# J|A|C|S

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

# Ligand-Controlled Asymmetric Arylation of Aliphatic α-Amino Anion Equivalents

Ye Zhu and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

**S** *Supporting Information*

**ABSTRACT:** A palladium-catalyzed asymmetric arylation of 9-aminofluorene-derived imines using a chiral dialkyl-biaryl phosphine as the supporting ligand has been developed. This transformation allows for enantioselective access to a diverse range of α-branched benzylamines.

Chiral amines serve as key intermediates in natural product synthesis[1] and are prevalent building blocks in the preparation of pharmaceuticals. Moreover, enantioenriched amines are widely employed as chiral auxiliaries,[2] ligands,[3] catalysts,[4] and components of supramolecular materials.[5] As a result, considerable effort has been directed toward their enantioselective synthesis.[6−9] While the addition of carbanions to electrophilic C=N double bonds has been widely applied,[10,11] the use of nucleophilic α-amino anions for the synthesis of chiral amines (except α-amino acids) has been less studied.[12] Several methods that take advantage of these valuable anions (or their equivalents) use Pd catalysis to achieve asymmetric arylation, where the chirality is introduced by a preformed reagent.[13] Alternatively, the enantioselective synthesis of diarylmethanamines was realized using Cr(CO)3 complexes of N-benzyl dialkylamines, and the asymmetry is controlled by the ligand.[14] However, there are no examples of similar processes that utilize the catalytic functionalization of α-amino anion equivalents of acyclic aliphatic amines to arrive at enantioenriched α-alkyl benzylamines.[15] Herein we report the realization of such a method that employs a ligand-controlled Pd-catalyzed asymmetric arylation process.

We began by exploring 2-azaallyl anions[16] as aliphatic α-amino anion equivalents. As outlined in Scheme 1, deprotonation at the α′-position of aldimine (**c**), derived from aliphatic aldehyde (**a**) (R = alkyl group) and diarylmethanamine (**b**), generates the corresponding 2-azaallyl anion (**d**).[17,18] A

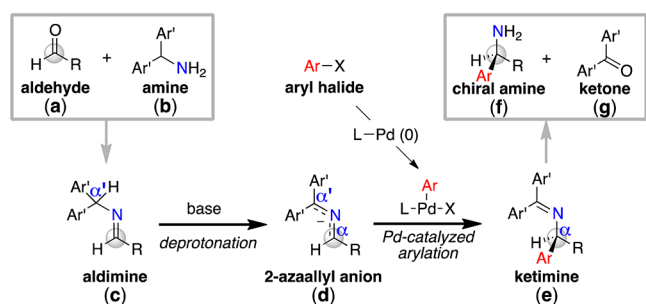## Scheme 1. Proposed Pd-Catalyzed Arylation Reaction



## Table 1. Pd-Catalyzed Arylation of Imine 2a[a]



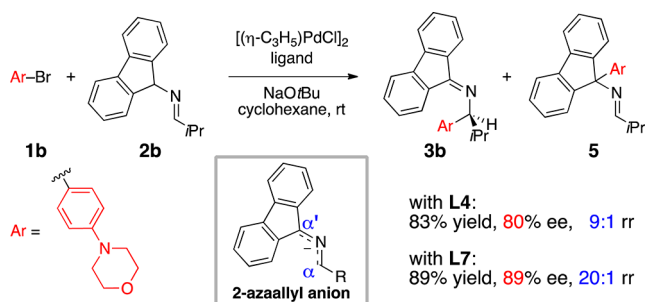| entry | ligand | | yield[b] (%) | ee[c] (%) |
|-------|--------|--------|--------------|-----------|
| **Reactions in toluene** | | | | |
| 1 | R = iPr | **L1** | 82 | 86 |
| 2 | c-C5H9 | **L2** | 87 | 44 |
| 3 | c-C6H11 | **L3** | 83 | 71 |
| 4 | c-C7H13 | **L4** | 78 | 87 |
| **Reactions in cyclohexane** | | | | |
| 5 | X = H | **L4** | 90 | 91 |
| 6 | NMe2 | **L5** | 90 | 87 |
| 7 | CN | **L6** | 41 | 91 |
| 8 | TMS | **L7** | 91 | 94 |

