Palladium-Catalyzed Coupling of Optically Active Amines with Aryl Bromides

Seble Wagaw, Roger A. Rennels, and Stephen L. Buchwald*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received May 15, 1997[⊗]

Abstract: The coupling of enantiomerically enriched amines with aryl bromides produces the corresponding *N*-aryl derivatives. The choice of ligand in the palladium-catalyzed coupling is critical to the formation of the anilines without loss of enantiomeric purity. While L_nPd (L = P(*o*-tolyl)$_3$) successfully catalyzes the intramolecular aryl amination of α-subsituted optically pure amines, intermolecular coupling reactions with this catalyst system gives racemized products. In contrast, intermolecular N-arylations employing L_nPd (L = (±)-BINAP) gives products in good yields with no erosion of enantiopurity. A mechanism for the observed racemization is proposed. The utility of the intramolecular process is demonstrated by the synthesis of **5**, an intermediate in the formal synthesis of **6**, a potent ACE inhibitor.

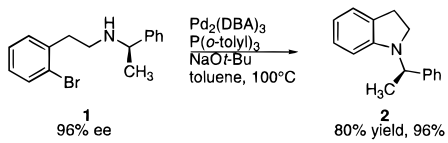
Introduction

Recently, the palladium-catalyzed intramolecular and intermolecular coupling of aryl halides with amines has been shown to be a mild and efficient method for the synthesis of a variety of aniline derivatives.[1−5] Initial reports on the palladium-catalyzed amination of aryl halides utilized Pd/P(*o*-tolyl)$_3$ catalysts, where the use of P(*o*-tolyl)$_3$ was key to the success of the reaction. Subsequently, Pd/bis(phosphine) catalysts have been shown to effect the amination of aryl halides and have been found to give superior results over those obtained in reactions catalyzed by Pd/P(*o*-tolyl)$_3$ for several classes of substrates.[6−9]

It would be desirable to extend the palladium-catalyzed carbon−nitrogen bond forming reaction to the preparation enantiomerically enriched aniline derivatives by coupling enantiomerically enriched amines with aryl bromides. Such compounds are common structural units in agricultural and pharmaceutical chemistry.[10−16] We now report that the use of Pd/P(*o*-tolyl)$_3$ catalysts for the intramolecular coupling of aryl bromides with enantiomerically enriched amines with stereogenic centers α to the nitrogen gives cyclized products without loss of stereochemical integrity. In addition, Pd/bis(phosphine) catalysts effect the intermolecular coupling of aryl bromides with enantiomerically enriched α-substituted amines with to give products without erosion of enantiopurity. The utility of these methods is demonstrated by the preparation of a variety of enantiomerically enriched aniline and indoline derivatives.

Results

Initial investigations into the $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$ catalyzed coupling of aryl bromides with enantiomerically enriched α-substituted amines gave promising results. A previously reported procedure for intramolecular carbon−nitrogen bond formation, utilizing catalytic $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$, successfully cyclizes enantiomerically enriched amine and amide substrates with either endocyclic or exocyclic chiral centers with no decrease in enantiomeric excess (ee).[17] For example, $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$ catalyzes the cyclization of **1** (96% ee) in high yield and without loss of enantiopurity (eq 1).



1 96% ee → **2** 80% yield, 96% ee (1)

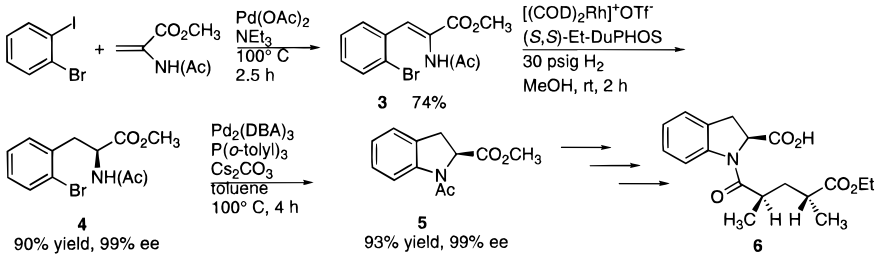
The utility of this methodology was further demonstrated in the preparation of (*S*)-*N*-acetylindoline-2-carboxylate methyl ester **5** (Scheme 1), a key intermediate in the synthesis of the ACE inhibitor **6**.[11] The stereochemistry of **4** is retained under the mild cyclization reaction conditions to give **5** in 99% ee. Optically active **4** is prepared by a Heck coupling reaction of *o*-bromoiodobenzene with methyl-2-acetamidoacrylate to produce **3**,[18] followed by an asymmetric hydrogenation of the resulting eneamide.[19] Alternate methods for the synthesis of

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1997.

(1) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett*. **1983**, 927−928.
(2) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc*. **1994**, *116*, 7901−7902.
(3) Guram, A. S.; Rennels, R. R.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1348−1350.
(4) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **1994**, *116*, 5969−5970.
(5) Louie, J.; Hartwig, J. F. *Tetrahedron Lett* **1995**, *36*, 3609−3612.
(6) Wagaw, S.; Buchwald, S. L. *J. Org. Chem*. **1996**, *61*, 7240−7241.
(7) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 7215−7216.
(8) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc*. **1996**, *118*, 7217−7218.
(9) Marcoux, J. F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem*. **1997**, *62*, 1568−1569.
(10) Gupton, J. T.; Tarrant, J. G.; Yu, R. H.; Solarz, T. L. *Synth. Comm*. **1992**, *22*, 3205−3214.
(11) Grundfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem*. **1983**, *26*, 1277−1293.
(12) LaMontagne, M. P.; Blumbergs, P.; Smith, D. C. *J. Med. Chem*. **1989**, *32*, 1728−1732.
(13) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc*. **1991**, *113*, 2311−2313.
(14) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *J. Am. Chem. Soc*. **1990**, *112*, 8195−8197.
(15) Queener, S. F.; Bartlett, M. S.; Nasar, M.; Smith, J. W. *Antimicrob. Agents Chemother*. **1993**, *37*, 2166−2172.
(16) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc*. **1992**, *114*, 10997−8.
(17) For previous exmaples of palladium-catalyzed intramolecular aryl aminations and aryl amidations, see: Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546.
(18) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc*. **1987**, *109*, 4335−4338.

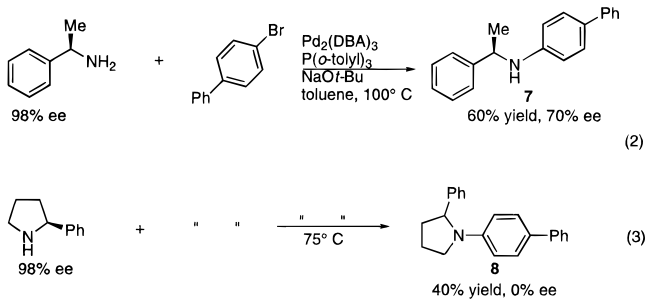
S0002-7863(97)01583-7 CCC: $14.00

Scheme 1



enantiopure **6** require either a low-yielding fractional recrystallization or an enantioselective enzymatic hydrolysis of the racemic ester **5**.[20]

We attempted to apply the Pd(0)/P(*o*-tolyl)$_3$ protocol to the intermolecular coupling of enantiomerically enriched amines with aryl bromides. Given the success of the $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$-catalyzed intramolecular coupling reactions, we were surprised to find that $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$-catalyzed intermolecular coupling of enantiomerically enriched α-chiral amines with aryl bromides yields products which are partially to fully racemized. For instance, when (*R*)-α-methylbenzylamine (98% ee) is coupled with 4-bromobiphenyl using this catalyst system, aniline **7** was obtained with 70% ee (eq 2). A racemic product is formed with this catalyst when (*S*)-2-phenylpyrrolidine (98% ee) and 4-bromobiphenyl are used as substrates (eq 3).

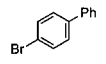
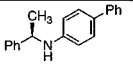
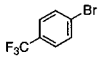
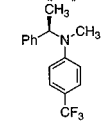
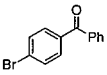
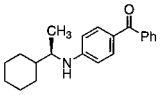
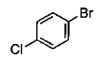
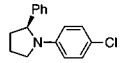
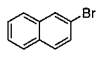
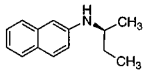
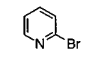
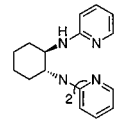
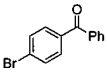
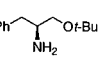
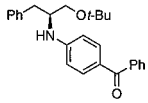
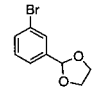
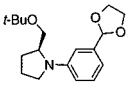


While determining which aspects of the reaction protocol in eq 2 were responsible for the observed racemization, we discovered that the intermolecular N-arylation of enantiomerically enriched α-substituted amines catalyzed by L_nPd/(±)-BINAP gives coupled products without erosion of optical activity (Table 1, entries 1,6,9−14).[21] For example, (*R*)-α-methylbenzylamine (1.2 mmol, >99% ee) and 4-bromobiphenyl (1 mmol) are coupled using NaO*t*-Bu (1.4 equiv), $Pd_2(DBA)_3$ (2 mol %, 4 mol % Pd), and (±)-BINAP (4 mol %) in toluene at 70 °C to give (*R*)-*N*-(α-methylbenzyl)-4-phenylaniline in 86% yield and >99% ee (Table 1, entry 1). The use of lower catalyst loadings (1 mol % $Pd_2(DBA)_3$, 2 mol % Pd) and higher reaction temperatures (100 °C) give the coupled product in 65% yield and >99% ee (Table 1, entry 2).

