Published in final edited form as:

Org Lett. 2012 December 7; 14(23): 5964–5967. doi:10.1021/ol302875x.

Direct Intermolecular Aniline *ortho*-Arylation via Benzyne Intermediates

Thanh Truong and Olafs Daugulis

Department of Chemistry, University of Houston, Houston, TX 77204-5003

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 last 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 Tc-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.

Correspondence to: Olafs Daugulis.

olafs@uh.edu.

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>.

We have recently reported direct *C*-arylation of heterocycles, arenes, alkynes, and phenols proceeding via benzyne 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 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 1-2). 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-e} 2-Chloroanisole, 2-chlorobenzotrifluoride, and 2-bromobiphenyl are reactive and the corresponding arylation products were obtained in good yields (entries 5, 6, and 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 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, and benzyl substituents all give products in good to excellent yields (entries 1, 3, 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 *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 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).

(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 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. Due to 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

References

1. Reviews: Colby DA, Bergman RG, Ellman JA. *Chem. Rev.* 2010; 110:624. [PubMed: 19438203] Ackermann L, Vicente R, Kapdi AR. *Angew. Chem., Int. Ed.* 2009; 48:9792. Chen X, Engle KM, Wang D-H, Yu J-Q. *Angew. Chem., Int. Ed.* 2009; 48:5094. Lyons TW, Sanford MS. *Chem. Rev.* 2010; 110:1147. [PubMed: 20078038] Daugulis O, Do H-Q, Shabashov D. *Acc. Chem. Res.* 2009; 42:1074. [PubMed: 19552413] Alberico D, Scott ME, Lautens M. *Chem. Rev.* 2007; 107:174. [PubMed: 17212475] Yeung CS, Dong VM. *Chem. Rev.* 2011; 111:1215. [PubMed: 21391561] Sun C-L, Li B-J, Shi Z-J. *Chem. Commun.* 2010:677. Li C-J. *Acc. Chem. Res.* 2009; 42:335. [PubMed: 19220064]
2. a Daugulis O, Zaitsev VG. *Angew. Chem., Int. Ed.* 2005; 44:4046. b Shabashov D, Daugulis O. *J. Org. Chem.* 2007; 72:7720. [PubMed: 17824657] c Kalyani D, Deprez NR, Desai LV, Sanford MS. *J. Am. Chem. Soc.* 2005; 127:7330. [PubMed: 15898779] d Huang C, Gevorgyan V. *J. Am. Chem. Soc.* 2009; 131:10844. [PubMed: 19722665] e Phipps RJ, Gaunt M. *Science.* 2009; 323:1593. [PubMed: 19299616] f Pirali T, Zhang F, Miller AH, Head JL, McAusland D, Greaney M. *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 CC, McDonald RI, Hartmann C, Sazama GT, Bergant A, Stahl SS. *J. Org. Chem.* 2009; 74:2613. [PubMed: 19219972] i Brasche G, García-Foranet J, Buchwald SL. *Org. Lett.* 2008; 10:2207. [PubMed: 18465866]
3. a Wetzel A, Ehrhardt V, Heinrich MR. *Angew. Chem., Int. Ed.* 2008; 47:9130. b Ciana C-L, Phipps RJ, Brandt JR, Meyer F-M, Gaunt MJ. *Angew. Chem., Int. Ed.* 2011; 50:458.
4. a Truong T, Daugulis O. *J. Am. Chem. Soc.* 2011; 133:4243. [PubMed: 21384889] b Truong T, Daugulis O. *Chem. Sci. Advance Article.* 2012 DOI: 10.1039/C2SC21288A. c Truong T, Daugulis O. *Org. Lett.* 2011; 13:4172. [PubMed: 21786825]
5. a Scardiglia F, Roberts JD. *Tetrahedron.* 1958; 3:197. b Beller M, Breindl C, Riermeier TH, Tillack A. *J. Org. Chem.* 2001; 66:1403. [PubMed: 11312973] c Bergstrom FW, Wright RE, Chandler C, Gilkey WA. *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, RC. Arylation reactions involving the formation of arynes. In: *Modern Arylation Methods.* Ackermann, L., editor. Wiley-VCH; 2009. p. 401-473.
7. a Olofson RA, Dougherty CM. *J. Am. Chem. Soc.* 1973; 95:582. b Huisgen R, Sauer J. *Angew. Chem.* 1960; 72:91. c Tadross PM, Gilmore CD, Bugga P, Virgil SC, Stoltz BM. *Org. Lett.* 2010; 12:1224. [PubMed: 20166704] d Im G-YJ, Bronner SM, Goetz AE, Paton RS, Cheong PH-Y, Houk KN, Garg NK. *J. Am. Chem. Soc.* 2010; 132:17933. [PubMed: 21114321] e Gold B, Shevchenko NE, Bonus N, Dudley GB, Alabugin IV. *J. Org. Chem.* 2012; 77:75. [PubMed: 22077877]
8. Pierini AB, Baumgartner MT, Rossi RA. *J. Org. Chem.* 1991; 56:580.
9. Schmid M, Eberhardt R, Klinga M, Leskelae M, Rieger B. *Organometallics.* 2001; 20:2321.
10. a Clegg W, Horsburgh L, Mackenzie FM, Mulvey RE. *J. Chem. Soc., Chem. Commun.* 1995:2011. b von Bülow R, Gornitzka H, Kottke T, Stalke D. *Chem. Commun.* 1996:1639.

