

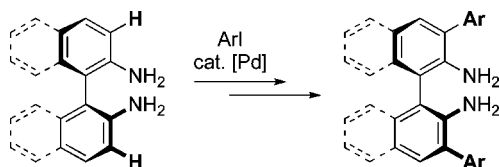
Steric Modulation of Chiral Biaryl Diamines via Pd-Catalyzed Directed C–H Arylation

Christopher C. Scarborough, Richard I. McDonald, Caroline Hartmann, Graham T. Szama, Ana Bergant, and Shannon S. Stahl*

Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706

stahl@chem.wisc.edu

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Palladium-catalyzed directed arylation of 2,2'-diacetamidobiphenyls with aryl iodides provides efficient access to chiral *ortho*-substituted biaryl diamines. Aryl iodides with *para*- and *meta*-substituents are tolerated. Deprotection of the acetyl groups under basic conditions furnishes the free diamines, which should find broad utility in asymmetric catalysis.

Chiral biaryl diamines (Chart 1)¹ find widespread use in asymmetric catalysis, ranging from oxidations^{2–5} and reductions^{6–8}

(1) 2,2'-Diamino-1,1'-binaphthyl (DABN) is commercially available. For information regarding the synthesis of diamines in Chart 1, see: (a) Takasaki, M.; Motoyama, Y.; Yoon, S. H.; Mochida, I.; Nagashima, H. *J. Org. Chem.* **2007**, *72*, 10291–10293. (b) Korostylev, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Börner, A. *J. Org. Chem.* **2004**, *69*, 3220–3221. (c) Guo, H.; Ding, K. *Tetrahedron Lett.* **2000**, *41*, 10061–10064. (d) Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P. *J. Org. Chem.* **2002**, *67*, 3450–3458. (e) Chen, Y. X.; Li, Y. M.; Lam, K. H.; Chan, A. S. C. *Chin. J. Chem.* **2001**, *19*, 794–799.

(2) Pd-catalyzed aerobic kinetic resolution of secondary alcohols: Chen, T.; Jiang, J. J.; Xu, Q.; Shi, M. *Org. Lett.* **2007**, *9*, 865–868.

(3) Cu-catalyzed aziridination: (a) Reference 1d. (b) Shi, M.; Wang, C. J. *Chirality* **2002**, *14*, 412–416. (c) Gillespie, K. M.; Crust, E. J.; Deeth, R. J.; Scott, P. *Chem. Commun.* **2001**, 785–786. (d) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132–7133.

(4) Cu-catalyzed aerobic oxidative coupling of 3-hydroxy-2-naphthoate: Kim, K. H.; Lee, D. W.; Lee, Y. S.; Ko, D. H.; Ha, D. C. *Tetrahedron* **2004**, *60*, 9037–9042.

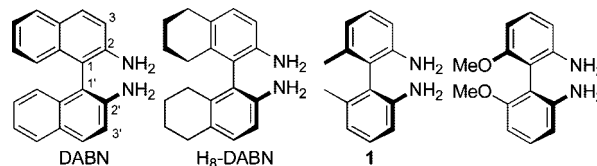
(5) Co-catalyzed epoxidation of styrene: Nishinaga, A.; Yamato, H.; Abe, T.; Maruyama, K.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 6309–6312.

(6) Rh- and Ru-catalyzed hydrogenation: (a) Huang, H.; Okuno, T.; Tsuda, K.; Yoshimura, M.; Kitamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 8716–8717. (b) Chen, Y. X.; Li, Y. M.; Lam, K. H.; Chan, A. S. C. *Chin. J. Chem.* **2003**, *21*, 66–70. (c) Pérez, C.; Pérez, S.; Fuentes, G. A.; Corma, A. *J. Mol. Catal. A: Chem.* **2003**, *197*, 275–281. (d) Chen, Y.-X.; Li, Y.-M.; Lam, K.-H.; Chan, A. S.-C. *Chin. J. Chem.* **2002**, *20*, 606–609. (e) Zhang, F. Y.; Kwok, W. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2337–2342. (f) Zhang, F. Y.; Pai, C. C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808–5809.

(7) Rh- and Y-catalyzed hydrosilylation: (a) Xu, Q.; Gu, X.; Liu, S.; Dou, Q.; Shi, M. *J. Org. Chem.* **2007**, *72*, 2240–2242. (b) Gountchev, T. I.; Tilley, T. D. *Organometallics* **1999**, *18*, 5661–5667.

(8) Reduction of ketones by LiAlH₄: Suda, H.; Motoi, M.; Fujii, M.; Kanoh, S.; Yoshida, H. *Tetrahedron Lett.* **1979**, 4565–4568.