Reactions catalyzed by (DPPF)$PdCl_2$·CH_2Cl_2 in the presence of excess DPPF give yields and ee's similar to those obtained when $Pd_2(DBA)_3$/(±)-BINAP is used to couple primary α-substituted amines with aryl bromides (entries 3 and 8).[8] The *in situ* generation of the active catalyst from $Pd(OAc)_2$ and an excess of DPPF gives similar results to those obtained with (DPPF)$PdCl_2$·CH_2Cl_2/DPPF (entry 4). Without an excess of DPPF, however, the yield is significantly lower though the ee remains high (entry 5).

Acyclic secondary amine substrates give lower yields of coupled products than those obtained with primary amines or cyclic secondary amine substrates in reactions catalyzed by $Pd_2(DBA)_3$/(±)-BINAP and generally require electron-deficient aryl bromides for complete conversion (entry 6). In these cases the side products, imine and hydrodehalogenated arene, result from

Table 1. Palladium-Catalyzed Coupling of Optically Active α-Substituted Amines with Aryl Bromides[g]

entry	aryl halide	amine	product	yield (%)[a]	ee (%)
1				86	>99
2[b]	" "	" "	" "	65	>99
3[c]	" "	" "	" "	80	>99
4[d]	" "	" "	" "	82	>99
5[e]	" "	" "	" "	40	>99
6				43	96
7[b]	" "	" "	" "	63	96
8[c]	" "	" "	" "	56	96
9				89	>99
10				82	>99
11				71	94
12[f]				77	>99
13				98	>99
14				72	>99

[a] Yields and ee's refer to the average of two isolated yields of >99% purity as determined by ^{1}H NMR and elemental analysis. [b] Reactions were run with 1 mol % $Pd_2(DBA)_3$, 2 mol % (±)-BINAP, 1.4 equiv of NaO*t*-Bu, 0.5 M in toluene at 100 °C. [c] Reactions were run with 5 mol % (DPPF)$PdCl_2$·CH_2Cl_2, 15 mol % DPPF, 1.25 equiv of NaO*t*-Bu, 1 M in THF at 100 °C. [d] Reactions were run with 5 mol % $Pd(OAc)_2$, 20 mol % DPPF, 1.25 equiv of NaO*t*-Bu, 1 M in THF at 100 °C. [e] Reactions were run with 5 mol % $Pd(OAc)_2$, 5 mol % DPPF, 1.25 equiv of NaO*t*-Bu, 1 M in THF at 100 °C. [f] Three equiv of 2-bromopyridine were used. [g] Reactions were run with 2 mol % $Pd_2(DBA)_3$, 4 mol % (±)-BINAP, 1.4 eequiv of NaO*t*-Bu, 0.5 M in toluene at 70 °C unless otherwise stated.

(19) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138.

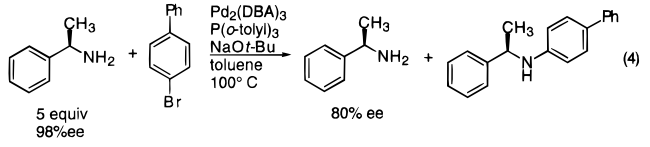
(20) Tombo, G. M. R.; Schär, H. P.; Ghisalba, O. *Agric. Biol. Chem.* **1987**, *51*, 1833−1838.

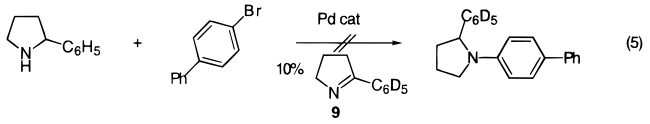
(21) The use of less expensive bis(phosphine) ligands, such as 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, and 1,2-bis(diphenylphosphino)benzene, also prevents racemization in these reactions. However, the yields of coupled products are significantly lower due to poor conversion and an increase of side products which arise from β-hydride elimination from Pd(II)−amido complexes. See ref 7.

β-hydride elimination from an intermediate Pd(II)-amido complex. However, higher yields of coupled products may be obtained by raising the reaction temperature to 100 °C (entry 7). The use of (DPPF)$PdCl_2$·CH_2Cl_2/DPPF as a catalyst at 100 °C also gives improved yields of coupled products with acyclic secondary amine substrates (entry 8).

Due to the importance of amino alcohols in the pharmaceutical industry, we hoped to extend this methodology to the selective N-arylation of enantiomerically enriched amino alcohols. However, protection of the hydroxyl group was required in order to obtain the desired product in good yield. A variety of protecting groups were surveyed, and we found that amino alcohols protected as their *tert*-butyl ethers underwent efficient coupling (entries 13 and 14).[22]

In order to probe the mechanism of racemization in intermolecular coupling reactions of enantiomerically enriched α-substituted amines with aryl bromides using the $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$ catalyst, the reaction protocol in eq 2 was varied in order to examine which reaction parameters have an effect on the ee of the coupled product. The following observations were made: (1) The ratio of $Pd_2(DBA)_3$:P(*o*-tolyl)$_3$ had little effect on the ee of the coupled product. (2) The use of other monodentate phosphine ligands such as P(1-naphthyl)$_3$, P(*o*-methoxyphenyl)$_3$, and PPh_3 gave products with similar ee's as those obtained with P(*o*-tolyl)$_3$. (3) Racemization was found to be temperature dependent, where higher reaction temperatures gave a more extensively racemized product. (4) Control experiments showed that amine racemization requires a palladium complex and an aryl bromide, which suggested that an (aryl)(Br)Pd(II)L_n (L = P(*o*-tolyl)$_3$) complex is involved in amine racemization. (5) A sample of **7** (>99% ee) was subjected to typical reaction conditions for 24 h and did not undergo racemization, indicating that amine racemization occurs prior to or during the coupling reaction and not after the product is formed. (6) When the coupling reaction was carried out in the presence of an excess of the enantiomerically enriched α-substituted amine, the recovered unreacted amine was partially racemized (eq 4). (7) When a deuterated imine was added to a $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$ catalyzed aryl amination, no deuterium was incorporated into coupled product as detected by ^{2}H NMR (eq 5).[23,24]

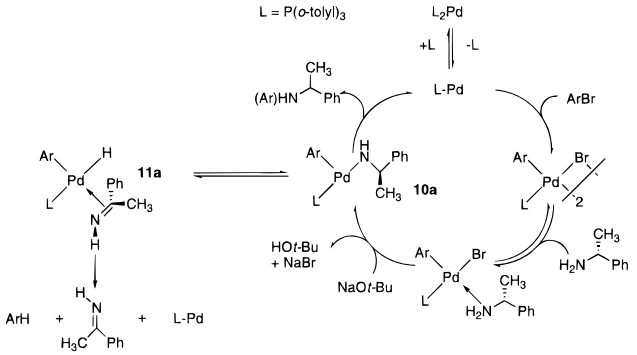




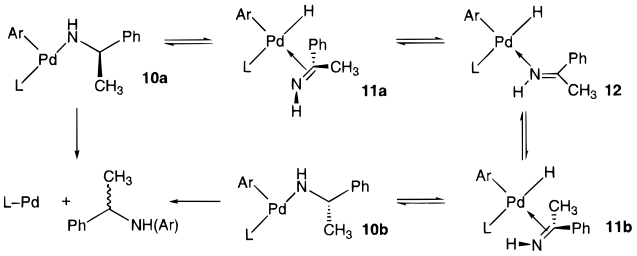
Discussion

β-Hydride elimination is known to be a facile and reversible process for late transition metal−amido complexes.[25−27] Palladium-mediated racemization of optically active amines has been observed by several research groups, where reversible β-hydride elimination of Pd(0)−amino or Pd(II)−amido complexes is responsible for racemization.[28,29]

Scheme 2



Scheme 3



Reports on the mechanism of Pd/P(*o*-tolyl)$_3$-catalyzed aryl amination reactions suggest that the use of P(*o*-tolyl)$_3$ favors the formation of mono(phosphine) palladium intermediates which are believed to be the catalytically active species (Scheme 2).[27] Oxidative addition of an aryl bromide then forms a dimeric Pd(II) species, which has been shown to form monomeric Pd(II)−amino complexes upon addition of an amine. Deprotonation then forms Pd(II)−amido complex **10a** which can undergo reductive elimination to give the coupled product. Alternately, if **10a** possesses β-hydrogens, reversible β-hydride elimination from **10a** can lead to the formation of imine and hydrodehalogenated arene, which are common side products in this reaction.

