

A Concise Asymmetric Synthesis of *cis*-2,6-Disubstituted *N*-Aryl Piperazines via Pd-Catalyzed Carboamination Reactions

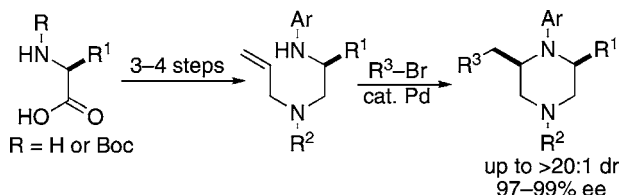
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ABSTRACT



A concise, modular, asymmetric synthesis of *cis*-2,6-disubstituted piperazines from readily available amino acid precursors is described. The key step in the synthesis is a Pd-catalyzed carboamination of a *N*¹-aryl-*N*²-allyl-1,2-diamine with an aryl bromide. The products are obtained in 14–20:1 dr, with >97% ee, and the key cyclizations are the first examples of six-membered ring formation via Pd-catalyzed carboamination reactions of unsaturated amines with aryl halides.

Substituted piperazines are of profound importance in medicinal chemistry and drug development. For example, a 2001 survey of biologically relevant templates in the MDDR revealed 2271 biologically active molecules that contained substituted *N*-aryl piperazines: 16 of these compounds were drugs on the market and an additional 23 were in phase II or III clinical trials.¹ The presence of substituents on C2, C3, C5, and C6 of the ring has a significant influence on the biological activity of these molecules, and the ability to prepare substituted piperazines is of value for the optimization of biological properties.²

Although the asymmetric synthesis of monosubstituted or 2,5-disubstituted piperazines can be accomplished in a straightforward manner by using readily available amino acid

precursors,³ the stereoselective preparation of enantiomerically enriched 2,6-disubstituted piperazines remains challenging, particularly when one of the substituents is not a carboxylic acid or ester. There are few asymmetric routes to *N,N*-disubstituted-2,6-dialkylpiperazines, and the existing syntheses of these molecules typically require ≥ 6 steps.^{4,5} In this Letter we describe a concise, modular, asymmetric synthesis of 2,6-disubstituted piperazines that allows the stereoselective preparation of compounds bearing four different groups at N1, C2, N4, and C6.⁶

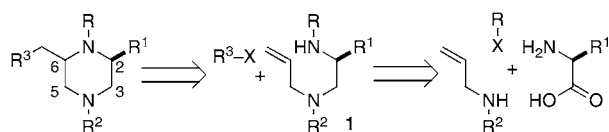
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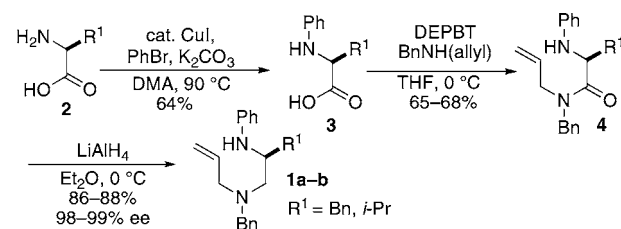
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Scheme 1. Retrosynthetic Analysis

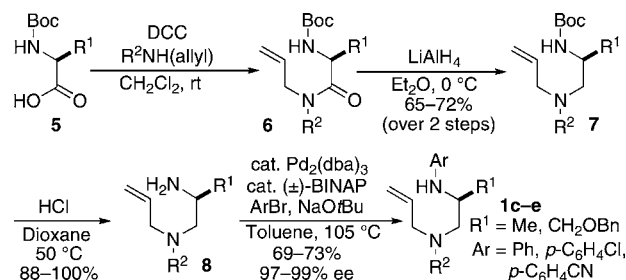
As shown in Scheme 1, our approach to the construction of 2,6-disubstituted piperazines employs a key Pd-catalyzed carboamination reaction,^{7,8} which generates the heterocyclic ring and forms two bonds simultaneously. Retrosynthetic analysis of the carboamination substrates (**1**) suggested these compounds could be prepared in a straightforward and modular fashion from simple precursors: amino acids (readily available in enantiopure form), allylic amines, and aryl halides. In addition to the synthetic utility of this strategy, the key cyclization reaction is a fundamentally interesting and challenging transformation. The generation of six-membered rings through Pd-catalyzed carboamination or carboetherification reactions between heteroatom-tethered alkenes and aryl/alkenyl halides has not been previously described, nor has the construction of heterocyclic rings bearing more than one nitrogen atom been achieved with this method. Thus, this transformation represents a significant advance in Pd-catalyzed alkene carboamination methodology.

