Ligand-Controlled Asymmetric Arylation of Aliphatic -Amino Anion Equivalents

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

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

ABSTRACT: A palladium-catalyzed asymmetric arylation of 9-aminofluorene-derived imines using a chiral dialkylbiaryl 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 synthesis1 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=NR 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 anions16 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 diarylmethane (b), generates the corresponding 2-azaallyl anion (d).17,18 A 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 NaOtfBu as the base and (R)-PrTrixiePhos (L1) as the supporting ligand, affording 9-fluorenylamine 4a in 82% yield with 86% ee upon reduction of 3a (entry

Table 1. Pd-Catalyzed Arylation of Imine 2a*

<table>
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<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<tr>
<td>1</td>
<td>R = iPr</td>
<td>L1</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>c-C6H4</td>
<td>L2</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>c-C6H11</td>
<td>L3</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>c-C6H13</td>
<td>L4</td>
<td>78</td>
</tr>
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*Reaction conditions: PhBr (0.25 mmol), 2a (0.325 mmol), NaOtfBu (0.275 mol%). Flu = 9-fluorenyl. TMS = trimethylsilyl. Isolated yields of 4a. The ee (enantiomeric excess) of 4a was determined by chiral HPLC.
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 through π-conjugation.

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. While diminished enantioselectivity was obtained when (R)-cyclopentylTrixiePhos (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). 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. Examination of 4'-substituted cycloheptylTrixiePhos derivatives L5−L7 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 2. Pd-Catalyzed Arylation of Imine 2b**

Scheme 2. Pd-Catalyzed Arylation of Imine 2b

**Scheme 3. Pd-Catalyzed Enantioselective Arylation Reactions**

Scheme 3. Pd-Catalyzed Enantioselective Arylation Reactions

**References:**

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2. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.

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

4. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.

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

6. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.

7. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.

8. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.

9. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.

10. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.

11. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.

12. Reaction conditions: see Table 1. The rr (regioisomeric ratio, 3b to 5) was determined by 1H NMR spectroscopy for the corresponding amines upon NaBH4 reduction.
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). Unlike the reaction of imine 2a, which yielded 3a as the only cross-coupled product, the isobutyaldehyde-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 hydrolysis 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. 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-ethylbutylaldehyde-derived imine yielded a significant amount of regioisomer 8 along with 4i. It should be noted that the imine of trimethylacetaldheyde 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 dialkyliibaryl 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 of 2-azaallyl anions are under investigation.

**REFERENCES**


(16) For recent reviews of chemical methods, see: (a) Albrecht, N. J. Am. Chem. Soc. 2013, 115, 11521.


(18) For recent reviews of chemical methods, see: (a) Roush, W. R.; Czarnik, A. W. J. Org. Chem. 2008, 73, 7469.
(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.
(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).