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Modular Approach for Synthesis of Vicinal Diamines Containing Axial Chiral 1,1′-Binaphthyl from 1,2-Diaminoethane by Pd-Catalyzed N-Arylation Reactions

Shifa Zhu,*[,†,‡] Chao Wang,[†] Lijuan Chen,[†] Renxiao Liang,[†] Yingfeng Yu,[†] and Huanfeng Jiang[†]

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, 510640, P. R. China, and Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, P. R. China

zhusf@scut.edu.cn

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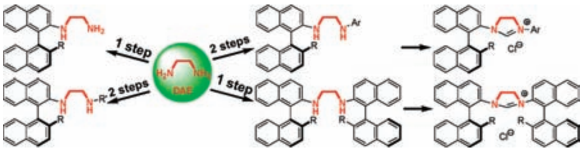
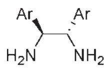
ABSTRACT



A very convenient and efficient modular approach for the synthesis of vicinal diamines containing axial chiral 1,1′-binaphthyl from 1,2-diaminoethane by Pd-catalyzed N-arylation reactions has been developed. The resulting chiral diamines could be easily converted into NHC precursors, imidazole salts, in good yields.

Chiral vicinal diamines and their derivatives have received much attention in the field of medicinal and asymmetric synthesis.[1] The most general and effective way to synthesize these important compounds is by metal-mediating and catalyzing the diamination of olefins.[2] Recently, Shi developed an elegant Cu- or Pd-catalyzed diamination of alkenes using di-*tert*-butyldiaziridinone as the nitrogen source.[3]

Among all the chiral vicinal diamines, **1** and **2** are most well-known and frequently used in the asymmetric catalytic process,[1a] in which, the chiral centers are on the carbon backbone. Interestingly, the diamine type **3**, where the chiral environment is attached to the nitrogen atoms, has received much less attention.[1−3]



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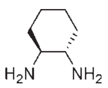

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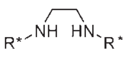

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We are interested in the N-Heterocyclic-Carbene (NHC) catalyzed asymmetric reactions; therefore,

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[†] South China University of Technology.

[‡] Chinese Academy of Sciences.

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designing and synthesizing new chiral NHC ligands are the focus of our research. At present, two large families of chiral NHC ligands dominate the literature: NHC-I (with the chiral elements on the N-heterocycle) and NHC-II (with N-substituents containing chirality) (Scheme 1).[4]

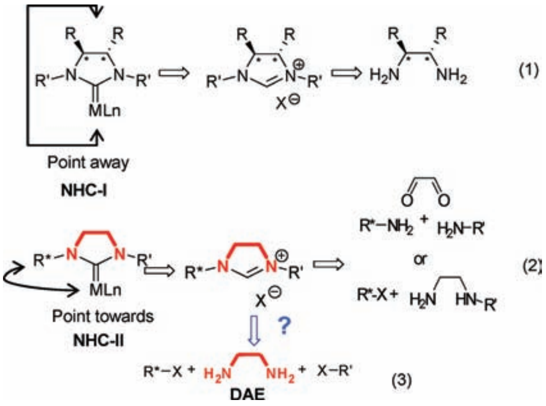
For NHC-I, the chiral center on the N-heterocycle points away from the metal center, which actually is the catalytic center. This, to some extent, will bring a negative effect to the asymmetric catalytic process. NHC-I is generally synthesized from diamine **1** or **2** by palladium catalyzed double N-arylation reactions (Scheme 1, eq 1). For NHC-II, the chirality elements are attached to the nitrogen atoms, which sit adjacent to the metal center. In this way, the chiral substituting groups are pointing toward the reactive center, which is important for the asymmetric induction process. NHC-II is often prepared by the reaction of two amines with the glyoxal or the N-arylation reaction between Ar-X or Ar-OTf with the monosubstituted diamine (Scheme 1, eq 2).[4c,d] It is curious that using simple 1,2-diaminoethane (DAE) as the starting material to get the desired chiral diamine **3** by double N-arylation reactions (Scheme 1, eq 3) has not been tried, because it is the most straightforward way to reach the diamine **3** from the viewpoint of retrosynthetic analysis.