The starting materials for the carboamination reactions were prepared from commercially available amino acids by using one of two 3–4-step sequences. As shown in Scheme 2, the first route employs unprotected amino acid starting materials, which were subjected to Cu-catalyzed *N*-phenylation using the anhydrous conditions developed by Ma, to generate **3** without significant degradation of enantiomeric purity.⁹ However, attempts to use biphasic conditions¹⁰ for the *N*-arylation of unhindered amino acids such as alanine or phenylalanine provided products with low enantiomeric purity (ca. 14–50% ee). Amide bond formation was achieved

Scheme 2. Synthesis of Substrates from Unprotected Amino Acids

by coupling **3** with *N*-(benzyl)allylamine using Goodman's DEPBT reagent.¹¹ Reduction of amide **4** with LiAlH₄ afforded **1a,b** with ≥98% ee.

Alternatively, in some instances it was advantageous to employ *N*-Boc-protected amino acids as starting materials due to their commercial availability, or due to partial loss of enantiomeric purity during the Cu-catalyzed *N*-arylation reaction.¹² These starting materials were converted to **7** in two steps via DCC-mediated coupling with an allylic amine followed by reduction with LiAlH₄ at 0 °C (Scheme 3).

Scheme 3. Synthesis of Substrates from Protected Amino Acids

Cleavage of the Boc group was accomplished by treatment of **7** with HCl/dioxane, and subsequent Pd-catalyzed *N*-arylation¹³ afforded the requisite substrates (**1c–e**) in high enantiomeric purity.

With suitable precursors in hand, we initially examined Pd-catalyzed reactions of phenylalanine-derived substrate **1a** with 4-bromoanisole using a number of different phosphine ligands. In contrast to the analogous 2,5-disubstituted pyrrolidine-forming cyclizations, which were effectively catalyzed by mixtures of Pd₂(dba)₃ and dppe,^{7a} use of catalysts supported by P(2-furyl)₃ provided optimal results in the

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(11) DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one. Use of other reagents (e.g., DCC/HOBT or CDI) resulted in partial epimerization to afford products with ~85–90% ee. See: Li, H.; Jiang, X.; Ye, Y.-h.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, 1, 91.

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Table 1. Optimization Studies

entry	ligand ^b	conversion (%) ^c	product ratio ^d	isolated yield (%)
1	dppe ^e	50	68:0:32	
2	Dpe-Phos	97	56:23:21	
3	Xantphos	82	50:35:15	
4	P(<i>o</i> -tol) ₃	87	9:17:74	
5	P(2-furyl) ₃	97	71:7:21	62 ^e

^a Reagents and conditions: 1.0 equiv of **1a**, 1.2 equiv of Ar¹Br, 1.2 equiv of NaOtBu, 1 mol % of Pd₂(dba)₃, 4 mol % of chelating ligand or 8 mol % of monodentate ligand, toluene (0.2 M), 105 °C, 8 h. ^b Dppe = 1,2-bis(diphenylphosphino)ethane, Dpe-Phos = 1,1-bis(diphenylphosphino)phenyl ether, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene. ^c Conversion refers to % starting material consumed; **9–11** were the sole products detected in the crude reaction mixture. ^d Determined by ¹H NMR analysis of crude reaction mixtures. ^e This yield was obtained after complete conversion.

piperazine-forming reactions (Table 1). Use of a 4:1 ratio of phosphine to Pd led to complete consumption of the diamine starting material, whereas reactions that employed a 2:1 L:Pd ratio frequently halted at ca. 85–90% conversion. The major side products generated in these transformations were unsaturated piperazines **10** and **11**. Resubjection of **11** to the reaction conditions did not result in the formation of **9** or **10**, and **9** was not converted to **10** under the reaction conditions.