[a]Reaction conditions: PhBr (0.25 mmol), **2a** (0.325 mmol), NaOtBu (0.275 mmol). Flu = 9-fluorenyl. TMS = trimethylsilyl. [b]Isolated yields of **4a**. [c]The ee (enantiomeric excess) of **4a** was determined by chiral HPLC.

subsequent Pd-catalyzed asymmetric arylation of (**d**) affords α-alkyl benzylamine (**f**) upon deprotection of ketimine (**e**). The overall transformation effectively converts a carbonyl compound to an α-branched amine via electrophilic substitution at the carbonyl carbon.[19] We postulated that the reactivity of (**d**) could be modulated by incorporating appropriate Ar′ substituents, while the development of a chiral catalyst would allow for effective enantiocontrol of the transformation.

At the outset, we chose 9-aminofluorene-derived imine **2a** as the nucleophilic coupling partner for the Pd-catalyzed arylation reaction (Table 1).[20] A survey of chiral phosphorus ligands and reaction conditions revealed that **2a** underwent the proposed transformation using NaOtBu as the base and (R)-iPrTrix-iePhos (**L1**) as the supporting ligand, affording 9-fluorenyl-amine **4a** in 82% yield with 86% ee upon reduction of **3a** (entry

## Scheme 2. Pd-Catalyzed Arylation of Imine 2b[a]



with **L4**:
83% yield, 80% ee, 9:1 rr

with **L7**:
89% yield, 89% ee, 20:1 rr

2-azaallyl anion

[a]Reaction conditions: see Table 1. The rr (regioisomeric ratio, **3b** to **5**) was determined by ^{1}H NMR spectroscopy for the corresponding amines upon NaBH₄ reduction.

1).[21] In contrast, the related diphenylmethanamine-derived imine did not participate in the reaction under the same conditions. This difference in reactivity apparently arises from the rigid fluorenyl substituent, which becomes aromatic upon deprotonation and enforces coplanarity to stabilize (**d**) through π-conjugation.[22]

Encouraged by our initial results, we evaluated the effect of altering the structure of the supporting ligand by changing the substituents on the phosphorus center.[23] While diminished enantioselectivity was obtained when (*R*)-cyclopentylTrixie-Phos (**L2**) or (*R*)-CyTrixiePhos (**L3**) was employed (Table 1, entries 2 and 3), the use of (*R*)-cycloheptylTrixiePhos (**L4**) as a supporting ligand yielded the product with slightly increased ee (entry 4).[24] Additionally, an improvement in ee was observed when the reaction was performed in cyclohexane instead of toluene (entry 5). Further optimization of the phosphorus ligand focused on introducing substituents on the binaphthyl backbone of **L4**.[25] Examination of 4′-substituted cycloheptyl-TrixiePhos derivatives **L5**−**L7**[26] showed that the electronic and steric properties of the 4′-substituent indeed influenced the outcome of the reaction. For example, a ligand with a π-donating NMe₂ substituent (**L5**; entry 6) gave the product with a lower level of enantioselectivity than **L4**, while the yield diminished when an electron-withdrawing cyano group was introduced (**L6**; entry 7). However, when a bulky TMS substituent was installed (**L7**; entry 8), the enantioselectivity was increased while retaining the reactivity.