In this paper, we report a modular synthesis of different kinds of chiral diamine from DAE by palladium catalyzed N-arylation reactions. This catalytic process would be highly desirable since the inexpensive and abundant DAE was used as the nitrogen source. Four different diamines derivatives: monosubstituted DAE **5**, C_2-symmetry disubstituted DAE **6**, and unsymmetry disubstituted DAE **7**, **8** could be prepared in only one to two steps by using this modular approach (Scheme 2).

Owing to the superior molecular skeleton, 1,1′-binaphthyl units are frequently used as chiral elements in catalyst design.[5] Therefore, in this paper, we chose (*R*)-BINOL derived monotriflate as the starting material to couple with DAE.

Initial efforts were made to systematically investigate various catalytic conditions for N-arylation reactions of monotriflate **4a** with DAE as a model reaction under different conditions. As summarized in Table 1, initially, we wanted to selectively synthesize monosubstituted amine **5a** and disubstituted diamine **6a** by controlling the ratio of triflate **4a** and DAE. When excess DAE (1.5 equiv) was employed for the N-arylation reaction, several common combinations of palladium sources and phosphine ligands were tested for the reaction. When $Pd(dba)_2$ was used as the palladium source, and DPE-Phos as the ligand, only the hydrolysis product was formed. By changing the ligand to BINAP, monosubstituted diamine **5a** could be formed in 29% isolated yield (entries 1−2). By varing the catalysts and ligands, $Pd(OAc)_2$ and BINAP were found to be the best catalyst and ligand combination for this reaction; the isolated yield could reach 49% (entry 4) when the reaction was set in toluene at 110 °C. It is interesting to find that almost no product was detected when THF was used as the solvent (entry 5), as, in many N-arylation reactions, ether solvents have been often proven superior to toluene. When the reaction was carried out in 1,4-dioxane, however, the yield of diamine **5a** was improved to 89% (entry 6). In order to remove the moisture adventitiously introduced by the reagent or operator, prior dried molecular sieves (MS) were added to the reaction system. Strangely, the yield of desired amine **5a** was decreased dramatically to 32%, and disubsituted amine **6a** was formed in 25% isolated yield (entry 7). It could be attributed to DAE being a very small organic molecule, which could enter into the MS cavity. The free DAE in the reaction solution was then decreased (less than 1.0 equiv), which resulted in the drop in yield of monosubstituted amine **5a** and rise in yield of disubstituted amine **6a**. It should be noted that disubstituted amine **6a** often was detected as the coexisting byproduct in the reaction system when the reaction was conducted at 110 °C, although the yields are very low (entries 4, 6, 7). The disubstituted amine **6a** must proceed through monosubstituted amine **5a**. Therefore, it is natural to think that we can further improve the yield of monosubstituted amine **5a** by lowering the reaction temperature to diminish the amount of disubstituted product **6a**. When the reaction was set at a temperature lower than 100 °C, disubstituted amine **6a** was