Though β-hydride elimination from Pd(II)−amido complex **10a** (Scheme 3) initially forms the π-coordinated imine **11a**, σ-coordination through the lone pair on nitrogen is favored for late transition metal−imine complexes.[30] An equilibrium between π-coordinated Pd(II)−imine complex **11a** and σ-coordinated Pd(II)−imine complex **12** provides a pathway for the formation of the π-coordinated imine complexes **11a** and **11b**, where either face of the prochiral imine is bound to the metal center.[31] Migratory insertion of the π-coordinated imine into the palladium−hydride bond of **11a** and **11b** then forms enantiomeric Pd(II)−amido complexes **10a** and **10b**.[32] Reductive elimination then produces a racemized mixture of the coupled product. Alternately, Pd(II)−amido complexes **10a** and **10b** can undergo exchange with another equivalent of amine,

(22) Overman has recently used our methodology to aid in the determination of the absolute configuration of an amino alcohol derivative. See: Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449−1456.

(23) The addition of imine inhibits the coupling reaction; therefore, only 10 mol % imine was used.

(24) Similarly, it has been shown that Pt-bound butene produced by β-hydride elimination from (DPPF)$PtBu_2$ does not undergo exchange with free butene in solution. See: Whitesides, G. M.; Gaasch, J. F.; Stedronsky, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 5258−5270.

(25) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163−1188.

(26) Diamond, S. E.; Mares, F. *J. Organomet. Chem.* **1977**, *142*, C55−C57.

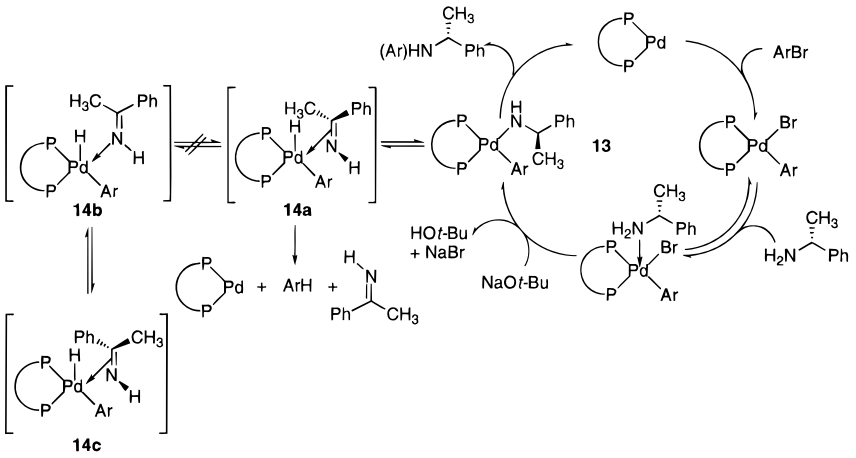
(27) Hartwig, J. F.; Richards, S.; Baraño, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626−3633.

(28) Murahashi, S. I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002−5011.

(29) Walker, H. W.; Kresge, C. T.; Ford, P. C.; Pearson, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 7429−7430.

(30) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

Scheme 4

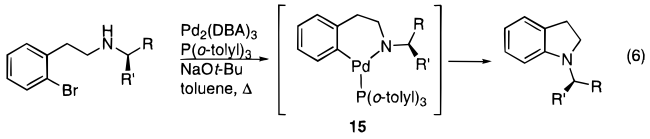


producing a new Pd(II)−amido complex plus racemized uncoupled amine (eq 4).[33]

An equilibrium between **11a** and **11b** could also result from the exchange of a palladium-bound imine with free imine in solution. However, the lack of deuterium incorporation in eq 5 indicates that the palladium-bound imine is not exchanging with free imine in solution. Therefore the equilibrium between **11a** and **11b** must proceed through the σ-coordinated Pd(II)−imine complex **12**.

Unlike reactions catalyzed by $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$, L_nPd/bis(phosphine) catalysts presumably have two phosphines on the palladium center throughout the catalytic cycle.[7,8] This precludes three-coordinate palladium intermediates in the catalytic cycle and creates a more sterically crowded metal center. We believe that the success of L_nPd/bis(phosphine) catalysts in coupling optically active amines with aryl halides without loss of enantiopurity is due to their ability to prevent the equilibration between the π-bound palladium imine complex **14a** and its diastereomer **14c** (Scheme 4). The formation of the σ-coordinated Pd(II)−imine complex **14b** may be prohibited for steric reasons. The formation of **14b** would require a Pd−N−C−CH_3 dihedral angle of 0°, placing the methyl group toward the sterically crowded metal center, in contrast to **14a** where the dihedral angle is 90° and the methyl group is pointed away from the metal center. If **14b** is not formed, the major pathway for facial equilibration of a π-coordinated Pd(II)−imine complex is eliminated. Instead **14a** reforms **13** without racemization. Alternately, **14a** may lose the coordinated imine prior to hydride reinsertion, due to steric reasons, followed by reductive elimination of the hydrodehalogenated arene. This side reaction leads to a lower yield but no loss of enantiomeric purity of the product. The use of chelating (bis)phosphine ligands minimizes β-hydride elimination from Pd(II)−amido complexes. That β-hydride elimination is not entirely suppressed is evidenced by the formation of products resulting from this process: imine and hydrodehalogenated arene.[34]

In intramolecular $Pd_2(DBA)_3$/P(*o*-tolyl)$_3$ catalyzed aryl aminations, we believe that β-hydride elimination is not competitive with reductive elimination of the aryl amine. The metallacycle intermediate **15** (eq 6) is formed by the oxidative addition of the aryl halide to palladium, followed by deprotonation of the amine. It has been shown that five- and six-membered late transition metal metallacycles, even those with exocyclic alkyl groups, are significantly more resistant toward β-hydride elimination than their acyclic analogs.[35] If reversible β-hydride elimination is not competitive with reductive elimination, then no pathway for racemization exists. Therefore bis(phosphine) ligands are not required to obtain unracemized coupled products in intramolecular coupling reactions.



Recently, it has been reported that catalytic mixtures of Pd-[P(*o*-tolyl)$_3$]$_2$Cl$_2$ or Pd(PPh$_3$)$_4$ with stoichiometric amounts of CuI under phase transfer conditions catalyze the coupling of optically active amino acids with aryl bromides and iodides without racemization.[36] The reaction does not proceed without CuI, though its role in the reaction is unknown. In contrast to our findings, products arising from β-hydride elimination are not reported. Copper ions are known to form chelates with amino acids through the carboxyl and amino groups. Formation of a chelate complex may disfavor β-hydride elimination due to geometric constraints, therefore preventing racemization of the amino acid during the coupling reaction.

Conclusion

$Pd_2(DBA)_3$/P(*o*-tolyl)$_3$ catalyzes the intramolecular coupling of optically active α-substituted amine substrates without racemization. However, L_nPd/bis(phosphine) catalysts are required to obtain unracemized products in intermolecular coupling reactions of optically active α-chiral amines with aryl

(31) A similar $\pi-\sigma-\pi$ equilibrium has been observed. See: Boone, B. J.; Klein, D. P.; Seyler, J. W.; Mendez, N. Q.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 2411−2421.

(32) It is believed that π-coordination in metal-imine complexes is required for insertion reactions to occur. See: Fryzuk, M. D.; Piers, W. E. *Organomet.* **1990**, *9*, 986−998.

(33) Bryndza, H. E.; Calabrese, J. C.; Marsi, M.; Roe, D. C.; Tam, W.; Bercaw, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 4805−4813.

(34) For example, when 2-phenylpyrrolidine and 4-bromobiphenyl were coupled using 2 mol % Pd2(DBA)3, 4 mol % (±)-BINAP, and 1.4 equiv of NaO*t*-Bu in toluene at 70 °C, a mixture of 46% 2-phenyl-1-pyrroline, 36% biphenyl, and 18% *N*-(*p*-biphenyl)-2-phenylpyrrolidine was obtained as determined by GC analysis. The percentages were corrected for the response factors of each component of the mixture.

(35) McDermott, J. X.; White, J. F.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6521−6528.

(36) Ma, D.; Yao, J. *Tetrahedron: Asymm.* **1996**, *7*, 3075−3078.

(37) Verdaguer, X.; Lange, U. E.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784−6785.

(38) Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579−588.