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 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 ₆ 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 Supporting Information for details.

^b Ratio 2/3; GC yield of 2 (%) in parentheses.

^c LDA base.

Table 2

Arylation of 2-Naphthylamine^a

entry	ArX	product	yield (%)
1 ^b	PhF	2	68
2 ^b	PhCl	2	72
3 ^b	PhBr	2	70
4 ^c	2-chlorostyrene		70
5 ^c	2-chloroanisole		67
6 ^c	2-chlorobenzo-trifluoride		65
7 ^d	2-bromobiphenyl		70

<div> </div>			
entry	ArX	product	yield (%)
8 ^d	9-chloro-phenanthrene		71
9 ^e	2-chloro-naphthalene		82
10 ^f	2-chloro- <i>N,N</i> -dimethylaniline		61
11 ^g	3-chlorophenyl triflate		50
12 ^h	<i>t</i> -butyl 3-bromo-benzoate		70
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.

Table 3

Arylamine Phenylation^a

$ \begin{array}{c} \text{Ph-NHR} \\ \\ \text{R}' \end{array} \xrightarrow[\text{-60 - 50 } ^\circ\text{C}]{\text{PhCl, LiTMP}} \begin{array}{c} \text{Ph} \\ \\ \text{Ph-NHR} \\ \\ \text{R}' \end{array} $ solvent 24-48 h			
entry	amine	product	yield (%)
1 ^b	PhNHMe		62
2 ^b	1,2,3,4-tetra-hydroquinoline		70
3 ^b	diphenylamine		78
4 ^b	N-phenyl-2-naphthylamine		80
5 ^c	N-benzylamine		70
6 ^d	aniline		55
7 ^e	p-chloroaniline		60

$ \text{C}_6\text{H}_4(\text{R}')\text{NHR} \xrightarrow[\text{-60 - 50 } ^\circ\text{C}]{\text{PhCl, LiTMP, solvent}} \text{C}_6\text{H}_3(\text{Ph})(\text{R}')\text{NHR} $ 24-48 h			
entry	amine	product	yield (%)
8 ^d	3,5-dimethylaniline		70
9 ^{d,f}	3-aminobenzotrifluoride		50
10 ^d	4- <i>t</i> -butylaniline		60
11 ^d	4-aminobiphenyl		67
12 ^b	1-naphthylamine		85
13 ^d	2-aminobiphenyl		70
14 ^g	4-cyanoaniline		65

^a Amine (1-2 mmol), PhCl (0.5 mmol), LiTMP (1.8-3.4 mmol), solvent (1.4-3 mL), -60-50 °C, 24-48 h. Yields are isolated yields. Please see 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.