Scheme 1



Scheme 2

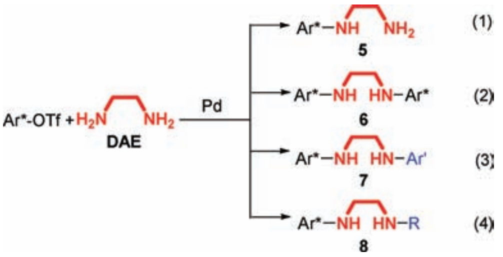


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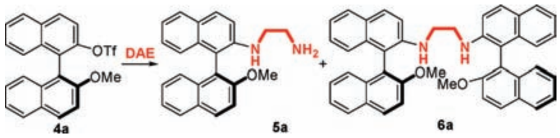
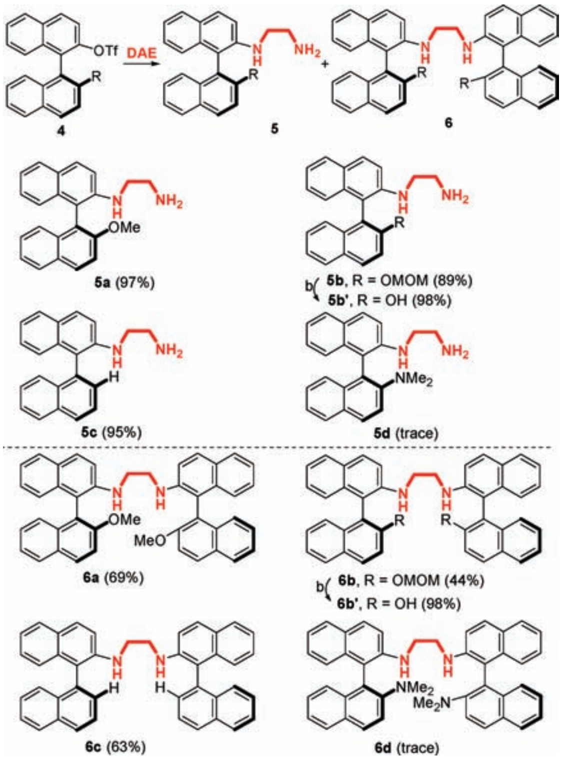
Table 1. Optimization of Reaction Conditions for the N-Arylation of DAE and **4a**[a]



					yield (%)[e]	
entry	cat.	ligand	**4a**:DAE	temp	**5a**	**6a**
1[b]	Pd(dba)$_2$	DPE-Phos	1:1.5	110	nd	nd
2[b]	Pd(dba)$_2$	BINAP	1:1.5	110	29	nd
3[b]	Pd(OAc)$_2$	DPE-Phos	1:1.5	110	3	nd
4[b]	Pd(OAc)$_2$	BINAP	1:1.5	110	49	trace
5[c]	Pd(OAc)$_2$	BINAP	1:1.5	110	trace	nd
6	Pd(OAc)$_2$	BINAP	1:1.5	110	89	trace
7[d]	Pd(OAc)$_2$	BINAP	1:1.5	110	32	25
8	Pd(OAc)$_2$	BINAP	1:1.5	80	71	nd
9	Pd(OAc)$_2$	BINAP	1:1.5	90	84	nd
10	**Pd(OAc)$_2$**	**BINAP**	**1:1.5**	**100**	**97**	nd
11	Pd(OAc)$_2$	BINAP	2.4:1	110	trace	61
12	**Pd(OAc)$_2$**	**BINAP**	**3.0:1**	**110**	nd	**69**
13[b]	Pd(OAc)$_2$	BINAP	3.0:1	110	nd	38

[a] Unless otherwise noted, the reaction was performed in 1,4-dioxane for 12 h using 10 mol % catalyst and 20 mol % ligand under N_2. [**4a**] = 0.25 M. [b] In toluene. [c] In THF. [d] In the presence of molecular sieve (100 mg MS/0.25 mmol of **4a**). [e] Isolated yield.

Scheme 3. Pd(OAc)$_2$-Catalyzed N-Arylation of DAE with Triflate **4**[a]



[a] Unless otherwise noted, the reaction was performed in 1,4-dioxane for 12 h (for **5**) or 17 h (for **6**) using 10 mol % Pd(OAc)$_2$ and 20 mol % BINAP under N_2. [**4a**] = 0.25 M. The substrate ratio for preparation of the monosubstituted diamine **5** is **4**:DAE = 1:1.5; for preparation of the disubstituted diamine **6** it is **4**:DAE = 3:1. The reaction temperature is 100 and 110 °C, respectively, for **5** and **6**. [b]Treated with HCl(concd) in MeOH at room temperature for 8 h.

not observed (entries 8, 9, 10). To our delight, the reaction yield rose surprisingly to almost quantitative yield (97%) when the reaction was executed at 100 °C (entry 10).

