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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.

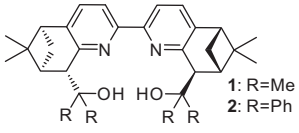

Figure 1. Structure of pinene-bipyridyldiol.

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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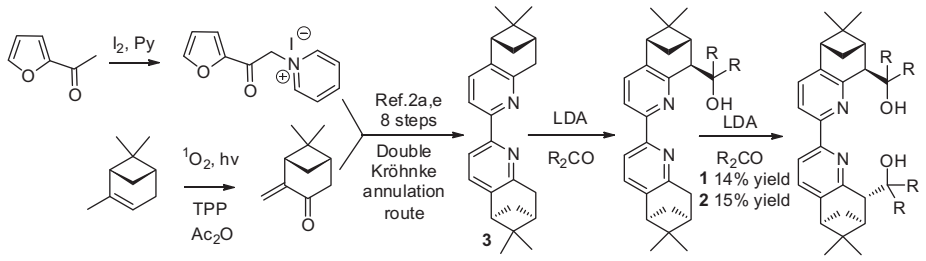
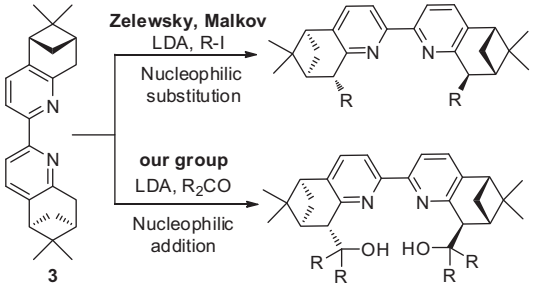


Scheme 1. Reported our synthetic double Kröhnke annulation route for **1** and **2**.



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**.

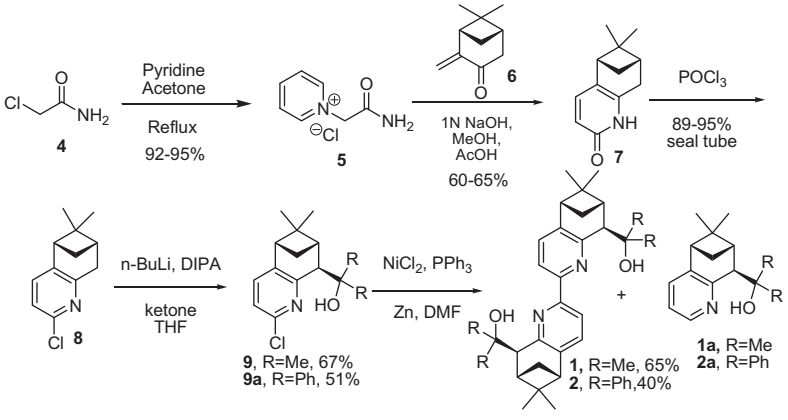
Results and discussion

Synthesis of pinene based bipyridyldiol 1 and 2

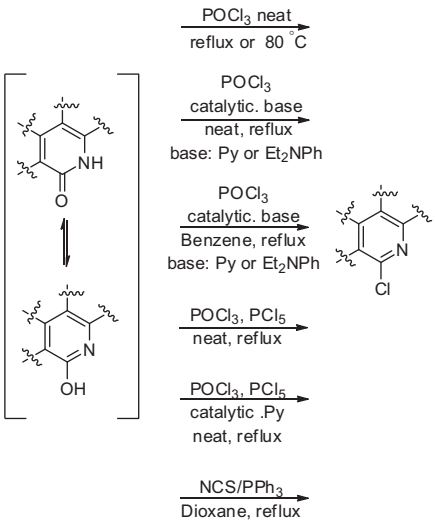
Scheme 3 shows the developed synthetic path for making **1** and **2**. The synthesis was commenced with the reaction of 2-chloroacetamide **4** with pyridine in acetone under reflux conditions that produced pyridinium salt **5**[5a] in an excellent yield (92–95%). To overcome the low yield (43%) in 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



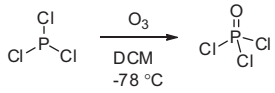
Scheme 3. Synthesis of α-pinene derived C_2-symmetric tetradentate bipyridyldiol **1** and **2**.



