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TETRAHEDRON: *ASYMMETRY*

Synthesis of chiral *N*,*N*′-disubstituted 1,2-benzenediamines from *o*-dibromobenzene

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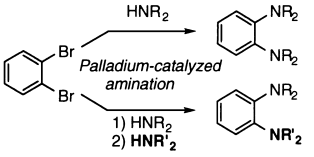
Abstract

Palladium-catalyzed amination of *o*-dibromobenzene provided chiral *N*,*N*′-disubstituted 1,2-benzenediamines in good to excellent yields. The amination was executed stepwise and in one pot to give unsymmetrically and symmetrically substituted 1,2-benzenediamines. Incorporation of chiral primary amines was possible without racemization using catalytic Pd_2dba_3–BINAP.

Many advances have been made in the palladium-catalyzed amination reaction since it was reported by Buchwald et al.[1a] and by Driver and Hartwig.[1b] Difficult substrates, usually sterically hindered aromatic halides, have generally yielded to amination thanks to a variety of ligand–palladium combinations available.[1] Double amination of dihalobenzenes is an important area of materials science and has seen a recent flurry of activity.[2] 1,2-Dibromobenzene has been coupled with morpholine;[3] however, the reaction of primary amines and the scope of the double amination has not been fully explored. Due to our interest in the preparation of chiral benzimidazolium salts beginning from 1,2-benzenediamines, we decided to explore this reaction in greater detail. The synthesis of a variety of chiral 1,2-benzenediamines from *o*-dibromobenzene is reported herein (Scheme 1).



Scheme 1.

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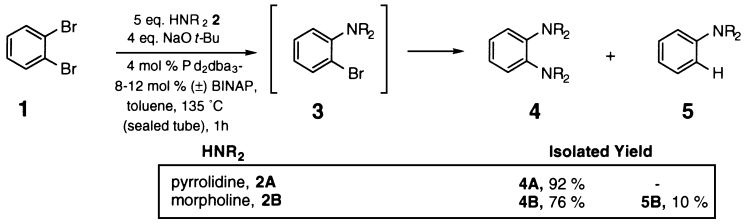
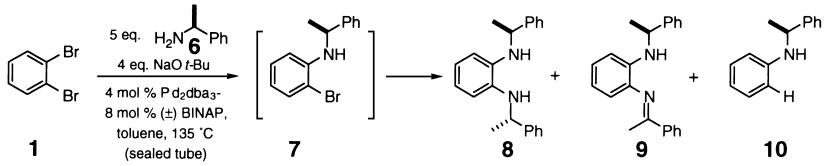
Bisamination of 1,2-dibromobenzene was achieved in one pot by using Pd_2dba_3–(±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) catalytic conditions (4 mol% Pd_2dba_3 and 8–12 mol% BINAP) and excess reagents at 135°C. Since the rate-determining step is thought to be deprotonation of the coordinated amine, a higher base concentration was used to accelerate the amination of **3** to **4**.[1d] The coupling of *o*-dibromobenzene with secondary amines was accelerated at 135°C, with reactants consumed in ca. 1 h (Scheme 2). Previous literature reports on the double amination of 1,2-dibromobenzene with secondary amines contain contrasting data.[3,4] Witulski et al.[3] obtained a 56 and 70% yield of **4A** using BINAP or dppf as a ligand, respectively. In both cases, the major by-product was reduction product **5**. A similar coupling by Beletskaya et al.[4b] using dppf as ligand failed with piperidine and gave the corresponding reduction product **5**, exclusively. Using our conditions, both morpholine and pyrrolidine were coupled smoothly (Scheme 2).



Scheme 2.