(39) Fry, D. F.; Fowler, C. B.; Dieter, R. K. *SynLett* **1994**, 836−838.

halides. The use of $L_nPd/(\pm)$-BINAP as a catalyst preserves the optical purity of the starting amine, in addition to giving higher yields of coupled products with primary amine substrates than those obtained using the $Pd_2(DBA)_3/P(o\text{-tolyl})_3$ catalyst. The comparison of these catalyst systems and substrates provides insight into the mechanism for the palladium-mediated racemization of α-substituted amines. Furthermore, this methodology provides a simple and efficient method for the N-arylation of optically active α-substituted amines and for the synthesis of optically active indoline derivatives.

Acknowledgment. We thank Pfizer Inc. and the National Science Foundation for their support of this research and Strem Chemical for their generous gifts of (±)-BINAP and (*S*,*S*)-Et-DuPHOS. We thank Dr. Xavier Verdaguer for the synthesis of (*S*)-2-phenylpyrrolidine.[37] S.W. is the recipient of a Ford Foundation Fellowship. R.A.R. was a NCI Postdoctoral Trainee supported by NIH Cancer Training Grant CI T32CA09122.

Experimental Procedure

General Considerations. All reactions were run in oven-dried test tubes under a nitrogen atmosphere unless otherwise stated. Toluene was distilled from molten sodium under argon. Sodium *tert*-butoxide was purchased from Aldrich Chemical Co., stored in a vacuum atmospheres drybox under nitrogen, and weighed out in the air. All reagents were commercially available and used without further purification unless noted otherwise.

Preparative flash chromatography was performed using ICN Flash Silica Gel, 230−400 mesh. Yields and ee's refer to the average of two isolated yields of 95% or higher purity as determined by GC, ^{1}H NMR, and elemental analysis (for new compounds). All products were characterized by ^{1}H NMR, ^{13}C NMR, and infrared (IR) spectroscopy. New compounds were further characterized by C, H analysis from E & R Microanalytical Laboratories. All ^{1}H NMR spectra (300 MHz) are reported in δ units, ppm down field from tetramethylsilane as an internal standard. All ^{13}C NMR spectra (75 MHz) are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77 ppm. Gas chromatography analyses were performed on a Hewlett-Packard 5890 gas chromatograph, with a FID, a 25 m capillary column with a dimethylpolysiloxane stationary phase, and a 3392A integrator. Melting points are uncorrected. Ee's were determined by HPLC analyses using a Hewlet Packard series 1050 HPLC with a 1040A detection system using a Chiralcel OD or OJ column. Alternately, ee's were determined by GC analysis with an Alltech G-TA 20 m capillary column, with 0.13 μm thickness and 0.25 mm diameter. Optical rotations were measured using a sodium lamp (589 nm) and are reported in degrees, with concentration units of g/100 mL.

Synthesis of (*R*)-*N*-(α-methylbenzyl)indoline (2). (*R*)-2-Bromo-*N*-(α-methyl)phenylacetamide. 2-Bromophenylacetic acid (2 g, 9.3 mmol) was added to $SOCl_2$ (5 mL, 68 mmol) in a Schlenk flash under argon at −78 °C, and the reaction mixture was stirred at room temperature for 2 h. The excess $SOCl_2$ was removed under vacuum, and THF (10 mL) was added. The solution was then cooled to 0 °C, and (*R*)-α-methylbenzylamine was added dropwise (3 mL, 23.25 mmol). The solution was warmed to room temperature and stirred for 3 hours. THF was removed under vacuum, CH_2Cl_2 (15 mL) was added, and the solution was washed with a saturated $NaHCO_3$ solution (2 × 10 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated to give the title compound as a white solid (2.74 g, 93% yield). mp 138−140 °C. ^{1}H NMR δ 7.58 (d, J = 7.7 Hz, 1 H), 7.20−7.34 (m, 7 H), 7.15 (dt, J = 1.8, 7.5 Hz, 1 H), 5.78 (d, J = 6.2 Hz, 1 H), 5.11−5.29 (m, 1 H), 3.70 (s, 2 H), 1.43 (d, J = 7.0 Hz, 3 H); ^{13}C{^{1}H} NMR δ 168.8, 143.1, 135.0, 133.3, 131.9, 129.3, 128.8, 128.2, 127.4, 126.2, 125.0, 48.9, 44.3, 21.8; IR (KBr) 3062, 2925, 1640, 1549, 1444, 1412 cm^{-1}; Anal. Calcd for $C_{16}H_{17}NOBr$: C, 60.53; H, 5.07. Found: C, 60.39; H, 5.07. $[\alpha]^{24°C}$ +15° (*c* 1.3, $CHCl_3$).

(*R*)-2-(*o*-Bromophenyl)-*N*-(α-methylbenzyl)ethylamine (1). (*R*)-2-Bromo-*N*-(α-methyl)phenylacetamide (1 g, 3.14 mmol) was dissolved in THF (10 mL) in a flame dried three-necked flask equipped with a reflux condenser and cooled to 0 °C. Commercial borane−THF solution was added dropwise (8.4 mL, 1 M in THF, 8.4 mmol, 2.7 equiv), and the solution was heated to reflux for 8 h. THF was removed under vacuum, the solution was acidified to pH = 1 with 10% HCl, and the reaction mixture was stirred for 30 min. The solution was made basic (pH = 14) with 1 M NaOH, stirred for 15 min, and then extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the crude product as a yellow oil. Flash column chromatography (10% EtOAc/Hex) afforded the product as a clear oil (862 mg, 95% yield). ^{1}H NMR δ 7.50 (d, J = 7.5 Hz, 1 H), 7.17−7.31 (m, 7 H), 7.01−7.07 (m, 1 H), 3.82 (q, J = 6.5 Hz, 1 H), 2.69−2.93(m, 4 H), 1.47 (s, 1 H), 1.35 (d, J = 6.6 Hz, 3 H); ^{13}C{^{1}H} NMR δ 145.5, 139.4, 132.8, 130.6, 128.4, 127.8, 127.3, 126.9, 126., 58.0, 47.2, 36.8, 24.4; IR (neat) 3059, 3024, 2960, 2837, 1470, 1449 cm^{-1}; Anal. Calcd for $C_{16}H_{18}NBr$: C, 63.17; H, 5.96. Found: C, 62.90; H, 5.96. $[\alpha]^{24}$ +46° (*c* 3.1, $CHCl_3$).

(*R*)-*N*-(α-Methylbenzyl)indoline (2). (*R*)-2-(*o*-bromophenyl)-*N*-(α-methylbenzyl)ethylamine (101 mg, 0.33 mmol, 96% ee), $Pd_2(DBA)_3$ (6 mg, 0.007 mmol, 4 mol % Pd), $P(o\text{-tolyl})_3$ (8 mg, 0.026 mmol, 8 mol %), and NaO*t*-Bu (41 mg, 0.43 mmol, 1.3 equiv) in 0.6 mL of toluene were heated to 100 °C in an oven dried Schlenk flask under nitrogen for 12 h. The crude reaction solution was diluted with Et_2O (5 mL) and filtered through Celite, the Celite was rinsed with Et_2O, and the combined organic layers were concentrated. Purification by flash column chromatography (1% EtOAc/Hex) gave the product as a clear oil (67 mg, 86 % yield). ^{1}H NMR δ 7.24−7.41 (m, 5 H), 7.04 (d, J = 7.05 Hz, 1 H), 6.98 (t, J = 7.5 Hz, 1 H), 6.59 (t, J = 6.9 Hz, 1 H), 6.35 (d, J = 8.8 Hz, 1 H), 4.71 (dd, J = 6.8, 13.6 Hz, 1 H), 3.27−3.40 (m, 2H), 2.94 (t, J = 8.4 Hz, 2 H), 1.53 (d, J = 6.9 Hz, 3 H); ^{13}C{^{1}H} NMR δ 151.6, 143.1, 130.3, 128.6, 127.3, 127.2, 127.1, 124.6, 117.1, 107.4, 77.6, 77.2, 76.8, 54.7, 48.1, 28.4, 16.7; IR (neat) 3025, 2973, 2932, 2843, 1606 cm^{-1}: Anal. Calcd for $C_{12}H_{13}N$: C, 86.05; H, 7.76. Found: C, 86.27; H, 7.72. The product was found to be of 96% ee as determined by Chiral GC analysis with a Alltech G-TA column, 110 °C isotherm, and a 2 mL/min flow rate. $[\alpha]^{26}$ +67° (*c* 1.1, $CHCl_3$).