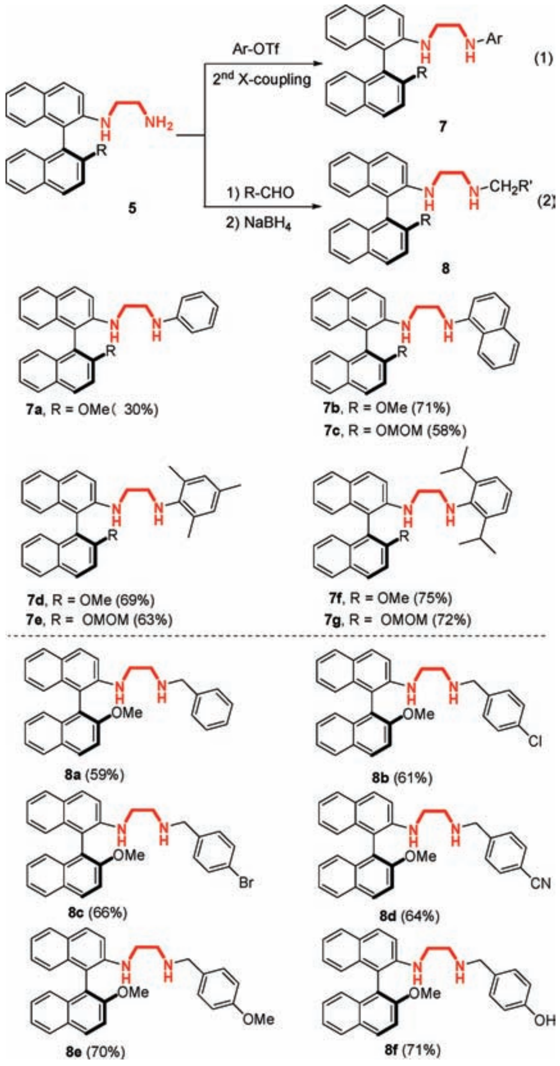
After success in the selective N-arylation of DAE with **4a** to give the monosubstituted amine **5a**, we then tried to selectively prepare disubstituted amine **6a** by controlling the starting material ratio. Using similar reaction conditions, changing the ratio of **4a**:DAE from 1:1.5 to 2.4:1, diamine **6a** was selectively formed in 61% yield (Table 1, entry 11). By increasing the ratio of **4a**:DAE to 3:1, the product yield was further enhanced to 69% (entry 12). Using toluene as the solvent gave a lower yield (entry 13), which is consistent with the trends found in the mono-N-arylation reactions in Table 1.

With the success in selecively obtaining mono- and disubstituted amine **5a** and **6a** from **4a** and DAE catalyzed by Pd(OAc)$_2$ and BINAP, the scope of the starting material was then investigated (Scheme 3). As summarized in the top part of Scheme 3, the substituted triflate **4b** (R = OMOM) and **4c** (R = H) could afford the products **5b** and **5c** as well in the same good yields. Among them, MOMO-protected amine **5b** could be easily deprotected in HCl alcohol solution affording **5b′** in almost quantitative yield. With triflate **4d** (R = NMe$_2$), however, only a trace product was given; presumably the relative strong cordination capability of the lone pair on the nitrogen atom prohibited the reductive elimination step.

