

Synthesis of chiral 2,2'-dipyridylamines and their use in the copper-catalyzed asymmetric allylic oxidation of cyclohexene

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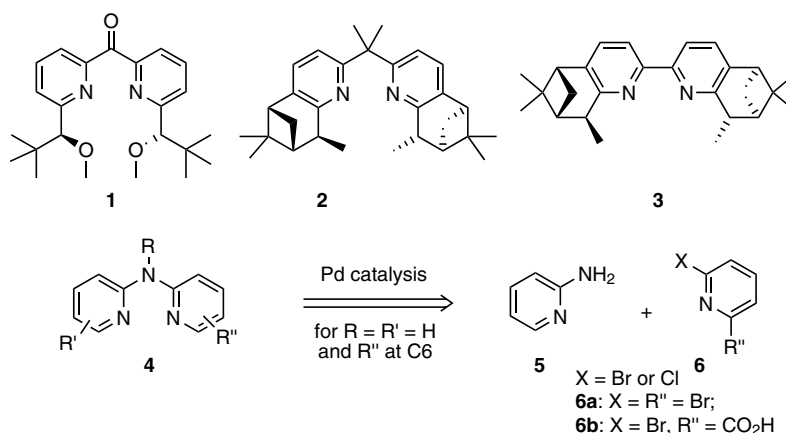
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Abstract—Chiral dipyridylamines have been synthesized by *N*-arylation reactions, and the applicability of those compounds to the copper-catalyzed asymmetric allylic oxidation of cyclohexene was demonstrated.

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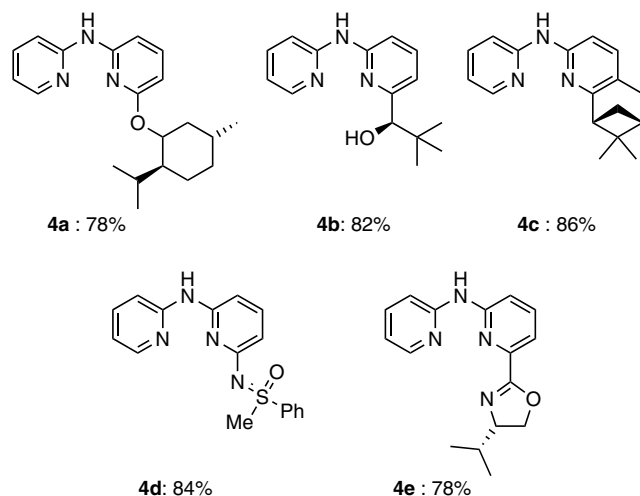
In recent years bidentate ligands containing pyridine units have attracted much attention.¹ A large variety of chiral bipyridines and phenanthrolines has been prepared and their applicability in asymmetric metal-catalyzed transformations has been demonstrated.^{1,2} Often, efficient catalysts are obtained with both high catalytic activity and enantioselectivity. Bipyridines and phenanthrolines form five-membered chelates with transition metals. Analogous pyridine-based ligands giving six-membered chelates have been much less studied, and only recently chiral dipyriddy ketone **1**³ and 2,2-disubstituted dipyriddy propane **2**⁴ were introduced. Their applicability in asymmetric catalysis has also been

established, and it was shown that a palladium catalyst derived from **2** was more efficient in an allylic alkylation reaction compared to the one obtained from the analogues bipyridine **3**. Other compounds with the potential to give six-membered chelates upon metal binding are 2,2'-dipyridylamines **4**. Taking into account that a number of 2,2'-dipyridylamines have already been applied in metal catalyses,⁵ it is rather surprising that only very few optically active derivatives have been described. Here, we report on the synthesis of *C*₁-symmetric 2,2'-dipyridylamines **4** (with R = R' = H and R'' = chiral unit at C6) and their application in copper-catalyzed asymmetric allylic oxidation reactions.



Keywords: Allylic oxidation; *N*-Arylation; Copper catalysis; 2,2'-Dipyridylamines.

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The desired compounds **4** are easily accessible by Buchwald–Hartwig aminations.^{6,7} Thus, starting from 2-aminopyridine (**5**) and various 6-substituted 2-halo pyridines (**6**) palladium-catalyzed cross-couplings using Pd(dba)₂ (5 mol%), BINAP (5 mol%), and 1.5 equiv of NaO^tBu in toluene at 80 °C gave 2,2'-dipyridylamines **4a–e** in good yields (78–86%). The substituted pyridines **6**, which were required for the syntheses of **4a**, **4b**, and **4c** were known,⁸ and the other two, which were used in the preparation of **4d** and **4e**, were obtained by palladium-catalyzed coupling of **6a** with (*S*)-phenylmethyl-sulfoximine^{9–11} and standard oxazoline synthesis¹² starting from 6-bromo-pyridine-2-carboxylic acid (**6b**), respectively. Noteworthy is the fact that the palladium-catalyzed amination of the bromopyridines possessing the coordinating sulfoximido and oxazolonyl groups also proceeded well to give **4d** and **4e**, respectively, without altering the reaction rate of the coupling.

Next, the applicability of the chiral 2,2'-dipyridylamines in asymmetric copper-catalyzed allylic oxidation reactions was studied. In order to allow an immediate comparison with known systems,¹³ cyclohexene (**7**) was selected as test substrate (Eq. 1). The catalyses were performed in acetone at ambient temperature with 5 mol% of each Cu(OTf)₂ and 2,2'-dipyridylamines **4** using a ratio of olefin **7** and *tert*-butylperoxy benzoate (**8**) of 10:1. In order to generate the active copper(I) catalysts in situ the Cu(OTf)₂/2,2'-dipyridylamine adducts were treated with 6 mol% of phenyl hydrazine.

Catalysts obtained from 2,2'-dipyridylamines **4b** and **4e** were entirely ineffective in promoting the reaction. Probably the presence of the additional coordinating group inhibited the catalysis. In contrast, 2,2'-dipyridylamines **4a**, **4c**, and **4d** gave very active catalysts, and product **9** was obtained in very good yield after a short reaction time (4–8 h). Thus, the use of menthyl-derived

2,2'-dipyridylamine **4a** and sulfoximido-substituted **4d** gave **9** in 83% and 84% yield, respectively. Unfortunately, however, the enantioselectivities were low (4% and 15% ee, respectively). The best result was achieved with pinene-derived 2,2'-dipyridylamine **4c**, which afforded the product with 17% ee in 91% yield after only 3 h.

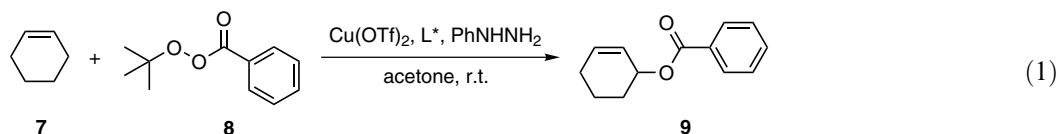
In summary, we have synthesized novel 2,2'-dipyridylamines and demonstrated their applicability as chiral ligands in asymmetric catalysis. Although the enantioselectivities in the asymmetric allylic oxidation reactions of cyclohexene are still low, we are confident that further ligand variations will result in an increase of the asymmetric induction in this synthetically important catalysis.

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