As shown in Table 2, the carboamination reactions are effective for transformations involving derivatives of several different amino acids including phenylalanine (**1a**), valine (**1b**), serine (**1c**), and alanine (**1d–e**). The reactions are tolerant of functionalized aryl groups on N1 (e.g., *p*-chlorophenyl and *p*-cyanophenyl) and several different protecting groups on N4 (e.g., benzyl, allyl, and *p*-methoxyphenyl).¹⁴ Electron-rich, -neutral, and -poor aryl bromides can be employed as coupling partners, although use of β -bromostyrene provided low yields (ca. 25%) of the desired allylpiperazine derivative. In most cases the cyclizations afforded *cis*-2,6-disubstituted piperazines with >20:1 dr, although cyclizations of **1c** proceed with slightly lower (14:1) diastereoselectivity.^{15,16}

A plausible mechanism for the Pd-catalyzed piperazine-forming reactions is shown below (Scheme 4). These transformations appear to be mechanistically analogous to previously described carboamination reactions of γ -ami-

Table 2. Asymmetric Synthesis of 2,6-Disubstituted Piperazines^a

entry	substrate	product	dr	ee yield ^b
1			>20:1	99% 63%
2			>20:1	99% 62%
3			>20:1	98% 59%
4			>20:1	99% 51% ^c
5			>20:1	99% 50%
6			14:1	97% 71%
7			14:1	98% 69%
8			>20:1	99% 53%
9			>20:1	99% 51%

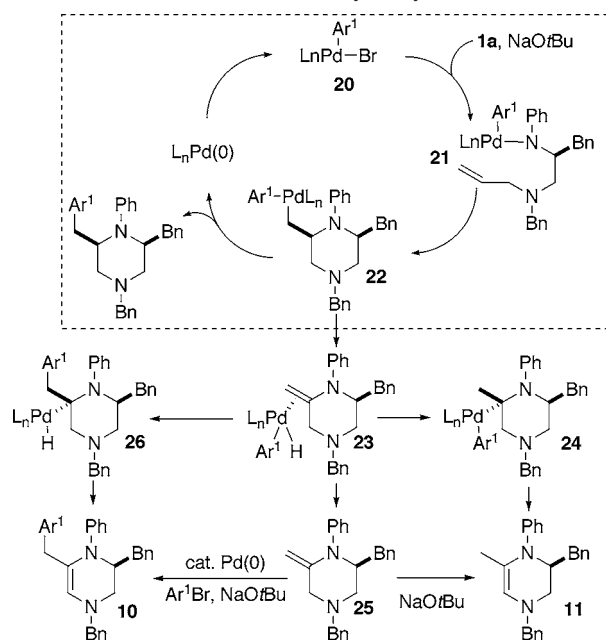
^a Reagents and conditions: 1.0 equiv of amine, 1.2 equiv of ArBr, 1.2 equiv of NaOtBu, 1 mol % of Pd₂(dba)₃, 8 mol % of P(2-furyl)₃, toluene (0.2 M), 105 °C, 8–10 h. ^b Average isolated yields obtained from two or more experiments. ^c The reaction was conducted with 2 mol % of Pd₂(dba)₃ and 16 mol % of P(2-furyl)₃.

(14) Initial studies on carboaminations of amides such as **4** or **6** suggest these transformations may be feasible, but further optimization is required; low yields (ca. 10–20%) of the desired products were obtained.

(15) Diastereomeric ratios observed in crude reaction mixtures were identical with those obtained upon isolation. In some cases the minor diastereomer could be separated by careful chromatography. See the Supporting Information for complete details.

(16) Preliminary efforts to employ a N1 Boc-protected substrate resulted in the formation of a 1:1 mixture of diastereomers. Attempts to cyclize substrates bearing N1 Piv or Ac groups have thus far been unsuccessful.

noalkenes with aryl bromides,⁷ and are likely initiated by oxidative addition of the aryl bromide to Pd(0) to generate **20**. This intermediate can react with the amine and NaOtBu to provide palladium (aryl)(amido) complex **21**, which can undergo *syn*-aminopalladation^{7a,d} to afford **22**. Carbon–carbon bond-forming reductive elimination would then yield the observed piperazine product.