Synthesis of (*S*)-2-Methylcarboxylate-*N*-acetylindoline (5).[18] **2-Acetamido-*o*-bromomethylcinnamate (3).** 2-Acetamidoacrylate (555 mg, 3.9 mmol) was added to a solution of $Pd(OAc)_2$ (39.6 mg, 0.18 mmol) and *o*-bromoiodobenzene (1 g, 3.53 mmol) in NEt_3 (615 mL, 4.41 mmol) in a Schlenk flask under nitrogen. The solution was heated to 100 °C for 2.5 h, cooled to room temperature, diluted with CH_2Cl_2 (50 mL), and washed with water (3 × 25 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to give the crude product. Recrystallization from CH_2Cl_2/Et_2O afforded the analytically pure product as a light brown solid (884 mg, 84% yield). mp 142−144 °C. ^{1}H NMR δ 7.62 (d, J = 8.8 Hz, 1 H), 7.44 (s, 1 H), 7.40 (s, 1 H), 7.25 (t, J = 13.55 Hz, 1 H), 7.17 (t, J = 8.0 Hz, 1 H), 6.99 (s, 1 H), 3.88 (s, 3 H), 2.05 (s, 3 H); ^{13}C{^{1}H} NMR δ 168.7, 165.2, 134.4, 132.8, 130.0, 129.8, 129.5, 127.1, 126.2, 124.3, 52.7, 23.0; IR (KBr) 3211, 3000, 1722, 1654, 1521, 1507 cm^{-1}; Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34; H, 4.06. Found: C, 48.60; H, 4.28.

(*S*)-2-Bromo-*N*-acetylphenylalanine Methyl Ester (4). 2-Acetamido-*o*-bromomethylcinnamate (298 mg, 1 mmol), $[(COD)Rh]^+OTf^-$ (0.47 mg, 1 × 10^{-3} mmol), and (*S*,*S*)-Et-DUPHOS (0.38 mg, 1.05 × 10^{-3} mmol) were added to a Fisher-Porter bottle in a drybox. The vessel was then closed, removed from the glovebox, and placed in the fume hood. Anhydrous MeOH (1.3 mL) was added via syringe to the sealed flask, which was then pressurized to 30 psig with H_2 and then carefully vented. This cycle was repeated two times. The reaction was then pressurized to 30 psig, and the reaction mixture was stirred at room temperature for 2.5 h. The H_2 was carefully vented, and MeOH was removed under vacuum. Flash column chromatography (50% EtOAc/Hex) afforded the analytically pure product as a white solid (285 mg, 95% yield). mp 95−100 °C. ^{1}H NMR δ 7.54 (d, J = 8.3 Hz, 1 H), 7.18−7.27 (m, 2 H), 7.11 (dt, J = 1.8, 7.2 Hz, 1 H), 6.06 (d, J = 7.9 Hz, 1 H), 4.92 (dd, J = 6.8 Hz, 1 H), 3.26 (ddd, J = 6.8, 13.9, 41.4 Hz, 2 H), 1.96 (s, 3 H); ^{13}C{^{1}H} NMR δ 172.0, 169.8, 135.8, 132.7, 130.9, 128.5, 127.3, 124.7, 52.2, 37.6, 22.7. IR (KBr) 3275, 1747, 1652, 1557, 1539 cm^{-1}; Anal. Calcd for $C_{12}H_{14}NO_3Br$: C, 48.02; H, 4.70. Found: C, 48.23; H, 4.86. The product was found to be of 99% ee as determined by HPLC analysis using a Chiralcel OJ column,

with a 10% IPA/hexane mobile phase, and a flow rate of 0.5 mL/min. $[\alpha]^{25}$ +29° (*c* 2.6, $CHCl_3$).

(*S*)-2-Methylcarboxylate-*N*-acetylindoline (5). 2-Bromo-*N*-acetylphenylalanine methyl ester (100 mg, 0.33 mmol), $Pd_2(DBA)_3$ (15.7 mg, 0.017 mmol, 10 mol % Pd), P(*o*-tolyl)$_3$ (18.3 mg, 0.06 mmol, 20 mol %), and Cs_2CO_3 (215 mg, 0.66 mmol) in toluene (0.6 mL) were heated to 100 °C in an oven-dried Schlenk flask under nitrogen for 15 h. The reaction mixture was then cooled to room temperature, directly loaded onto a chromatographic column, and purified by flash column chromatography (50% EtOAc/Hex) to give the product as a clear oil (69 mg, 98% yield). ^{1}H NMR 1.3:1 ratio of rotamers: δ major 8.21 (d, J = 7.8 Hz, 0.57 H) minor 7.13 (d, J = 7.3 Hz, 0.43 H), 7.19−7.28 (m, 2 H), 7.01 (t, J = 7.4, 1 H), major 4.91 (d, J = 9.7 Hz, 0.57 H) minor 5.15 (dd, J = 3.1, 11.1 Hz, 0.43 H), major 3.75 (s, 1.7 H) minor 3.71 (s, 1.3 H), 3.41−3.63 (m, 1 H), major 3.24 (d, J = 16.1 Hz, 0.57 H) minor 3.08 (dd, J = 2.7, 16.8 Hz, 0.43 H), major 2.15 (s, 1.7 H) minor 2.47 (s, 1.3 H); ^{13}C{^{1}H} NMR δ 171.6, 168.7, 168.2, 142.4, 141.0, 130.6, 128.3, 127.6, 125.5, 124.1, 123.8, 123.2, 117.0, 113.6, 61.1, 59.9, 52.7, 52.2, 33.3, 31.2, 24.3, 23.5; IR (neat) 2918, 2849, 1868, 1682, 1652 cm^{-1}; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98. Found: C, 65.86; H, 6.12. The product was found to be of 99% ee as determined by HPLC analysis with a Diacel OJ column, with a 10% isopropyl alcohol/hexane mobile phase and a flow rate of 0.5 mL/min. $[\alpha]^{26}$ −48° (*c* 0.8, $CHCl_3$).

Mechanistic Experiments. (1) The Effect of Pd:P(*o*-tolyl)$_3$ Ratios on Product ee's. Ratio of 2:1 (Eq 3). 4-Bromobiphenyl (233 mg, 1 mmol), (*S*)-2-phenylpyrrolidine (172 mg, 1.2 mmol, 98% ee), $Pd_2(DBA)_3$ (18 mg, 0.02 mmol, 4 mol % Pd), P(*o*-tolyl)$_3$ (24 mg, 0.08 mmol, 8 mol %), NaO*t*-Bu (134 mg, 1.4 mmol, 1.4 equiv), and toluene (9 mL) were added to an oven-dried Schlenk flask which was capped with a septum, purged with nitrogen, and then heated to 100 °C under nitrogen until the aryl bromide was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated to give the crude product. The product was found to be racemic using the procedure described for entry 1.

Ratio of 3:1. The procedure described above was repeated using 12 mol % P(*o*-tolyl)$_3$ (36 mg, 0.012 mmol, 12 mol %). The product was found to be racemic using the procedure described for entry 1.

(2) Pd-Catalyzed Coupling of α-Chiral Amines with Aryl Bromides Using Monodentate Phosphine Ligands Other than P(*o*-tolyl)$_3$. P(1-naphthyl)$_3$. 4-Bromobiphenyl (233 mg, 1 mmol), (*S*)-2-phenylpyrrolidine (172 mg, 1.2 mmol, 98% ee), $Pd_2(DBA)_3$ (18 mg, 0.02 mmol, 4 mol % Pd), P(1-naphthyl)$_3$ (34 mg, 0.08 mmol, 8 mol %), NaO*t*-Bu (134 mg, 1.4 mmol, 1.4 equiv), and toluene (9 mL) were added to an oven-dried Schlenk flask which was capped with a septum, purged with nitrogen, and then heated to 65 °C under nitrogen until the aryl bromide was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated to give the crude product. The product was found to be racemic using the procedure described for entry 1.

P(*o*-methoxyphenyl)$_3$. The experiment described above was repeated using 8 mol % P(*o*-methoxyphenyl)$_3$ (28 mg, 0.08 mmol). The product was found to be racemic using the procedure described for entry 1.

PPh$_3$. The experiment described above was repeated using 8 mol % PPh_3 (21 mg, 0.08 mmol). The product was found to be racemic using the procedure described for entry 1.

(3) The Effect of Reaction Temperature on Product ee's. At 100 °C (Eq 2). 4-Bromobiphenyl (233 mg, 1 mmol), (*R*)-α-methylbenzylamine (0.1 mL, 1.2 mmol, > 99% ee), $Pd_2(DBA)_3$ (18 mg, 0.02 mmol, 4 mol % Pd), P(*o*-tolyl)$_3$ (24 mg, 0.08 mmol, 8 mol %), NaO*t*-Bu (134 mg, 1.4 mmol, 1.4 equiv), and toluene (9 mL) were added to an oven-dried Schlenk flask which was capped with a septum, purged with nitrogen, and then heated to 100 °C under nitrogen until the aryl bromide was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The product was found to have a 70% ee using the procedure described for entry 1.