## Scheme 3. Pd-Catalyzed Enantioselective Arylation Reactions[a,b]
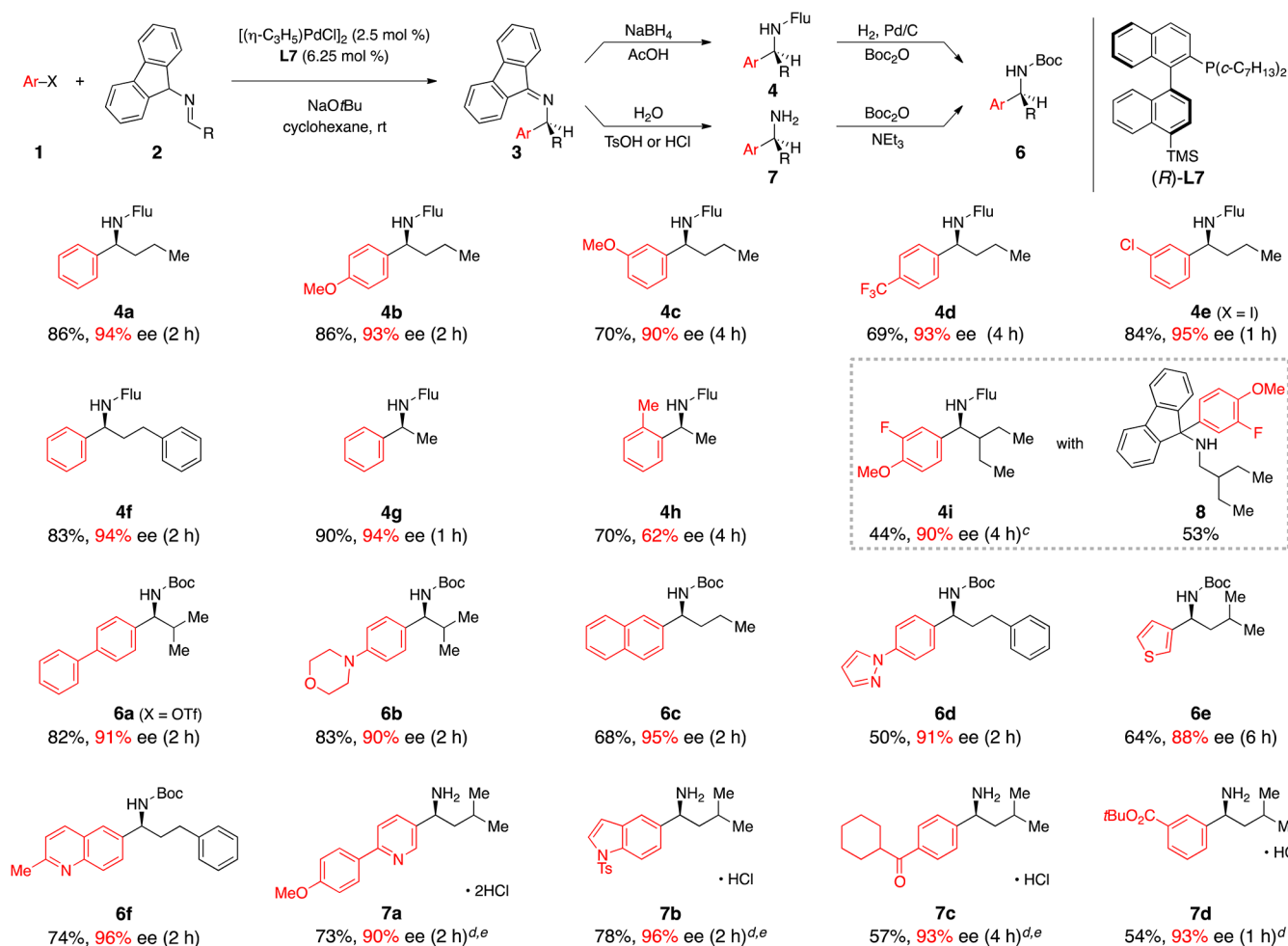


[a]Reaction conditions: Ar−X (1 mmol, X = Br unless otherwise noted), **2** (1.15 mmol), NaO*t*Bu (1.1 mmol). Isolated yields (averages of two runs) are shown. Boc = *tert*-butoxycarbonyl. Ts = *p*-toluenesulfonyl. [b]The absolute configuration of **6c** was assigned as *S*. See the Supporting Information for details. [c][(η-C₃H₅)PdCl]₂ (5 mol %), **L7** (12.5 mol %), **2** (1.25 mmol), NaO*t*Bu (1.2 mmol). [d]The ee was determined for the corresponding *N*-Boc amine. [e]**2** (1.05 mmol).

