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An improved and efficient synthesis of pinene based bipyridyldiols and bipyridine

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ABSTRACT

An improved and efficient synthesis of pinene based two bipyridyldiols and bipyridine is reported. For the first time, the sealed tube-pressure reaction of pinene based pyridone with phosphoryl chloride produced an excellent yield (95%) of pinene based 2-chloropyridine, which renders synthesizing pinene based bipyridyldiols a highly inexpensive and high yielding process. Moreover, highly effective reaction condition was developed for homocoupling of chloropyridine with Ni(0) that afforded pinene based bipyridine in a high yield (84%). These newly demonstrated sealed tube-pressure chlorination and homocoupling reaction of chloropyridine afford extremely effect route for the synthesis of pinene based bipyridine.

Introduction

In the past three decades, numerous developments in the field of asymmetric synthesis have facilitated the synthesis of numerous enantioenriched compounds for organic chemists.[1] Many chiral ligands or catalysts have been used for stereoselective reactions; they are mostly either directly available from natural sources or synthesized from naturally available chiral starting materials through chiral pool synthesis.[1] Although many catalytic systems are available for each enantioselective and diastereoselective reaction, a new catalyst is still required in asymmetric synthesis for advancing the field. We studied the application of α-pinene derived *O*,*N*,*N*,*O*-tetradentate-bipyridyldiol ligands **1** and **2** (Fig. 1) to various stereoselective reactions[2] such as diethylzinc addition to prochiral aldehydes, Strecker type trimethylsilyl cyanide addition to prochiral aldehydes and imines, epoxide ring opening by a thiol nucleophile, and Nozaki–Hiyama–Kishi allylation.

Although pinene based bipyridyldiol has been investigated for almost a decade, among the two bipyridyldiols, **1** generates the highest chiral induction (up to 99% ee) for the chromium catalyzed Nozaki–Hiyama–Kishi allylation of a wide range of aldehydes.[2e] Although ligands **1** and **2** are promising ligands, they have a lack of an efficient synthetic route; for instance, among its synthetic reactions (Scheme 1), the yields of the final step was only 14% and 15%.[2e] Therefore, to explore the application of these ligands to various asymmetric transformation reactions, designing an efficient synthetic procedure is necessary.

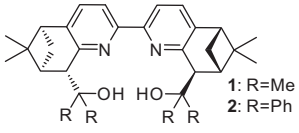

Figure 1. Structure of pinene-bipyridyldiol.

The synthesis and application of modified pinene derived bipyridine ligands have been studied mainly by Zelewsky et al.,[3] Malkov et al.,[4] and our group. The structural modification of pinene derived bipyridine predominantly involved simple pinene based bipyridine **3** as the main intermediate, which was subsequently modified into a tetradentate ligand through nucleophilic addition to ketone, as well as into alkylated bidentate ligand through nucleophilic substitution (Scheme 2).

Although a bis-nucleophilic substitution reaction with primary alkyl halide was a facile process, the presence of high steric hindrance in the constrained pinene based bipyridine **3** rendered the second nucleophilic addition reaction that hindered and lowered the yield process. Consequently, only 14% (ligand **1**) and 15% (ligand **2**) of yields were achieved in the second nucleophilic addition reaction (Scheme 1).

Among the reported methods, Malkov's synthetic procedure[4d] is the most concise (five steps) for preparing bidentate pinene based

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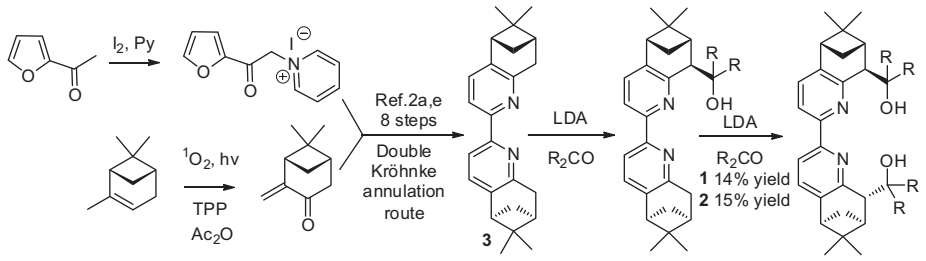
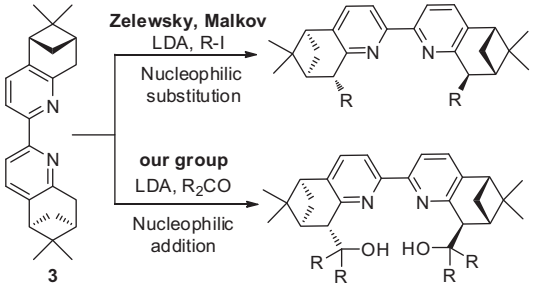


Scheme 1. Reported our synthetic double Kröhnke annulation route for **1** and **2**.



