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Atropisomerism at C–N Bonds of Acyclic Amines: Synthesis and Application to Palladium-Catalyzed Asymmetric Allylic Alkylations

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Acyclic amines **1** were obtained by a nucleophilic aromatic substitution (S_NAr) reaction and *N*-methylation followed by silane reduction. The optical resolution of C(aryl)–N(amine) bond atropisomers of amines **1** is described. We found that chiral acyclic amine **1a** can be resolved by crystallization without any outside chiral source. Finally, we demonstrate the ability of chiral amines **1** as a ligand in a palladium-catalyzed asymmetric allylic alkylation (up to 93 % *ee*).

Introduction

After the discovery and application of BINAP,[1] biaryl-type atropisomeric compounds have been widely used as chiral ligands in asymmetric catalysis.[2] We previously reported C–C bond axially chiral, biaryl-type compounds such as BICMAP.[3] On the other hand, C–N bond axially chiral compounds[4–6] have also been reported including the *N*-arylquinazolinone-,[7] *N*-arylimide-,[8] indoline-,[9] indole-,[10] and benzimidazole-type[11] phosphane ligand for palladium-catalyzed asymmetric reactions. But these phosphane ligands are cyclic nitrogen-containing compounds. Although many acyclic C–N bond axially chiral amide-type[4g,4l,4m,5] and imide-type[6] compounds have been reported, the synthesis of an acyclic-type amine compound, such as a binaphthyl surrogate with an inner N–H–N hydrogen bond has only been reported by Kawabata.[12] A C–N bond axially chiral acyclic nitrogen-containing compound for applications in asymmetric catalysis, such as an amide-type hydrazine *N*,*N*′-dicarboxylic-type organocatalyst, has only been reported by Jørgensen.[13] To the best of our knowledge, C(aryl)–N(amine) bond atropisomers of acyclic amines for chiral ligands in a catalytic asymmetric reaction have never been reported. Here, we report the first example of the synthesis of C(aryl)–N(amine) bond atropisomers of acyclic amines **1** and their application as chiral ligands for catalytic asymmetric reactions such as palladium-catalyzed asymmetric allylic alkylations (Figure 1).

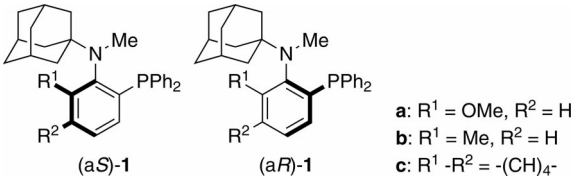
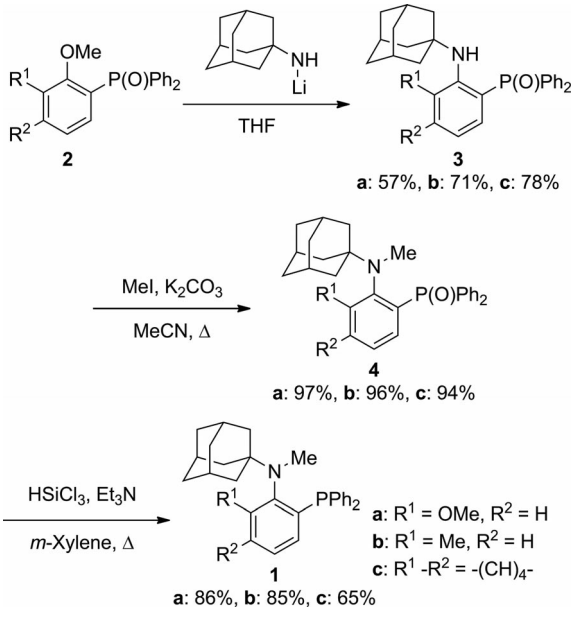


Figure 1. Acyclic amines **1**.

Results and Discussion

Acyclic amines **1** were easily prepared in three steps. A nucleophilic aromatic substitution (S_NAr) reaction of the corresponding phosphane oxide 2,3-dimethoxyphenyldiphenylphosphane oxide (**2a**)[14] with the lithium salt of 1-adamantylamine gave the corresponding aminophosphane oxide **3a**. *N*-Methylation of **3a** was carried out with MeI in the presence of K_2CO_3. This aminophosphane oxide **4a** was converted into the desired acyclic amine (±)-**1a** by using trichlorosilane-triethylamine in good yield (Scheme 1). Acy-



Scheme 1. Preparation of acyclic amines **1**.

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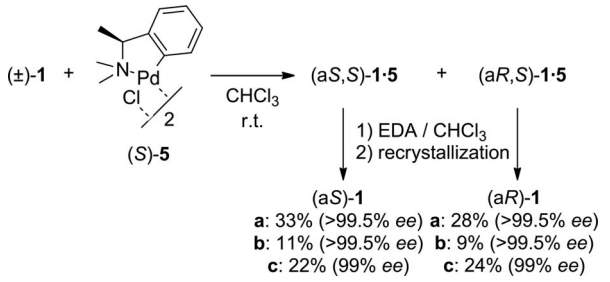
clic amines (±)-**1b** and (±)-**1c** were also easily prepared from **2b**[14] and **2c**[15] in the same manner. A suitable crystal of amine (±)-**1a** was obtained from hexane/$CHCl_3$. X-ray analysis of (±)-**1a** was carried out (Figures S1 and S2, see Supporting Information). The C(aryl)–N(amine) bonds were twisted between the aryl ring with a diphenylphosphanyl group and the adamantyl moiety.