Scheme 4. Methods for conversion of pyridone/hydroxypyridine to chloropyridine.

produced **8** in low yield (ca. 30%). After the effective chlorination optimization, the next challenge was purchasing $POCl_3$, which has been banned by the United Nations in Taiwan. Therefore, $POCl_3$ was synthesized from PCl_3 through ozonolysis (Scheme 5).

Having chloropyridine **8** in hand, next, the nucleophilic addition reaction of **8** was performed by reacting it with lithium diisopropylamide followed by acetone to produce hydroxypropylchloropyridine **9** (Scheme 3). **9** was obtained in moderate yield (67–70%). The yield of this reaction was mainly dependent on the dryness



Scheme 5. Synthesis of phosphorous oxychloride.

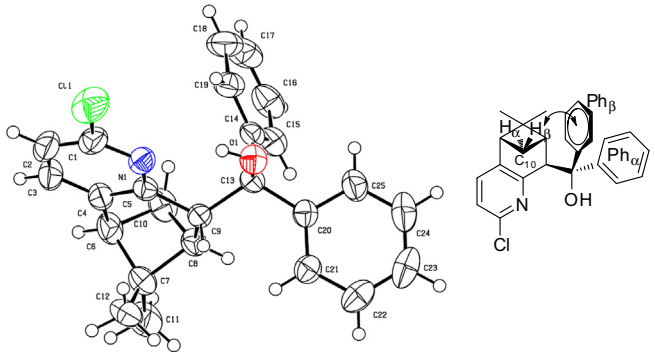


Figure 3. X-ray crystal structure of **9a** (CCDC 1463133) and its chem draw structure.

of acetone. When highly dry acetone, obtained from pyrolysis of the sodium iodide-acetone adduct, was used, the yield improved to 80%. Gratifyingly, the nucleophilic reaction of **8** with more bulky ketone, benzophenone, also produced the corresponding product **9a** in 51% yield. This reaction was successful only using highly dried benzophenone (dried over P_2O_5 in vacuum desiccator for 15 h). Interestingly, ^{1}H NMR of compound **9a** (Fig. 2) showed an unusual up-field chemical shift (δ) for a proton at −0.11 ppm (d, J = 10.28 Hz) compared to ^{1}H NMR of compound **9** that showed similar doublet at 1.34 ppm. To identify the cause for up-field chemical shift, X-ray structure was obtained for single crystal of **9a** (Fig. 3) that revealed one of C_{10} proton (H_β) resided just above one of the phenyl group (Ph_β). As in NMR, proton resides above aromatic ring more shielded by ring current of л-bond compared to lateral proton. The same ring current of phenyl group (Ph_β) might cause an up-field shift of $C_{10}H_\beta$ hence H_β is above the ring current region.

Finally, the obtained hydroxypropylchloropyridine **9** and hydroxydiphenylmethylchloropyridine **9a** underwent Ni(0) mediated homocoupling reaction, as reported earlier.[4d] For this