CHART 1. Common Biaryl Diamine Structures (DABN = 2,2'-Diamino-1,1'-binaphthyl)



to addition reactions.^{9–19} Derivatives of these diamines have been employed as ligands for transition-metal catalysts and directly as nonmetal-based catalysts, for example, as chiral nucleophilic catalysts. In several cases, enantioselectivities of reactions with DABN and H₈-DABN-based catalysts (cf. Chart 1) can be increased substantially by introducing substituents in the 3- and 3'-positions of the aromatic rings (i.e., *ortho* to the amino groups).^{6a,14b,17–19} Here, we describe a Pd-catalyzed C–H arylation method that provides efficient access to *ortho*-functionalized biaryl diamine derivatives.

Recent studies in our laboratory have employed biphenyl diamines as a scaffold for the development of axially chiral, seven-membered *N*-heterocyclic carbenes (A).²⁰ In the course of this work, we sought access to derivatives with bulky substituents in the 3- and 3'-positions of biphenyl diamine derivative **1** (Chart 1). Existing methods for the introduction of substituents in these positions are based on Suzuki–Miyaura coupling and require preparation of the corresponding halogenated biaryl diamines.^{6a,14b,17–19} The synthetic inefficiency and low selectivity that we encountered with the halogenation

(9) Pd-catalyzed allylic alkylation: Chen, X.; Guo, R.; Li, Y.; Chen, G.; Yeung, C. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 213–217.

(10) Cu-catalyzed alkylation of aldimines: Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2008**, *49*, 379–382.

(11) Cu- and Ru-catalyzed cyclopropanation: (a) Sanders, C. J.; Gillespie, K. M.; Scott, P. *Tetrahedron: Asymmetry* **2001**, *12*, 1055–1061. (b) Munslow, I. J.; Gillespie, K. M.; Deeth, R. J.; Scott, P. *Chem. Commun.* **2001**, 1638–1639. (c) Bachmann, S.; Furler, M.; Mezzetti, A. *Organometallics* **2001**, *20*, 2102–2108.

(12) Zr-, Y-, Sm-, and La-catalyzed intramolecular hydroamination of alkenes: (a) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354–358. (b) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Organometallics* **2007**, *26*, 1729–1737. (c) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894–895. (d) O'Shaughnessy, P. N.; Gillespie, K. M.; Knight, P. D.; Munslow, I. J.; Scott, P. *Dalton Trans.* **2004**, 2251–2256. (e) O'Shaughnessy, P. N.; Knight, P. D.; Morton, C.; Gillespie, K. M.; Scott, P. *Chem. Commun.* **2003**, 1770–1771. (f) O'Shaughnessy, P. N.; Scott, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1979–1983.

(13) Dialkylzinc addition to cyclic enones: Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2007**, *48*, 8590–8594.

(14) Diels–Alder cycloadditions: (a) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457–2465. (b) Kano, T.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2006**, *8*, 2687–2689.

(15) Glyoxylate-ene reactions: Mikami, K.; Aikawa, K. *Org. Lett.* **2002**, *4*, 99–101.

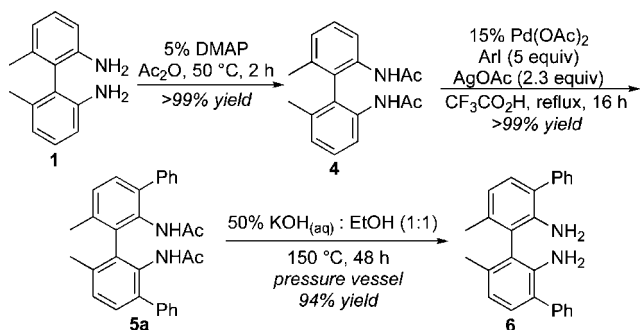
(16) Silylcyanation of aldehydes: Zhou, X. G.; Huang, J. S.; Ko, P. H.; Cheung, K. K.; Che, C. M. *J. Chem. Soc.; Dalton Trans.* **1999**, 3303–3309.

(17) Morita–Baylis–Hillman reactions: Shi, M.; Liu, X. G. *Org. Lett.* **2008**, *10*, 1043–1046.

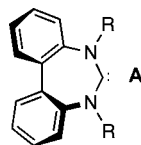
(18) Oxy–Michael addition reactions: Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*, 8658–8664.

(19) Henry reactions: Liu, X. G.; Jiang, J. J.; Shi, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2773–2781.

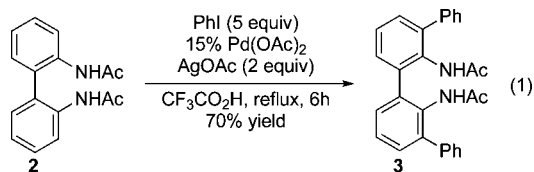
(20) Scarborough, C. C.; Popp, B. V.; Guzei, I. A.; Stahl, S. S. *J. Organomet. Chem.* **2005**, *690*, 6143–6155. (b) Scarborough, C. C.; Grady, M. J. W.; Guzei, I. A.; Gandhi, B. A.; Bunel, E. E.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5269–5272.