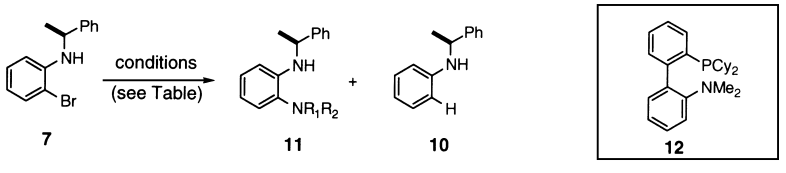
These results indicate that nucleophilic secondary amines couple effectively with 1,2-dibromobenzene without adverse steric or electronic effects on the second amination. The reduction product **5** likely originates from an intermediate palladium hydride, formed through β-hydride elimination of a coordinated amine.[5] Hydride elimination can be suppressed by chelating diphosphines,[1c,6] which may help explain the effectiveness of BINAP in this particular case. Coupling of a chiral primary amine was also successful (Scheme 3).[7] A further problem in the synthesis of dianiline **8** is the formation of imine **9**. In this demanding case, reduction and imine formation could be suppressed, but not completely eliminated when complete conversion of intermediate **7** was attained. The reactions were monitored by GC and stopped promptly when **7** was consumed. The by-products were separated by column chromatography to provide **8** in 61% yield (91% *de*, >99% *ee*; HPLC, Chiracel OD column).[8]



Scheme 3.

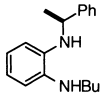
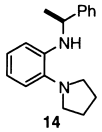
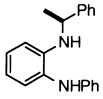
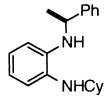
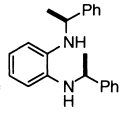
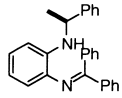
The preparation of unsymmetrical 1,2-benzenediamines is also possible using a sequential application of the amination.[9] Coupling of enantiomerically enriched **7** to various amines[10] is illustrative (Table 1). Monobromide **7** (>99% *ee*) was readily prepared by Pd-catalyzed amination of 1,2-dibromobenzene using 1 equiv. of amine **6**. Based on prior literature,[3,4] the coupling in Scheme 4 was expected to be slow, and benefited from a higher catalyst loading (4 mol%

Pd_2dba_3). Two different sets of reaction conditions were used for Scheme 4. Condition A utilizes Pd_2dba_3–BINAP heated in toluene (sealed tube) at 135°C. That the higher temperature does not result in racemization is borne out by the enantiomeric excess determinations (Table 1). The coupling of primary and secondary amines is efficient using the Pd_2dba_3–BINAP–135°C combination (entries 1, 2, 4, 6, and 7). Longer reaction times were sometimes needed for the complete conversion of **7**. In contrast, condition B uses the electron rich mixed donor ligand **12**[11] which gave shorter reaction times, although in some cases, reduction product **10** became a major by-product (e.g. entry 3, 33% isolated **10**). Each of the conditions produced imines (e.g. **9**, Scheme 3), but shorter reaction times minimized their formation. The imines are thought to arise by elimination of coordinated diamines **11**, since imine formation increased over time as the concentration of **11** was diminished. This was further supported by resubjecting **8** to the reaction conditions (condition B) which indicated a formation of **9** evidenced by ^{1}H NMR analysis. For the coupling with aniline using mixed donor **12** (entry 5) a higher base concentration is not needed and actually gave decreased yields (1.3 equiv. NaOtBu, 92% yield **15**; 2.0 equiv. NaOtBu, 65% yield **15** after 30 min and complete consumption of **7**). The lower yield using 2 equiv. base was accompanied by a deep purple–red color, possibly a result of oxidation to the *o*-quinone diimine.[12] Benzophenone



Scheme 4.

Table 1
Synthesis of unsymmetrical *N*,*N*′-disubstituted 1,2-benzenediamines

Entry	Conditions	Isol. Yield (% ee)	Product
1	A, 10 h	77 % (99 % ee)	 **13**
2	A, 10 h	76 % (99 % ee)	 **14**
3	B, 0.5 h	53 % (>99 % ee)[c]	
4	A, 1.5 h	92 % (99 % ee)	 **15**
5	B, 0.5 h	92 % (>99 % ee)	
6	A, 24 h	65 % (98 % ee)[d]	 **16**
7	A, 1.5 h	70 % (>99 % ee)	 **8**
8	B, 0.5 h	81 % (99% ee, 43 % de)[e,f]	
9	B, 1 h	93 % (>99 % ee)	 **17**