Side products **10** and **11** most likely derive from a common intermediate (**23**) that results from competing β -hydride elimination of **22**. Compound **11** could be generated by insertion of the alkene into the Pd–H bond of **23** followed by β -hydride elimination from the C5 position of **24**. Alternatively, displacement of Pd from **23** would afford **25**, which could be converted to the more thermodynamically stable derivative **11** by reaction with NaOtBu. Side product **10** most likely results from Heck-type arylation of **25**, although formation of **10** via carbopalladation of **23** followed by C5 β -hydride elimination from **26** cannot be ruled out.¹⁷ The generation of **10** and **11** provides further evidence to support the mechanism of 2,6-disubstituted piperazine formation shown above, rather than a mechanism involving alkene carbopalladation of **21**.^{7a,d}

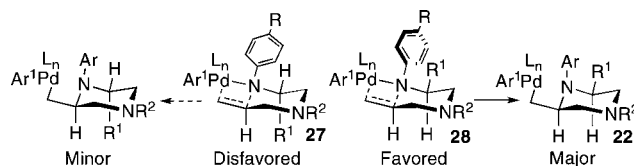
Interestingly, the production of undesired compounds resulting from β -hydride elimination of **22** is much more problematic in the *N*-arylpiperazine-forming reactions than the analogous *N*-arylpyrrolidine-forming reactions.^{7a,18} This may be due to the fact that the transition state for β -hydride elimination from the five-membered pyrrolidine ring is more

(17) Alkene insertion into late M–H bonds is usually much faster than alkene insertion into late M–C bonds. See: (a) Brookhart, M.; Hauptman, E.; Lincoln, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 10394. (b) Siegbahn, P. E. M.; Stromberg, S.; Zetterberg, K. *Organometallics* **1996**, *15*, 5542.

(18) The formation of unsaturated five-membered heterocycles analogous to **10** and **11** is generally not observed in *N*-aryl-2-benzylpyrrolidine-forming reactions. Instead, the generation of regioisomeric *N*-aryl-2-methyl-3-arylpyrrolidine side products, which result from reversible β -hydride elimination/reinsertion processes, is observed. These side products are usually formed in ca. 10% yield, whereas the combined yields of **10** and **11** is usually ca. 20–30%. For further discussion, see refs 7a and 7j.

strained (due to rehybridization of the C2-carbon from sp^3 to sp^2) than the analogous transition state for conversion of the six-membered ring **22** to **23**.

The stereochemical outcome of the piperazine-forming reactions contrasts with our model for the analogous pyrrolidine-forming processes, which are believed to proceed via a transition state in which the C1-substituent is placed in a pseudoaxial orientation to minimize A^(1,3) strain between the C1-group and the N-substituent (Ar, Boc, or Cbz).^{7a,g,j} A similar transition state structure (**27**) should afford *trans*-2,6-disubstituted piperazines, which are not the major products in these reactions. Our current working hypothesis for piperazine formation involves cyclization via transition state **28**, in which the N1-Ar group is rotated such that N1 is pyramidalized. This eliminates the A^(1,3) interaction and allows pseudoequatorial orientation of R¹, which leads to the *cis*-2,6-disubstituted stereoisomers. This hypothesis is consistent with the observation that cyclizations of substrates bearing N1-(*p*-cyanophenyl) or N1-Boc groups, which should have a decreased degree of N1-pyramidalization, proceed with lower selectivity.¹⁶



In conclusion, we have developed a new, stereoselective, asymmetric synthesis of *N*-aryl-2,6-disubstituted piperazines. This strategy allows the modular construction of a number of derivatives containing different substituents at C2, C6, N1, and N4 from simple starting materials. The key cyclizations are the first examples of six-membered-ring formation in Pd-catalyzed carboamination reactions between alkene-tethered amines and aryl halides. Further studies on the scope, stereochemical outcome, and applications of these transformations are currently underway.

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Supporting Information Available: Characterization data for all new compounds in Schemes 2 and 3 and Tables 1 and 2, and descriptions of stereochemical assignments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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