SCHEME 1. Synthetic Sequence for Bis-*ortho*-Arylation of Biphenyl Diamine 1

procedures prompted us to consider alternative strategies for *ortho*-functionalization of biphenyl diamines.



Several methods have been reported recently for arylation of aromatic C–H bonds, directed by an adjacent functional group.²¹ Daugulis and Zaitsev, for example, have shown that anilides undergo arylation selectively in the *ortho* position(s) with aryl iodides in the presence of stoichiometric AgOAc and catalytic Pd(OAc)₂ in trifluoroacetic acid.^{21a,22} These methods are attractive because they employ aryl iodides, which are more readily available than the diaryliodonium salts^{21c} and trialkoxylarylsilanes^{21d} employed in other C–H arylation methods. We first attempted a Daugulis–Zaitsev (DZ) coupling reaction with iodobenzene and 2,2'-diacetylaminobiphenyl (**2**).²³ This reaction was successful and afforded the quaterphenyl-diamine **3** in 70% isolated yield (eq 1). Extension of this reactivity to *chiral* biaryldiamines was also successful. The *N,N'*-diacetyl derivative of diamine **1** is a highly effective substrate for this reaction (Scheme 1); the C–H arylation product **5a** is obtained in essentially quantitative yield from the DZ coupling reaction (Scheme 1). Removal of the acetyl directing groups under basic conditions (1:1 EtOH/50% KOH_(aq)) in a stainless steel pressure vessel, 150 °C, 48 h affords the quaterphenyl diamine **6** in very good overall yield.



In order to probe the scope of the DZ coupling conditions for the synthesis of *ortho*-arylated biphenyldiamines, we examined other iodoarene substrates (Table 1). A number of

(21) See, for example: (a) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046–4048. (b) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720–7725. (c) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331. (d) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066–6067.

(22) For an earlier demonstration of related reactivity with alkyl iodides and stoichiometric Pd, see: Tremont, S. J.; Rahmann, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760.

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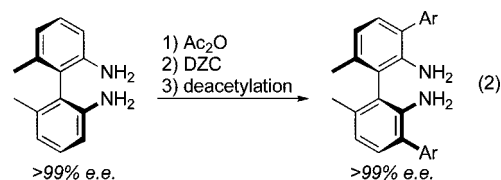
TABLE 1. Scope of *ortho*-Arylation of **4**^a

entry	Arl	product	% yield
1		5a	>99%
2		5b	>99%
3		5c	76%
4		--	0%
5		5d	93% ^b
6		5e	68% ^b
7		--	0%

^a Substrate (1.0 mmol), ArI (5.0 mmol), Pd(OAc)₂ (0.15 mmol), AgOAc (2.2 mmol), 3 mL of CF₃CO₂H, reflux, 6 h. ^b 20% Pd(OAc)₂, 3.0 equiv of AgOAc, 14 h.

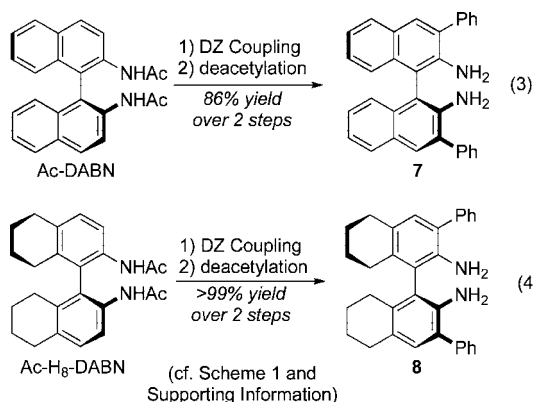
the reactions proceed in good-to-excellent yields (entries 1–3, 5, and 6). Limitations include strongly electron-withdrawing groups and the presence of *ortho*-substitution in the aryl iodide (entries 4 and 7). The presence of *meta*-substituents is tolerated, although somewhat more forcing conditions were required in these reactions (20% Pd loading, 3.0 equiv of AgOAc, 14 h, entries 5 and 6).

Both the DZ coupling and amide hydrolysis conditions require rather high temperatures, and it was unclear if these conditions could lead to epimerization of the atropisomeric biaryls. Enantiomerically resolved (*S*)-**1** (>99% ee) was subjected to the diacetylation, DZ coupling, and hydrolysis conditions in Scheme 1. The expected quaterphenyl diamine (*S*)-**5a** was obtained in 94% overall yield, and chiral HPLC analysis demonstrated that the product retained >99% ee (eq 2). Therefore, these conditions are well suited for the preparation of enantiomerically resolved diamines.