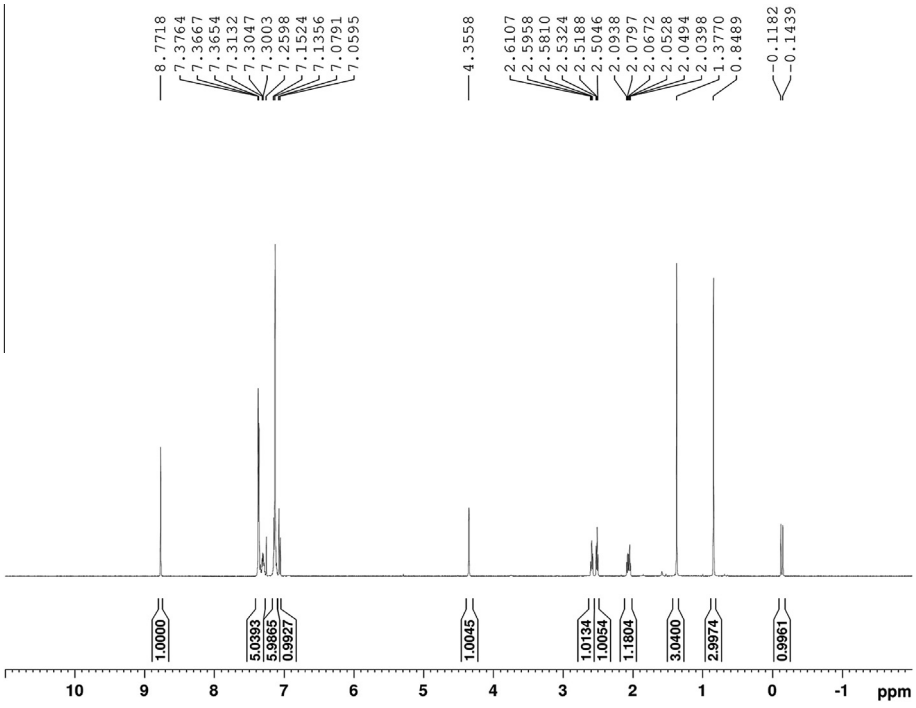


Figure 2. ^{1}H NMR of compound **9a**.

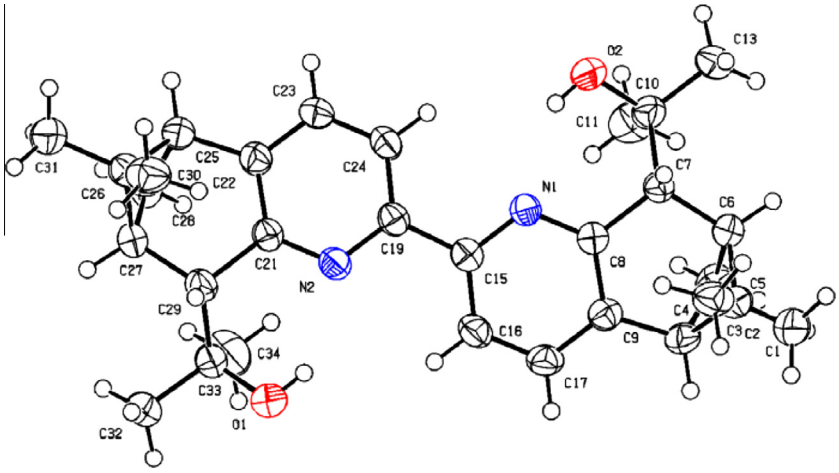


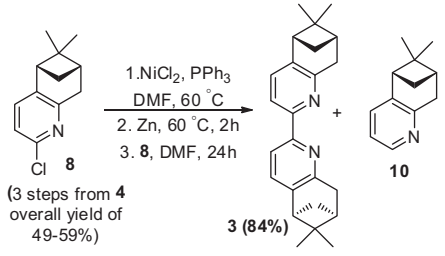
Figure 4. X-ray crystal structure of pinene based bipyridyldiol **1** (CCDC 1441174).

purpose, nickel dichloride ($NiCl_2$) was reduced with zinc (Zn) and triphenylphosphine (PPh_3) in a polar aprotic solvent dimethylformamide (DMF) in an argon atmosphere to generate reddish tetrakis(triphenylphosphine)nickel(0), which was then reacted with **9** and **9a** to afford the desired tetradentate ligands **1** and **2** in yields of 65% and 40%, respectively. The structure of obtained ligands was confirmed through X-ray crystallography of **1** (Fig. 4).