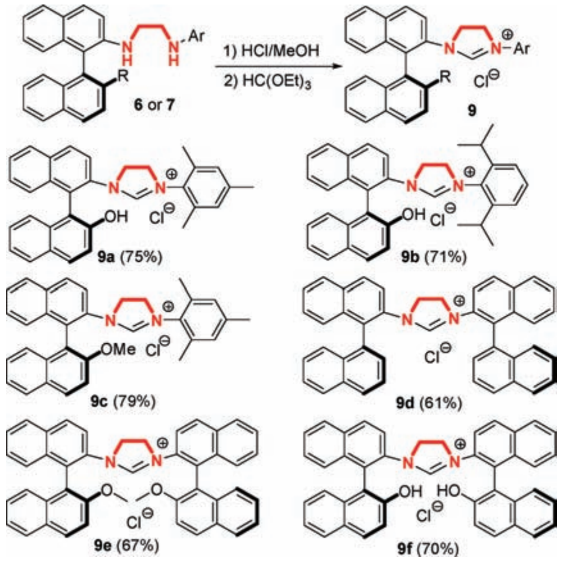
Similarly, two molecular triflates **4b** (R = OMOM) and **4c** (R = H) could also be coupled with one DAE giving the corresponding disubstituted amine **6b** and **6c**, although in relatively lower yields (44% and 63%). When amine **6b** was treated with HCl, two hydroxyl groups were released leading to the corresponding C_2-symmetry product **6b′** in 98% yield. Once again, Me$_2$N-substituted **6d** was formed only in a trace amount.

We developed a very efficient method for N-arylation of simple DAE with (*R*)-BINOL-derived triflates to prepare mono- and disubstituted diamines. This system works particularly well for mono-N-arylation reactions, in which the yield is up to 97% for product **5a**. Therefore, we next wanted to explore the further transformation of amine **5**. As shown in Scheme 4, amine **5** could be easily converted into the unsymmetric diamine **7** (by second N-arylation) and **8** (by reductive amination). Interestingly, as summarized in the top part of Scheme 4, the more bulky substrates such as naphthyl-OTf, 2,4,6-mesityl-OTf, and 2,6-diisopropylphenyl-OTf gave more satisfactory yields of products of **7** (58−75%). The less bulky phenyl-OTf, however, gave only a 30% yield of the desired amine product **7a**; a possible reason could be formation of trisubstituted amine products due to the relatively small steric hindrance of the phenyl group. For the reductive amination (the bottom part of Scheme 4), the results are more general for different kinds of aldehyde substrates with the yields ranging from 59% to 71%. It is worth mentioning that the reaction conditions for the reductive amination reaction in Scheme 4 are not optimized.

Scheme 4. Preparation of Diamine **7** and **8** by Second N-Arylation or Reductive Amination Reactions



Scheme 5. Preparation of Imidazole Salt **9** from Diamine **6** or **7**



As mentioned in the introduction of this paper, our ultimate goal is synthesizing structurally interesting chiral NHCs and studying their catalytic applications in asymmetric reactions. With synthesizing these versatile vicinal diamines containing axial chiral 1,1′-binaphtyl from DAE, we then worked on their potential applications for the synthesis of imidazole salts, the most common precursors of NHC. By simply following the literature procedure with a bit of modification,[6] six different imidazole salts **9a**−**9f** were synthesized in good yields (61%−79%) (Scheme 5). Among them, imidazole salts **9a** and **9b** are known compounds which were first reported by Hoveyda[6a] in 2002 and have already found a variety of applications in asymmetric olefin metathesis, allylic alkylations, etc.[6,7] By using our methods, imidazole salts **9a** and **9b** could be prepared in only three steps in good yields. More importantly, three different C_2-symmetry imidazole salts, **9d**, **9e**, and **9f**, could be synthesized in only two steps with satisfactory yields (61%−70%). They are potentially very hopeful chiral NHC precursors due to the important C_2-symmetry element.

In conclusion, we have developed a very convenient and efficient modular approach for the synthesis of vicinal diamines containing axial chiral 1,1′-binaphthyl from DAE by Pd-catalyzed N-arylation reactions. The resulting chiral diamine **6** or **7** reacted with triethyl orthoformate affording imidazole salt **9** in good yields, which are the most commonly used NHC precursors. We believe these structures to be interesting chiral vicinal diamines and imidazole salts, particularly the C_2-symmetric ones, and will find broad applications in asymmetric catalytic processes. Further applications of these vicinal diamines and imidazole salts in catalysis are underway in our laboratory.

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Supporting Information Available. Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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