At 110 °C. The experiment described above was repeated at 110 °C. The product was found to have a 40% ee using the procedure described for entry 1.

(4) Control Experiments. Eq 2 without $Pd_2(DBA)_3$. 4-Bromobiphenyl (233 mg, 1 mmol), (*R*)-α-Methylbenzylamine (0.1 mL, 1.2 mmol, > 99% ee), $Pd_2(DBA)_3$ (9 mg, 0.01 mmol, 4 mol % Pd), P(*o*-tolyl)$_3$ (24 mg, 0.08 mmol, 8 mol %), NaO*T*-Bu (67 mg, 0.7 mmol, 1.4 equiv), and toluene (9 mL) were added to an oven-dried test tube which was capped with a septum, purged with nitrogen, and then heated to 100 °C under nitrogen for 12 h. The reaction mixture was then allowed to cool to room temperature and worked up as described above. The naphthylamide was found to be of 99% ee as determined by HPLC analysis using the procedure described above.

Eq 2 without an Aryl Bromide. 4-Bromobiphenyl (233 mg, 1 mmol), (*R*)-α-methylbenzylamine (0.1 mL, 1.2 mmol, >99% ee), P(*o*-tolyl)$_3$ (24 mg, 0.08 mmol, 8 mol %), NaO*t*-Bu (134 mg, 1.4 mmol, 1.4 equiv), and toluene (9 mL) were added to an oven-dried Schlenk flask which was capped with a septum, purged with nitrogen, and then heated to 100 °C under nitrogen for 12 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O, and the solution was concentrated under vacuum. CH_2Cl_2 (10 mL) was added to the crude reaction mixture, followed by an excess of NEt_3 (∼0.5 mL) and 1-napthoyl chloride (∼0.2 mL). The mixture was stirred at room temperature for 30 min and washed with saturated brine (1 × 10 mL), and the organic layer was separated, passed through silica gel, and concentrated under vacuum. The resulting naphthoyl amide was found to have a 99% ee as determined by HPLC analysis using a Chiracel OD column, with a 10% IPA/hexane mobile phase, and a flow rate of 0.5 mL/min.

(5) Lack of Racemization of 7. A sample of **7** (136 mg, 0.5 mmol, >99% ee), $Pd_2(DBA)_3$ (9 mg, 0.01 mmol, 4 mol % Pd), P(*o*-tolyl)$_3$ (12 mg, 0.04 mmol, 8 mol %), NaO*t*-Bu (67 mg, 0.7 mmol, 1.4 equiv), and toluene (5 mL) were added to an oven-dried Schlenk flask which was capped with a septum, purged with nitrogen, and then heated to 100 °C for 16 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography (2% EtOAc/hexane) afforded the product. The product was found to be >99% ee as determined by HPLC analysis using the procedure described above.

(6) Racemization of (*R*)-α-Methylbenzylamine (Eq 4). 4-Bromobiphenyl (233 mg, 1 mmol), (*R*)-α-methylbenzylamine (0.5 mL, 5 mmol, >99% ee), $Pd_2(DBA)_3$ (18 mg, 0.02 mmol, 4 mol % Pd), P(*o*-tolyl)$_3$ (24 mg, 0.08 mmol, 8 mol %), NaO*t*-Bu (134 mg, 1.4 mmol, 1.4 equiv), and toluene (9 mL) were added to an oven-dried Schlenk flask which was capped with a septum, purged with nitrogen, and then heated to 100 °C under nitrogen until the aryl bromide was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, the Celite was rinsed with Et_2O, and the combined organic layer was concentrated under vacuum. Distillation of the resulting crude reaction mixture (70 °C, 1 mmHg) afforded the unreacted starting amine (197 mg, 33%). The 1-naphthylamide was prepared using the procedure described above and was found to have an 80% ee as determined by HPLC analysis using a Chiracel OD column, with a 10% IPA/hexane mobile phase, and a flow rate of 0.5 mL/min.

(7) Exchange Experiment (Eq 5). 4-Bromobiphenyl (233 mg, 1 mmol), 2-phenylpyrrolidine (172 mg, 1.2 mmol), 2-(d_5-phenyl)-1-pyrroline (15 mg, 0.1 mmol) $Pd_2(DBA)_3$ (18 mg, 0.02 mmol, 4 mol % Pd), P(o-tolyl)$_3$ (24 mg, 0.08 mmol, 8 mol %), NaO*t*-Bu (134 mg, 1.4 mmol, 1.4 eq), and toluene (5 mL) were added to an oven-dried Schlenk flask which was capped with a septum, purged with nitrogen, and then heated to 70 °C under nitrogen until the aryl bromide was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated to give the crude product.

Purification by flash column chromatography (2% EtOAc/Hex) afforded the product. ^{2}H NMR showed that no deuterated coupled product was formed.

Pd-Catalyzed Coupling of α-Substituted Optically Active Amines with Aryl Bromides. Procedure A. The aryl bromide (0.5 mmol), amine (0.6 mmol), $Pd_2(DBA)_3$ (9 mg, 0.01 mmol, 4 mol % Pd), (±)-BINAP (12 mg, 0.02 mmol, 4 mol %), NaO*t*-Bu (67 mg, 0.7 mmol, 1.4 eq), and toluene (5 mL) were added to an oven-dried test tube which was capped with a septum, purged with nitrogen, and then heated to 70 °C under nitrogen until the aryl bromide was consumed as determined by GC analsis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography afforded the pure product.

Procedure B. In the drybox, the aryl bromide (0.5 mmol), (DPPF)-$PdCl_2$·CH_2Cl_2, (20.5 mg, 0.025 mmol, 5 mol % Pd), DPPF (42 mg, 0.075 mmol, 15 mol %), and NaO*t*-Bu (60 mg, 0.625 mmol, 1.25 equiv) were added to an oven-dried sealable Schlenk flask. The flask was then sealed, removed from the glovebox, and attached to a Schlenk line. The amine (0.625 mmol) and THF were added under positive argon pressure. The flask was then sealed and heated to 100 °C, behind a blast shield, for 4 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was then dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography afforded the pure product.

(*R*)-*N*-(α-Methylbenzyl)-4-phenylaniline (Table 1, Entry 1). Procedure A was used to convert 4-bromobiphenyl and (*R*)-α-methylbenzylamine (>99% ee) to the title compound. Purification by flash column chromatography (2% EtOAc/Hex) gave the product as a white solid (119 mg, 88% yield). mp 98−100 °C. ^{1}H NMR δ 7.47 (d, J = 7.4 Hz, 2 H), 7.29−7.39 (m, 8 H), 7.21 (m, 2 H), 6.56 (dd, J = 5.2, 2.0 Hz, 2 H), 4.51 (q, J = 6.9 Hz, 1 H), 4.12 (s, 1 H), 1.52 (d, J = 6.9 Hz, 3 H); ^{13}C{^{1}H} NMR δ 146.8, 145.2, 141.36, 130.23, 128.8, 128.7, 127.9, 127.1, 126.4, 126.1, 125.9, 113.7, 53.6, 25.1; IR (neat) 2920, 1460, 1377 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N$: C, 87.87; H, 7.01. Found: C, 87.84; H, 7.25. The product was found to be of >99% ee as determined by HPLC analysis using a Chiralcel OD column, with a 10% isopropyl alcohol (IPA)/hexane mobile phase, and a flow rate of 0.5 mL/min. $[\alpha]^{24}$ +54° (*c* 0.5, $CHCl_3$).

(*R*)-*N*-(α-Methylbenzyl)-4-phenylaniline (Entry 2). 4-Bromobiphenyl (0.5 mmol, 117 mg), (*R*)-α-methylbenzylamine (0.6 mmol, 0.05 mL, >99% ee), $Pd_2(DBA)_3$ (4.5 mg, 0.005 mmol, 2 mol % Pd), (±)-BINAP (6 mg, 0.01 mmol, 2 mol %), NaO*t*-Bu (67 mg, 0.7 mmol, 1.4 equiv), and toluene (5 mL) were added to an oven-dried test tube which was capped with a septum, purged with nitrogen, and then heated to 100 °C under nitrogen until the aryl bromide was consumed, as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography (2% EtOAc/Hex) afforded the pure product (89 mg, 65% yield). The product was found to be of >99% ee using the procedure described for entry 1.

(*R*)-*N*-(α-Methylbenzyl)-4-phenylaniline (Entry 3). Procedure B was used to convert 4-bromobiphenyl and (R)-α-methylbenzylamine (>99% ee) to the title compound (110 mg, 80% yield). The product was found to be of >99% ee using the procedure described for entry 1.