Scheme 2. Modification of simple pinene based bipyridine 3 into di- or tetradentate ligands.

bipyridine intermediate **3**. This method involves a Ni/Zn mediated homocoupling reaction of pinene based pyridine-2-triflate for constructing a bipyridine motif, which reduces the synthetic route compared with Zelewsky's route that involves sequential double Kröhnke annulations (similar to our method[2a]). Although Malkov's procedure is concise, it has a limitation of applying Kröhnke annulations, which engender poor yield (43%), and use highly expensive triflic anhydride. Therefore, we intended to modify this process for improving synthetic process of **3** and performed a nucleophilic addition reaction before homocoupling to realize an efficient route for making pinene based bipyridyldiols. Herein, we report an efficient and concise synthesis of **1**, **2**, and **3**.

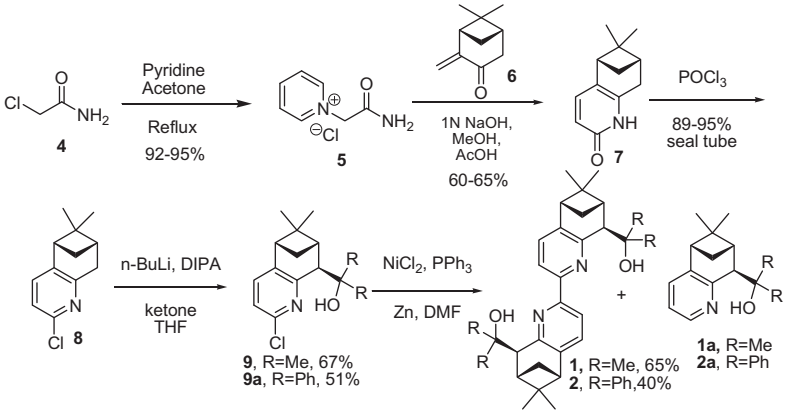
Results and discussion

Synthesis of pinene based bipyridyldiol 1 and 2

Scheme 3 shows the developed synthetic path for making **1** and **2**. The synthesis was commenced with the reaction of 2-chloroacetamide **4** with pyridine in acetone under reflux conditions that produced pyridinium salt **5**[5a] in an excellent yield (92–95%). To overcome the low yield (43%) in the Kröhnke annulations of Malkov's method,[4d] we then design a new route to synthesize pyridone **7** that one pot base-catalyzed Michael addition followed by an acid-catalyzed cyclization.[6] Thus, the reaction of pyridinium salt **5** with pinocarvone **6**[7] resulted in pyridone **7** in 60–65% yield. The yield was consistent regardless of the batch size of the reaction. The utilized pyridinium salt **5** has an advantage over Malkov's pyridinium salt [1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide][4d] by possessing an amide group that presented in pyridone **7**; consequently, it obviates the use of an external nitrogen source (ammonium acetate) required for the Kröhnke annulation approach.

With pyridone **7** in hand, we then optimized the reaction condition for conversion of pyridone **7** to chloropyridine **8**. In the literature, a similar conversion is demonstrated for numerous simple achiral pyridone moieties under various reaction conditions,[8] which are shown in Scheme 4. Although this reaction was reported to be extremely facile; initially, chloropyridine **8** was obtained only in very low yield (30−40%) by all aforementioned reaction conditions. Similar yields (30–40%) were obtained by Zelewsky and coworkers[3d] and Malkov et al.[4d] for the bromination and chlorination of similar chiral pyridones, respectively. Consequently, Malkov et al. used highly expensive triflic anhydride instead of an inexpensive chlorinating agent phosphoryl chloride ($POCl_3$); triflic anhydride enabled them to achieve the corresponding triflate product in an extremely high yield.

We envisioned that a pressure reaction could overcome this drawback. As our assumption, when the chlorination was performed with neat $POCl_3$ in a sealed tube at 130–140 °C, chloropyridine **8** was obtained in an extremely high yield (89–95%). This remarkable sealed tube reaction was reproducible even at 7-g scale, however, when this reaction was performed using round bottom flask-heating method, the reaction was very sluggish and



Scheme 3. Synthesis of α-pinene derived C_2-symmetric tetradentate bipyridyldiol **1** and **2**.