C ₅ H ₁₂ /Et ₂ O 20:1	12/1 (27)
10	2/1/3.6	25	C ₅ H ₁₂ /Et ₂ O 1:1	9/1 (64)
11	2/1/3.6	25	C ₅ H ₁₂ /Et ₂ O 1:1	18/1 (74)
12	1/2/3.6	25	C ₅ H ₁₂ /Et ₂ O 1:1	1/2.2 (25)
13	3/1/4.8	50	C ₅ H ₁₂ /Et ₂ O 14:1	50/1 (78)
14	3/1/4.8	50	C ₅ H ₁₂ /Et ₂ O 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 photo-stimulated 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,

(8) Pierini, A. B.; Baumgartner, M. T.; Rossi, R. A. *J. Org. Chem.* **1991**, *56*, 580.

(4) (a) Truong, T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 4243. (b) Truong, T.; Daugulis, O. *Chem. Sci.* **2012**, Advance Article, DOI: 10.1039/C2SC21288A. (c) Truong, T.; Daugulis, O. *Org. Lett.* **2011**, *13*, 4172.

(5) (a) Scardiglia, F.; Roberts, J. D. *Tetrahedron* **1958**, *3*, 197. (b) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403. (c) Bergstrom, F. W.; Wright, R. E.; Chandler, C.; Gilkey, W. A. *J. Org. Chem.* **1936**, *1*, 170. (d) Haberfield, P.; Seif, L. *J. Org. Chem.* **1969**, *34*, 1508.

(6) (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *8*, 1211. (b) Chen, Y.; Larock, R. C. Arylation Reactions Involving the Formation of Arynes. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: New York, 2009; pp 401–473.

(7) (a) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582. (b) Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, *72*, 91. (c) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224. (d) Im, G.-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933. (e) Gold, B.; Shevchenko, N. E.; Bonus, N.; Dudley, G. B.; Alabugin, I. V. *J. Org. Chem.* **2012**, *77*, 75.

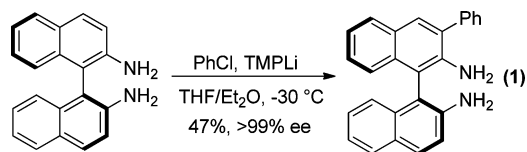
Table 2. Arylation of 2-Naphthylamine^a

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

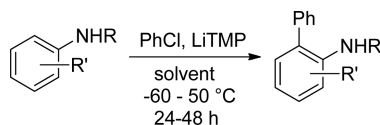
^a 2-Naphthylamine (1–2 mmol), ArX (0.5 mmol), LiTMP (1.8–3.4 mmol), solvent (1.4–3 mL), –85 to +50 °C, 12–48 h. Yields are isolated yields. ^b Cyclohexane/Et₂O (14/1), 25 °C, < 5% *N*-arylation product observed in crude reaction mixture. ^c Et₂O, –25 °C, ca. 10% *N*-arylation. ^d Cyclohexane/Et₂O (14/1), 50 °C, < 10% *N*-arylation. ^e Cyclohexane/Et₂O (1/1), 25 °C, < 5% *N*-arylation. ^f Et₂O, –30 °C, 8% *N*-arylation. ^g THF, –85 °C, 7% *N*-arylation. ^h Cyclohexane/Et₂O (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 binaphthyl diamine 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- <i>t</i> -butylaniline		60
3 ^b	diphenylamine		78	11 ^d	4-aminobiphenyl		67
4 ^b	<i>N</i> -phenyl-2-naphthylamine		80	12 ^b	1-naphthylamine		85
5 ^c	<i>N</i> -benzylamine		70	13 ^d	2-aminobiphenyl		70
6 ^d	aniline		55	14 ^g	4-cyanoaniline		65
7 ^e	<i>p</i> -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/Et₂O (1/1), 25 °C. ^c Pentane/THF (36/1), 25 °C. ^d Cyclohexane/Et₂O (14/1), 50 °C. ^e Pentane/Et₂O (1/1), –50 °C, PhOTf. ^f Isomeric 2-phenyl-3-trifluoromethylaniline also isolated (17%). ^g THF/Et₂O (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.

Acknowledgment. We thank the Welch Foundation (Grant No. E-1571), NIGMS (Grant No. R01GM077635), the A. P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation for supporting this research.

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>.

The authors declare no competing financial interest.

(9) Schmid, M.; Eberhardt, R.; Klinga, M.; Leskelae, M.; Rieger, B. *Organometallics* **2001**, *20*, 2321.

(10) (a) Clegg, W.; Horsburgh, L.; Mackenzie, F. M.; Mulvey, R. E. *J. Chem. Soc., Chem. Commun.* **1995**, 2011. (b) von Bülow, R.; Gornitzka, H.; Kottke, T.; Stalke, D. *Chem. Commun.* **1996**, 1639.