(*R*)-*N*-(α-Methylbenzyl)-4-phenylaniline (Entry 4). 4-Bromobiphenyl (177 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol % Pd), DPPF (55.5 mg, 0.01 mmol, 20 mol %), and NaO*t*-Bu (60 mg, 0.625 mmol, 1.25 equiv) were added to an oven-dried sealable Schlenk flask in a drybox under nitrogen. The flask was then sealed, removed from the drybox, and attached to a Schlenk line. (*R*)-α-Methylbenzylamine (80 μL, 0.625 mmol, >99% ee) and THF (0.5 mL) were added under positive argon pressure. The flask was sealed and heated to 100 °C, behind a blast shield for 4 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography (2% EtOAc/Hex) afforded the product as a white solid (112 mg, 82% yield). The product was found to be of >99% ee using the procedure described for entry 1.

(*R*)-*N*-(α-Methylbenzyl)-4-phenylaniline (Entry 5). 4-Bromobiphenyl (177 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol, 5 mol % Pd), DPPF (14 mg, 0.025 mmol, 5 mol %), and NaO*t*-Bu (60 mg, 0.625 mmol, 1.25 equiv) were added to an oven-dried Schlenk flask in a drybox under nitrogen. The flask was then capped with a septum, removed from the glovebox, and attached to a Schlenk line. (*R*)-α-Methylbenzylamine (0.08 mL, 0.625 mmol, 1.25 equiv, >99% ee) and THF (0.5 mL) were added under positive argon pressure. The flask was then sealed and heated to 100 °C, behind a blast shield, for 12 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite were rinsed with Et_2O. The filtrate was then dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography (2% EtOAc/Hex) afforded the product as a white solid (54 mg, 40% yield). The product was found to be of >99% ee using the procedure described for entry 1.

(*R*)-*N*-(4-Benzotrifluoro)-*N*-α-dimethylbenzylamine (Entry 6). Procedure A was used to convert 4-bromobenzotrifluoride and (*R*)-*N*-α-methylbenzylamine (96% ee) to the title compound. Purification by flash column chromatography (1% EtOAc/Hex) gave the product as a white solid (61 mg, 44% yield). mp 72−74 °C. ^{1}H NMR δ 7.45 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 6.0 Hz, 2 H), 7.27 (d, J = 8.3 Hz, 3 H), 6.82 (d, J = 9.0 Hz, 2 H), 5.18 (qd, J = 6.7, 13.8 Hz, 1 H), 2.74 (s, 3 H), 1.57 (d, J = 6.7 Hz, 3 H); ^{13}C{^{1}H} NMR δ 152.3, 142.1, 128.8, 127.3, 126.9, 126.8, 126.73, 126.68, 126.64, 111.8, 56.3, 32.2, 16.9; IR (neat) 2981, 2914, 2832, 1613 cm^{-1}; Anal. Calcd for $C_{16}H_{16}NF_3$: C, 68.81; H, 5.77. Found: C, 68.59; H, 5.45. The product was found to be of 96% ee as determined by HPLC analysis using a Chiralcel OJ column with a 10% IPA/hexane mobile phase and a flow rate of 0.5 mL/min. $[\alpha]^{26}$ +138° (*c* 1.0, $CHCl_3$).

(*R*)-*N*-(4-Benzotrifluoro)-*N*-α-dimethylbenzylamine (Entry 7). 4-Bromobenzotrifluoride (0.5 mmol, 0.07 mL), (*R*)-*N*-α-methylbenzylamine (0.6 mmol, 0.06 mL, 96% ee), $Pd_2(DBA)_3$ (4.5 mg, 0.005 mmol, 2 mol % Pd), (±)-BINAP (6 mg, 0.02 mmol, 2 mol %), NaO*t*-Bu (67 mg, 0.7 mmol, 1.4 eq), and toluene (5 mL) were added to an oven-dried test tube which was capped with a septum, purged with nitrogen, and then heated to 100 °C under nitrogen until the aryl bromide was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL), and filtered through Celite, and the Celite was rinsed with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography (1% EtOAc/Hex) afforded the pure product (88 mg, 63% yield). The product was found to be of >99% ee using the procedure described for entry 6.

(*R*)-*N*-(4-Benzotrifluoro)-*N*-α-dimethylbenzylamine (Entry 8). Procedure B was used to convert 4-bromobenzotrifluoride and (*R*)-*N*-α-methylbenzylamine (96% ee) to the title compound (78 mg, 56% yield). The product was found to be of 96% ee as determined by the procedure described in entry 6.

(*R*)-*N*-(4-Benzophenone)-1-cyclohexylethylamine (Entry 9). Procedure A was used to convert 4-bromobenzophenone and (*R*)-1-(cyclohexyl)ethylamine (>99% ee) to the title compound. Purification by flash column chromatography (10% EtOAc/Hex) gave the product as a viscous yellow oil (131 mg, 89% yield). ^{1}H NMR δ 7.69−7.75 (m, 4 H), 7.41−7.54 (m, 3 H), 6.53 (dt, J = 5.8 Hz, 3.15 Hz, 2 H), 4.17 (d, J = 8.4 Hz), 3.43 (dd, J = 6.3 Hz, 14.3 Hz, 1 H), 1.66−1.84 (m, 5H), 1.44−1.46 (m, 1 H), 0.99−1.26 (m, 8 H); ^{13}C{^{1}H} NMR δ 195.1, 151.9, 139.5, 133.3, 131.2, 129.6, 128.2, 125.6, 111.6, 52.9, 43.3, 29.8, 28.7, 26.7, 26.5, 26.4, 17.6; IR (neat) 3346, 2926, 2850, 1590, 1493 cm^{-1}; Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20. Found: C, 82.06; H, 8.37. The product was found to be >99% ee as determined by HPLC analysis using a Chiralcel OJ column, with a 2% IPA/hexane mobile phase, and a flow rate of 0.7 mL/min. $[\alpha]^{25}$ +11° (*c* 0.4, $CHCl_3$).

(*S*)-*N*-(4-Chlorophenyl)-2-phenylpyrrolidine (Entry 10). Procedure A was used to convert 4-bromochlorobenzene and (*S*)-2-phenylpyrrolidine[37] (>99% ee) to the title compound. Purification by flash column chromatography (2% EtOAc/Hex) gave the product as white

solid (101 mg, 79% yield). mp 50−52 °C. ^{1}H NMR δ 7.16−7.29 (m, 6 H), 7.05 (d, J = 8.7 Hz, 2 H), 6.37 (d, J = 8.7 Hz, 2 H), 4.67 (d, J = 7.7 Hz, 1 H), 3.65 (dt, J = 8.04 Hz, 2.75 Hz, 1 H), 3.36 (dd, J = 15.78 Hz, 8.81 Hz, 1 H), 2.35−2.40 (m, 1 H), 1.89−2.04 (m, 3 H); ^{13}C{^{1}H} NMR δ 145.8, 144.2, 128.9, 128.7, 126.9, 126.0, 120.7, 113.6, 63.2, 49.4, 36.3, 23.3; IR (neat) 2968, 2849, 1596, 1490 cm^{-1}. Anal. Calcd for $C_{16}H_{16}NCl$: C, 74.56; H, 6.26. Found: C, 74.34; H, 6.43. The product was found to be of >99% ee as determined by HPLC analysis using a Chiralcel OD column, with a 2% IPA/hexane mobile phase and a flow rate of 0.5 mL/min. $[\alpha]^{25}$ −99° (*c* 2.8, $CHCl_3$).

(*R*)-*N*-(*sec*-Butyl)-2-aminonaphthalene (Entry 11). Procedure A was used to convert 2-bromonaphthalene and (*R*)-*sec*-butylamine (94% ee) to the title product. Purification by flash column chromatography (2% EtOAc/Hex) gave the product as a light brown oil (70 mg, 70% yield). ^{1}H NMR δ 7.57−7.66 (m, 3H), 7.31−7.36 (m, 1 H), 7.16 (dt, *J* = 7.2 Hz, 2.0 Hz, 1 H), 6.83 (dd, *J* = 2.5 Hz, 8.8 Hz, 1 H), 6.77 (d, *J* = 1.6 Hz, 1 H), 3.62 (s, 1 H), 3.49−3.58 (m, 1 H), 1.50−1.71 (m, 2 H), 1.23 (d, *J* = 5.5 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H); ^{13}C{^{1}H} NMR δ 145.5, 135.5, 129.1, 127.8, 127.4, 126.4, 125.9, 121.8, 118.5, 104.8, 49.9, 29.7, 20.3, 10.6; IR (neat) 3404, 3050, 2963, 2929, 2874, 1628, 1520, 1484, 1398 cm^{-1}. Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60. Found: C, 84.59; H, 8.76. The product was found to be of 94% ee as determined by HPLC analysis using a Chiralcel OD column, with a 5% IPA, 0.05% diethylamine/hexane mobile phase, and a flow rate of 0.5 mL/min. $[\alpha]^{25}$ +35° (*c* 3.2, $CHCl_3$).