We have briefly investigated whether the methods described here can be applied to other common biaryl diamines. DABN is an attractive biaryl diamine substrate because the resolved enantiomers are commercially available. Pd-catalyzed *ortho* arylation of *N,N'*-diacetyl-DABN with PhI was successful, and

the desired diamine **7** was obtained in 86% yield following removal of the acetyl groups (eq 3).²⁴ The partially hydrogenated DABN derivative H₈-DABN²⁵ also undergoes effective arylation: DZ coupling of the *N,N'*-diacetyl derivative of H₈-DABN with PhI, followed by amide hydrolysis, afforded quaterphenyldiamine **8** in nearly quantitative yield (eq 4).^{17–19}



In conclusion, we have developed a simple and efficient three-step procedure for the installation of *o*-aryl groups onto 2,2'-diaminobiaryls. This procedure takes advantage of the Daugulis–Zaitsev coupling method for amide-directed arylation of aromatic C–H bonds. The incorporation of bulky *ortho*-substituents onto BINOL has had dramatic beneficial effects in asymmetric catalysis.²⁶ We anticipate the methods described here will provide the basis for similar advances in asymmetric reactions with biaryl diamine-derived catalysts.

Experimental Section

General Procedure for the Daugulis–Zaitsev Coupling. A representative example is given for the synthesis of **5a**. Bisamide

(24) The DABN substrate appears to be more reactive and susceptible to side reactions. Efforts to perform reactions with aryl iodides other than PhI typically resulted in lower yields. For example, DZ coupling of *N,N'*-diacetyl-DABN with 1-iodo-3,5-dimethylbenzene proceeded in 46% yield with complete consumption of starting material (cf. entry 5, Table 1).

(25) Partial hydrogenation of DABN to form H₈-DABN can be achieved without loss of enantiopurity.

(26) (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. (b) Pihko, P. M. *Lett. Org. Chem.* **2005**, *2*, 398–403. (c) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3211.

4 (296 mg, 1.0 mmol), Pd(OAc)₂ (34 mg, 0.15 mmol), AgOAc (384 mg, 2.3 mmol), and PhI (560 μL, 5.0 mmol) were dissolved in 3 mL of trifluoroacetic acid. A reflux condenser was attached, and the reaction was heated to a vigorous reflux for 6 h. After the mixture was cooled to room temperature, 10 mL of toluene was added to the dark mixture, which was then filtered over Celite, and the solvent removed under vacuum. The mixture was purified by flash chromatography with silica gel (gradient, 1:1 Et₂O/toluene to pure Et₂O, *R_f* = 0.29 in 1:1 Et₂O/toluene) to afford 446 mg of off-white powder: 99.6% yield; ¹H NMR (300 MHz, CDCl₃, δ) 1.60 (s, 6H), 1.94 (s, 6H), 7.26–7.40 (m, 14H); ¹³C NMR (75 MHz, CDCl₃, δ) 20.1, 23.0, 127.3, 128.4, 128.8, 129.4, 129.8, 132.8, 138.8, 140.2; HRMS *m/z* (ESI) calcd [MH]⁺ = 449.2224, measured 449.2242 (Δ = 4.0 ppm).

General Procedure for the Deacetylation of 2,2'-Diacetamidobiaryls. A representative example is given for the synthesis of **6**. Compound **5a** (1.19 g, 2.65 mmol) was added to 100 mL of a 1:1 mixture of EtOH and 50% KOH_(aq) in a stainless steel Parr bomb. The bomb was sealed and heated to 150 °C (based on an internal temperature probe) for 48 h. After the mixture was cooled to room temperature, 100 mL saturated NH₄Cl_(aq) was added to the suspension, which was then extracted 2× with CH₂Cl₂. The combined CH₂Cl₂ solutions were dried over MgSO₄ and filtered, and the solvent was removed in vacuo to afford 905 mg of pure **6** (94% yield) without further purification: ¹H NMR (300 MHz, CDCl₃, δ) 2.04 (s, 6H), 3.67 (br. s, 4H), 6.79 (dd, *J* = 7.5, 0.3 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 7.30 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.39–7.44 (m, 4H), 7.46–7.50 (m, 4H); ¹³C NMR (75 MHz, CDCl₃, δ) 19.9, 120.1, 122.7, 125.5, 127.1, 128.9, 129.4, 129.7, 137.3, 140.2, 141.5; (*S*)-**6**: [α]_D²⁵ –81.4 (c 8.9, CH₂Cl₂); HRMS *m/z* (ESI) calcd [MH]⁺ = 365.2013, measured 365.2027 (Δ = 3.8 ppm).

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Supporting Information Available: Procedure for the synthesis of **4**, characterization data and NMR spectra for all new compounds, as well as chiral HPLC data for **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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