Synthesis of pinene based bipyridine 3

In addition to the successful synthesis of **1**, we intended to have a concise, efficient, and inexpensive synthetic route for obtaining pinene based bipyridine **3**. Although Malkov et al. synthesized **3** through the Ni(0) mediated homocoupling reaction of pyridine triflate, their synthetic route had limitations: (1) they used highly expensive triflic anhydride for the synthesis of starting material, 2-pyridine triflate; (2) the synthetic procedure utilized expensive $(Ph_3P)_2NiCl_2$ instead of inexpensive $NiCl_2$ for the homocoupling reaction [although they used $NiCl_2$ for synthesizing similar bipyridine ligands, $(Ph_3P)_2NiCl_2$ was used particularly in the preparation of **3**]; (3) the yield of homocoupling reaction was only average (51%).

To overcome these limitations, we optimized conditions for the Ni(0) mediated homocoupling reaction of chloropyridine **8** by reacting it with Ni(0) generated from anhydrous $NiCl_2$ or $NiCl_2$-$\cdot 6H_2O$, Zn, and PPh_3 in DMF. For more than 50 years, several studies investigated the Ni(0) mediated aryl halide coupling reaction.[9] Ni (II) salts are used stoichiometrically or substoichiometrically for this dimerization reaction. Various additives, such as tetraalkylammonium iodide, potassium iodide, and pyridine, have improved the yield of the homocoupling reaction of aryl halides. However, despite adding these additives, the yield of pinene based bipyridine **3** we obtained was only 40–50% yield. The major byproduct of this reaction is a reduction product **10** (Scheme 6). According to our



Scheme 6. Concise, efficient, and inexpensive synthesis of pinene based *N*,*N*-bidentate bipyridine **3**.

series of optimization reactions, we realized that the reaction was highly sensitive to moisture and air.

Gratifyingly, generating the blood red Ni(0) complex by adding zinc through a side-arm solid addition adaptor to the pre-heated blue solution of anhydrous $NiCl_2$ and PPh_3 in DMF at 60 °C in an argon atmosphere followed by adding a degassed DMF solution of chloropyridine **8** produced the desired product **3** in an optimal yield (84%) with a low amount of a reduced product, pinene based pyridine **10** (Scheme 6). A notable observation of this reaction during the optimization was that the generation of Ni(0) complex by the premixing of all solid starting materials (Zn, PPh_3, and $NiCl_2$) in degassed DMF at room temperature in an argon atmosphere, then addition of chloropyridine **8** at 60 °C produced ligand **3** only in 60% yield. Therefore, the late addition of zinc to the preheated $NiCl_2$-PPh_3 mixture was determined to be crucial for the success of this homocoupling reaction.

Conclusion

An efficient and concise route to synthesize *O*,*N*,*N*,*O*-tetradentate bipyridyldiol **1** and **2** was developed. The key features of the developed method are as follows: (1) compared with Kröhnke annulation, the Michael addition-cyclization reaction afforded pinene based pyridone **7** in a high yield. (2) an exceptionally high yielding $POCl_3$ sealed tube-pressure reaction was used for chlorinating pyridone **7**. (3) a novel concept was developed, and it involved the nucleophile addition at an early stage to generate half part of desired bipyridyldiol, followed by homocoupling, thus enhancing the overall yield and reducing the synthetic steps for ligands **1** and **2**. (4) The structure of synthesized ligands and penultimate intermediates were confirmed by X-ray crystallography especially X-ray structure of intermediate **9a** is explained the most probable reason for up-field chemical shift of a proton in ^1H NMR of **9a** and **2**. Moreover, an efficient and inexpensive synthetic route was developed for *N*,*N*-bidentate pinene based bipyridine **3**. Compared with the previous reported method, our methodology applied inexpensive starting materials; for instance, chloroacetamide is cheaper than ethyl bromoacetate and $POCl_3$ is considerably cheaper than triflic anhydride. The overall yield for the synthesis of the bipyridine ligand **3** was 41–49%.

X-ray study

The final atomic coordinates and crystallographic data (excluding structure factors) for compound **1** have been deposited at the

Cambridge Crystallographic Data Centre (CCDC) and are available on request upon quoting the deposition numbers CCDC 1441174. These data can be obtained free of charge from CCDC through www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.075.

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