(*R,R*)-*trans*-*N,N′*-(Tri-2-pyridyl)-1,2-cyclohexyldiamine (Entry 12). 2-Bromopyridine (0.3 mL, 3 mmol), (*R,R*)-*trans*-1,2-cyclohexyldiamine (0.12 mL, 1 mmol, >99% ee), $Pd_2(DBA)_3$ (14 mg, 0.015 mmol, 6 mol % Pd), (±)-BINAP (20 mg, 0.03 mmol), and NaO*t*-Bu (327 mg, 3.4 mmol, 3.4 eq) were heated to 70 °C in an oven-dried Schlenk flask under argon for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with Et_2O (10 mL), and washed with saturated brine (3 × 10 ml), and the organic layer was dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash column chromatography (15% EtOAc/Hex, with 5% NEt_3) afforded the product as a yellow solid (258 mg, 77% yield). mp 104−105 °C. ^{1}H NMR δ 8.37 (d, *J* = 4.1 Hz, 2 H), 7.93 (d, *J* = 4.4 Hz, 1 H), 7.37 (dt, *J* = 7.76 Hz, 2 H), 7.19 (dt, *J* = 7.74 Hz, *J* = 1.77 Hz, 1H), 6.86 (dd, *J* = 6.55 Hz, *J* = 5.2 Hz, 2 H), 6.58 (d, *J* = 8.06 Hz, 2 H), 6.37 (dd, *J* = 6.2 Hz, J = 5.2 Hz, 1 H), 6.09 (d, *J* = 8.4 Hz, 1 H), 5.49 (d, *J* = 7.4 Hz, 1 H), 5.03 (dt, *J* = 11.4 Hz, *J* = 3.7 Hz, 1 H), 3.91−3.95 (m, 1 H), 2.31−2.34 (m, 1 H), 2.03−2.08 (m, 1 H), 1.71−1.79 (m, 3 H), 1.30−1.44 (m, 3 H); ^{13}C{^{1}H} NMR δ 158.5, 157.8, 148.4, 148.0, 137.6, 136.8, 117.8, 117.7, 111.7, 107.4, 59.7, 53.8, 33.9, 32.0, 26.2, 24.9; IR (nujol) 2971, 2880, 2836, 1465 cm^{-1}; Anal. Calcd for $C_{21}H_{23}N_5$: C, 73.02; H, 6.71. Found: C, 73.29; H, 6.98. The product was found to be of >99% ee as determined by HPLC analysis using a Chiralcel OD column, with a 10% IPA/hexane mobile phase and a flow rate of 0.5 mL/min. $[\alpha]^{25}$ +149° (*c* 0.9, $CHCl_3$).

***tert*-Butyl Ether of (*S*)-*N*-(4-Benzophenone)phenylalaninol (Entry 13).** Procedure A was used to convert the *tert*-butyl ether of (*S*)-phenylalaninol (>99% ee) and 4-bromobenzophenone to the title compound. Purification by flash column chromatography (10% EtOAc/Hex) gave the product as a thick yellow oil (190 mg, 98% yield). ^{1}H NMR δ 7.73 (t, *J* = 7.9 Hz, 4 H), 7.42−7.52 (m, 3 H), 7.23−7.33 (m, 5 H), 6.61 (d, *J* = 8.7 Hz, 2 H), 4.66 (d, *J* = 8.9 Hz, 1 H); ^{13}C{^{1}H} NMR δ 195.0, 151.3, 139.2, 138.4, 133.1, 131.1, 129.4, 129.3, 128.5, 128.0, 126.4, 125.9, 111.8, 73.1, 61.1, 53.8, 37.0, 27.6; IR (nujol) 2972, 2928, 1639, 1590, 1526, 1317, 1282 cm^{-1}; Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54. Found: C, 80.81; H, 7.70. The product was found to be of >99% ee as determined by HPLC analysis using a Chiralcel OD column, with a 5% IPA/hexane mobile phase and a flow rate of 0.5 mL/min. $[\alpha]^{26}$ −100° (*c* 2.1, $CHCl_3$).

***tert*-Butyl Ether of (*S*)-*N*-(3-(2-(1,3-Dioxolanyl))phenyl)prolinol (Entry 14).** Procedure A was used to couple the *tert*-butyl ether of (*S*)-prolinol (99% ee) with 2-(3-bromophenyl)-1,3-dioxolane to give the title product. Purification by flash column chromatography (10% EtOAc/Hex) afforded the title product as a thick clear oil (106 mg, 70% yield). ^{1}H NMR δ 7.22 (t, *J* = 7.3 Hz, 1 H), 6.74−6.79 (m, 2 H), 6.63 (dd, *J* = 2.3 Hz, 14.3 Hz, 1 H), 5.78 (s, 1 H), 4.00−4.12 (m, 4 H), 3.79−3.86 (m, 1 H), 3.51 (dd, *J* = 3.4 Hz, 8.7 Hz, 1 H), 3.03−3.14 (m, 2 H), 1.96−2.06 (m, 4 H), 1.19 (s, 9 H); ^{13}C{^{1}H} NMR δ 147.6, 138.9, 129.2, 113.5, 112.6, 109.5, 104.2, 72.8, 65.2, 61.6, 58.9, 48.3, 28.7, 27.5, 23.2; IR (neat) 2971, 2875, 1606 cm^{-1}; Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91. Found: C, 70.40; H, 8.89. The product was found to be of 99% ee as determined by HPLC analyses with a Diacel OD column, with a 10% isopropyl alcohol/hexane mobile phase and a flow rate of 0.5 mL/min. $[\alpha]^{25}$ +136° (*c* 0.5, $CHCl_3$).

Preparation of Starting Materials. *tert*-Butyl Ether of (*S*)-Phenylalaninol. Isobutylene (~10 mL) was added to Fisher-Porter bottle charged with (*S*)-phenylalaninol (5 g, 33 mmol) and H_2SO_4 (2.12 mL, 40 mmol) in CH_2Cl_2 (10 mL) and stirred at room temperature for 12 h. The isobutylene was carefully vented, and 1 N NaOH was added till the solution reached pH = 12. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried over anhydrous K_2CO_3, filtered, and concentrated under vacuum to give the crude product as a yellow oil. Purification by Kugelrohr distillation gave the product as a clear oil (4.22 g, 62% yield). ^{1}H NMR δ 7.20−7.33 (m, 5 H), 3.35−3.37 (m, 1 H), 3.1503.22 (m, 2 H), 2.79 (dd, *J* = 4.4, 13.1 Hz, 1 H0, 2.52 (dd, *J* = 8.1, 13.5 Hz, 1 H), 1.39 (s, 2 H), 1.19 (s, 9 H); ^{13}C{^{1}H} NMR δ 139.22, 129.22, 128.36, 126.13, 72.68, 66.33, 52.77, 40.84, 27.55; IR (neat) 2973, 1363, 1198, 1083 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21. Found: C, 75.24; H, 10.42. $[\alpha]^{25°C}$ −9° (*c* 1.3, $CHCl_3$).

***tert*-Butyl Ether of (*S*)-Prolinol.** The procedure described above was used to convert (*S*)-prolinol (2.5 g, 25 mmol), isobutylene (~10 mL), and H_2SO_4 (1.6 mL, 30 mmol) to the title product (1.25 g, 32% yield). Spectral data was in accord with that reported by Vedejs.[38]

2-(*d*$_5$-Phenyl)-1-pyrroline (9).[39] Bromobenzene-d_5 (0.65 mL, 6.17 mmol) was dissolved in Et_2O (5 mL) and added dropwise to a solution of Mg shavings (151 mg, 6.17 mmol) and an I_2 crystal in Et_2O (5 mL) in a three-necked flask equipped with a reflux condenser. The solution was stirred at room temperature until the magnesium was consumed (2 h). 4-Chlorobutyronitrile (0.46 mL, 5.14 mmol) was then added, and the solution was heated to reflux for 2 h. The reaction mixture was cooled to room temperature, and Et_2O (20 mL) was added. The ether solution was washed with saturated brine (2 × 20 mL), stired with charcoal, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by Kugelrohr distillation gave the product as a white solid (632 mg, 68% yield). ^{1}H NMR δ 4.04−4.10 (m, 2 H), 2.92−2.98 (m, 2 H), 1.99−2.09 (m, 2 H); ^{13}C{^{1}H} NMR (125 MHz) δ 173.16, 134.29, 129.67 (t, *J* = 0.2 Hz, 1 H), 127.79 (t, *J* = 0.2 Hz, 1 H), 127.05 (t, *J* = 0.2 Hz, 1 H), 61.44, 34.81, 22.56; IR(KBr) 2966, 2919, 2849, 1613, 1537, 1446, 1431, 1400 cm^{-1}.

JA971583O