(a) Condition **A**: 4 mol % Pd_2dba_3, 8 mol % (±) BINAP, 2.5 eq. amine, 2.05 eq NaOtBu, toluene, 135 °C, 0.1-0.2 M in **7**.
(b) Condition **B**: 3.4 mol % Pd_2dba_3, 10.2 mol % **12**, 1.3 eq. amine,1.3 eq. NaOtBu, DME, 80 °C, 0.25 M in **7**.
(c) also isolated: 33 % **10**. (d) also isolated: 19.3 % **10**. (e) also isolated: 16.1 % **10**. (f) The minor diastereomer was *meso*-**8** (hplc).
All new compounds were fully characterized on the basis of their ^{1}H, ^{13}C NMR and high resolution mass spectra.

imine (1.3 equiv.) was coupled smoothly (entry 9) providing **17**. Hydrolysis[13] of imine **17** would provide access to monosubstituted 1,2-benzenediamines.

The synthesis of C_2-symmetrical diamine **8** (entries 7 and 8) is noteworthy. Longer reaction times had to be avoided since imine by-product **9** was produced. Monitoring this reaction by GC–MS indicated complete conversion to diamine after 1.5 h; however, the isolated yield of **8** was 70%. The amination using ligand **12** was complete in only 0.5 h (entry 8), but dianiline **8** was found to be a mixture of stereoisomers, 2.4:1 ratio (*S,S)*-**8** to *meso*-**8**. The major diastereomer was found to be of >99% *ee* and recovered **7** had >99% *ee*. Using excess amine, unreacted **6** was recovered and found to be 60% *ee* (after conversion to its benzoate; HPLC), suggesting that racemization of the amine is competitive with coupling.[6] To our knowledge, racemization of α-chiral primary amines has not been documented using ligand **12**. The *dr* did not change significantly (^{1}H NMR) over time even as more imine was produced.

In conclusion, direct amination of 1,2-dibromobenzene has been used to prepare a variety of 1,2-benzenediamines using the BINAP–Pd_2dba_3 system. A combination of elevated reaction temperature and excess base accelerated the reaction sufficiently for one-pot bisamination. Chiral, unsymmetrical dianilines were efficiently prepared by a sequential application of the amination. The couplings were successful for a range of aliphatic amines. The incorporation of an α-chiral primary amine can likewise be accomplished using this protocol without racemization. We have successfully converted the substituted 1,2-benzenediamines into benzimidazoles and benzimidazolium salts, the full details of which will be reported soon.

Acknowledgements

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7. General procedure for 'double amination': Preparation of **8** (Scheme 3): an oven-dried, sealable Schlenk tube equipped with a threaded teflon plug and magnetic stirbar was cooled under Ar and charged with Pd_2dba_3 (Strem, 18 mg, 0.02 mmol, 4 mol%) and *rac*-BINAP (Strem, 25 mg, 0.04 mmol, 8 mol%) in 2.5 ml of toluene. The mixture was degassed, backfilled with Ar and then heated at 135°C in an oil bath for 15 min. After cooling to room temperature, the reaction vessel was charged with NaO*t*-Bu (192 mg, 2.03 mmol, 4.05 equiv.), *(S)*-α-methylbenzylamine (0.32 mL, 2.5 mmol, 5 equiv.), 1,2-dibromobenzene (60 μL, 0.5 mmol, 1.00 equiv.), and toluene (1.0 ml). The mixture was degassed, backfilled with Ar, sealed and then heated in an oil bath at 135°C with stirring until **1** and intermediate **7** had been completely consumed as judged by glpc analysis. The solution was then allowed to cool to room temperature, diluted with ether, filtered through a pad of Celite and concentrated in vacuo (rotary evaporator) to give a crude dark brown oil which was purified by flash chromatography (4″ column, gradient elution with 5–15% CH_2Cl_2–hexane) to provide 28 mg **10** (28%) and 97 mg **8** (61%) as colorless oils, R_f 0.55 and 0.50 (70% CH_2Cl_2–hexane), respectively.
8. In separate runs, < 5% *meso*-**8** could be detected (^{1}H NMR or HPLC).
9. For a similar approach to the sequential arylation of primary amines using two different Pd-ligand combinations, see: Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.
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