We next attempted the optical resolution of amines (±)-**1** into each atropisomer by using (*S*)-(+)-di-μ-chlorobis{2-[(dimethylamino)ethyl]phenyl-C^2,*N*}dipalladium(II) {(*S*)-**5**}[16] as a chiral resolving agent. The resulting diastereomeric palladium complex mixtures were easily separated by silica gel column chromatography. The individual diastereomers were treated with ethylenediamine (EDA) to release optically active (a*S*)-**1** or (a*R*)-**1**(Scheme 2). After recrystallization, both the optical purity of (a*S*)-**1** and (a*R*)-**1** exceeded 99% *ee*. The determination of the absolute configurations of **1** was decided by single-crystal X-ray analysis of (–)-**1a**–**c** (Figures S3–S5, see Supporting Information).[17]



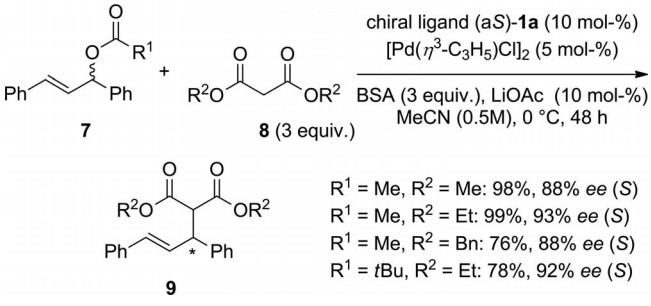
Scheme 2. Optical resolution of (±)-**1**.

On the other hand, we prepared chiral acyclic amine **1a** by crystallization without any outside chiral source. After single-crystal X-ray analysis, (±)-**1a** crystallized in a chiral fashion in the space group $P2_12_12_1$ {CIF file of (±)-**1a**-1 [absolute structure parameter = 0.47(3)] and (±)-**1a**-2 [absolute structure parameter = –0.04(9)]}.[17] This means that the crystals of (±)-**1a** formed conglomerates,[18] each consisting exclusively of either (a*R*)-(–)- or (a*S*)-(+)-enantiomers. Using 10 mg (24 crystals) of recrystallized amine (±)-**1a**, we prepared 24 samples of a small amount of hexane solutions with each crystal and checked the optical purity of each sample by chiral HPLC analysis. We obtained 6.9 mg of (a*S*)-**1** (99.6% *ee*) from 14 crystals and 1.7 mg of (a*R*)-**1** (99.7% *ee*) from four crystals. Other crystals formed twin-type chiral crystals;[19] the absolute structure parameters were different from 0, and their *ee* values were low. We repeated this experiment using 20 crystals (11.8 mg) of amine (±)-**1a** and obtained 2.1 mg of (a*S*)-**1** (99.8% *ee*) from seven crystals and 4.3 mg of (a*R*)-**1** (99.8% *ee*) from seven crystals. We successfully obtained chiral acyclic amine **1a** spontaneously by crystallization without any outside chiral source.

To investigate the nature of the structure of the palladium complex, amine (±)-**1a** was treated with $PdCl_2(MeCN)_2$ to produce palladium complex (±)-**6**, and a suitable crystal was obtained from hexane/$CHCl_3$. X-ray analysis of (±)-**6** was carried out (Figure S6, see Supporting Information).[17] The solid-state structure shows that amine **1a** is coordinated to palladium with a five-membered chelate ring by phosphorus and nitrogen atoms. The *trans* influence of the P,N-ligand is reflected in the lengthening of the Pd–Cl bond that is in a *trans* disposition to the phosphorus atom relative to the Pd–Cl bond that is in the *trans* disposition to the nitrogen atom [2.4138(8) vs. 2.3017(8) Å].

Barriers to the racemization of amines **1** in nonane for the stability of the C–N bond axial chirality were also determined (Figure S7–S9, see Supporting Information). For example, the rotational barrier ($\Delta G^{\ddagger}_{rac}$) of **1a** was found to be 29.3 kcal/mol in nonane at 25 °C, on the basis of the Arrhenius and Eyring equations.[20] This result corresponds to an estimated half-life of approximately 5.7 years.

Finally, we investigated the ability of chiral amines **1** as ligands for palladium-catalyzed asymmetric allylic alkylation.[21] Chiral ligands **1** can induce good enantioselectivities in toluene at room temperature by using 1,3-diphenyl-2-propenyl acetate (**7a**) with dimethyl malonate (**8a**). When the reaction was carried out with (a*S*)-**1a** as a ligand, the enantioselectivity of product (*S*)-**9a** obtained was higher than those obtained with chiral amines **1b** and **1c**, with good yield. Under the optimized reaction conditions (Table S1, see Supporting Information), we investigated the asymmetric allylic alkylation of similar allylic esters and malonates (Scheme 3). The reaction gave corresponding products (*S*)-**9** in good yields with high enantioselectivities.



Scheme 3. Palladium-catalyzed asymmetric allylic alkylation by using (a*S*)-**1a**.

Conclusions

We found that C–N bond axially chiral acyclic amines **1** were effective ligands for palladium-catalyzed asymmetric allylic alkylation (up to 93% *ee*). We successfully achieved spontaneous resolution without any outside chiral source. Further, we have demonstrated that acyclic amine **1a** can successfully be used in a catalytic asymmetric reaction. The combination of spontaneous resolution and application to catalytic asymmetric reactions was only reported by Balavoine.[22] In this case, the product enantioselectivity in the catalytic asymmetric reaction was moderate, 80% *ee*. We successfully combined the spontaneous resolution and application to a catalytic asymmetric reaction with high enantioselectivity. This phenomenon is the model for the

generation of an optically active compound from a fully racemic system.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data for products, ORTEP drawings, copies of NMR spectra of the products, and copies of HPLC charts are presented.

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