The regiochemical outcome of the transformation was also influenced by the phosphorus ligand. In the course of the reaction, the 2-azaallyl anion can potentially undergo arylation at either the α- or α′-carbon (Scheme 2).[17] Unlike the reaction of imine **2a**, which yielded **3a** as the only cross-coupled product, the isobutyraldehyde-derived imine **2b** afforded a mixture of regioisomers **3b** and **5**. Presumably, **3b** was favored because the α-carbon is the less hindered position. When **L7** was employed as the supporting ligand, **3b** was produced with improved enantioselectivity and regioselectivity compared with when **L4** was employed. Therefore, **L7** was used for the remainder of our study.

With the optimized reaction conditions, the Pd-catalyzed arylation was successfully applied to a range of substrates (Scheme 3). Reduction of the 9-fluorenimine products (**3**) afforded 9-fluorenylamines (**4**). Subsequently, **4** could be readily deprotected under hydrogenolysis conditions, yielding the corresponding N-Boc amines (**6a** and **6b**) in the presence of Boc₂O. Alternatively, acid-mediated hydrolysis of **3** provided direct access to amines (**7**), which could be converted to N-Boc amines (**6c**−**6f**). Various aryl halides possessing electron-rich (e.g., **4b** and **6b**) and electron-deficient (e.g., **4d** and **4e**) substituents, including carbonyl groups (**7c** and **7d**), participated in the transformation, furnishing the amine products with high enantioselectivity. In addition to aryl bromides, the reactions proceeded equally well using an aryl iodide (**4e**) and an aryl triflate (**6a**) as substrates.[27] Notably, heteroaromatic halides, including bromo-substituted thiophene (**6e**), quinoline (**6f**), pyridine (**7a**), and indole (**7b**), proved to be suitable coupling partners for this transformation, although a lower level of enantioselectivity was observed with an ortho-substituted aryl bromide (**4h**). Various imines derived from aliphatic aldehydes underwent the desired arylation reactions. However, the reaction of a sterically demanding 2-ethylbutyraldehyde-derived imine yielded a significant amount of regioisomer **8** along with **4i**. It should be noted that the imine of trimethylacetaldehyde was unreactive, presumably because of the steric hindrance introduced by the adjacent tert-butyl group.

In conclusion, we have developed a Pd-catalyzed arylation of 9-aminofluorene-derived imines that uses a chiral dialkylbiaryl phosphine **L7** as the supporting ligand. This transformation accommodates a broad scope of aryl halides and is effective for imines derived from various aliphatic aldehydes. A diverse range of α-branched benzylamines was prepared with high enantioselectivity. The application of this method to imines derived from aromatic aldehydes and ketones and the development of vinylation and alkylation[28] of 2-azaallyl anions are under investigation.

## ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

### Corresponding Author

sbuchwal@mit.edu

### Notes

The authors declare the following competing financial interest(s): MIT has or has filed patents on ligands that are described in the paper from which SLB and former/current coworkers receive royalty payments.

## ACKNOWLEDGMENTS

## REFERENCES

(1) (a) Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180. (b) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 1930.

(2) (a) Evans, D. A.; Adams, D. J.; Kwan, E. E. *J. Am. Chem. Soc.* **2012**, *134*, 8162. (b) Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568.

(3) (a) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455. (b) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794.

(4) (a) Stevens, J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11756. (b) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. (c) Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747.

(5) (a) Zhao, C.; Sun, Q.-F.; Hart-Cooper, W. M.; DiPasquale, A. G.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 18802. (b) Castilla, A. M.; Ousaka, N.; Bilbeisi, R. A.; Valeri, E.; Ronson, T. K.; Nitschke, J. R. *J. Am. Chem. Soc.* **2013**, *135*, 17999.

(6) *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, Germany, 2010.

(7) For recent reviews of biocatalytic methods, see: (a) Reetz, M. T. *J. Am. Chem. Soc.* **2013**, *135*, 12480. (b) Bornscheuer, U. T.; Huisman, G. W.; Kazlauskas, R. J.; Lutz, S.; Moore, J. C.; Robins, K. *Nature* **2012**, *485*, 185.

(8) For recent reviews of chemical methods, see: (a) Bartoszewicz, A.; Ahlsten, N.; Martín-Matute, B. *Chem.—Eur. J.* **2013**, *19*, 7274. (b) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713. (c) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(9) For recent examples, see: (a) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344. (b) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746. (c) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521.

(10) For reviews, see: (a) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

(11) For selected examples, see: (a) Xu, H.-C.; Chowdhury, S.; Ellman, J. A. *Nat. Protoc.* **2013**, *8*, 2271. (b) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216. (c) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.

(12) (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (b) Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59.

(13) (a) Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607. (b) Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738. (c) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538.

(14) McGrew, G. I.; Stanciu, C.; Zhang, J.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11510.

(15) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(16) (a) Kauffmann, T.; Köppelmann, E.; Berg, H. *Angew. Chem., Int. Ed.* **1970**, *9*, 163. (b) Cram, D. J.; Guthrie, R. D. *J. Am. Chem. Soc.* **1966**, *88*, 5760.

(17) For Pd-catalyzed allylation of 2-azaallyl anions generated from decarboxylation of α-imino acid derivatives, see: (a) Ding, L.; Chen, J.; Hu, Y.; Xu, J.; Gong, X.; Xu, D.; Zhao, B.; Li, H. *Org. Lett.* **2014**, *16*, 720. (b) Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2007**, *9*, 2879. (c) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002.

(18) For Pd-catalyzed arylation of *N*-benzylxanthone imines, see: (a) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 4689. (b) Niwa, T.; Suehiro, T.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2009**, *65*, 5125.

(19) (a) Wu, Y.; Deng, L. *J. Am. Chem. Soc.* **2012**, *134*, 14334. (b) Xiao, X.; Xie, Y.; Su, C.; Liu, M.; Shi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 12914. (c) Solladie-Cavallo, A.; Farchani, D. *Tetrahedron Lett.* **1986**, *27*, 1331.

(20) For an example using the tautomeric 9-fluorenimine derivatives in asymmetric catalysis, see: (a) Chen, Y.-J.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 3244. For an example of asymmetric Strecker reactions using *N*-9-fluorenyl imines, see: (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650.

(21) For examples of Pd-catalyzed enantioselective aryaltion reactions using chiral dialkylbiaryl ligands, see: (a) Huang, Z.; Liu, Z.; Zhou, J. *J. Am. Chem. Soc.* **2011**, *133*, 15882. (b) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900. (c) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (d) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.

(22) O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520.

(23) Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841.

(24) We evaluated the error limits of our HPLC method by examining samples six times each for both **L1** and **L4**. Table 1, entry 1 (**L1**): average value 86.0, standard deviation 0.1. Table 1, entry 4 (**L4**): average value 87.1, standard deviation 0.1.

(25) Harper, K. C.; Sigman, M. S. *Science* **2011**, *333*, 1875.

(26) See the Supporting Information for preparation of ligands.

(27) Chlorobenzene also underwent the transformation, although it showed low reactivity (38% yield of **4a** after 21 h).

(28) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946.