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Tetrahedron Letters 49 (2008) 668–671
Tetrahedron Letters

Synthesis of a new type of chiral N,P- and N,O-ligands

Jianqing Feng, Sarim Dastgir, Chao-Jun Li *

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Canada QC H3A 2K6

Received 7 November 2007; revised 17 November 2007; accepted 21 November 2007

Abstract

Novel chiral ligands of dihydro-QUINAP (FLiNAP) and dihydro-QUINOL (FLiNOL) have been synthesized in optically pure forms.

Asymmetric synthesis has been one of the most important research subjects in modern organic chemistry.[1] Chiral N,P and N,O ligands represent important types of chiral bidentate agents for various asymmetric catalysis.[2] These ligands regulate the enantioselectivity of various transition-metal catalysis through their steric and ligand effects. In particular, coordination of ligands with different donor abilities stabilizes intermediate valency of otherwise unstable transition metals.[16] One of the privileged chiral ligands is (phosphinonaphthyl)isoquinoline (QUINAP) (Fig. 1, **a**).[3] This ligand has shown wide applications in various asymmetric catalysis to provide high enantioselectivities.[4] However, the known synthesis route for QUINAP is lengthy and the two enantiomers are separated by using a stoichiometric quantity of chiral palladium complexes. Such limitations prevent the ready fine tuning of the structure electronically or sterically. Recently, progress has been made to address some aspects of these limitations.[5] In addition, the corresponding QUINOL (Fig. 1, **b**) could not be used in asymmetric synthesis due to its rapid racemization. On the other hand, we envisioned a novel class of chiral N,P and N,O ligands (Fig. 1, **c** and **d**) that will have tunable electronic and steric properties. With such flexibilities, chiral dihydro-QUINOL derivatives could also be stable enough to be useful for asymmetric catalyses. In addition, the increased electron-density on the imine-nitrogen in the dihydro-system compared to quinoline-nitrogen will increase the 'push–pull' effect, which could be beneficial for coordinating with a metal center.

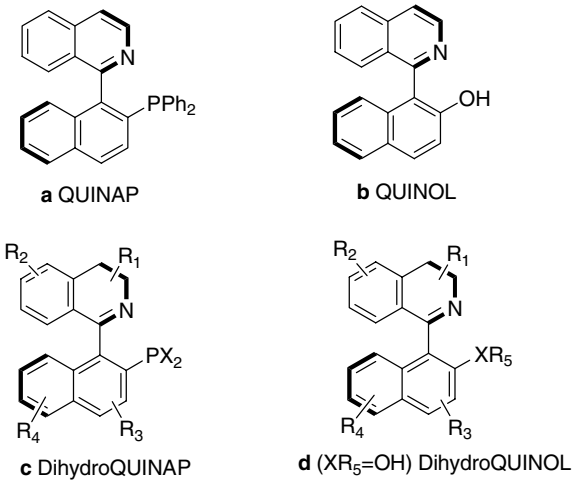
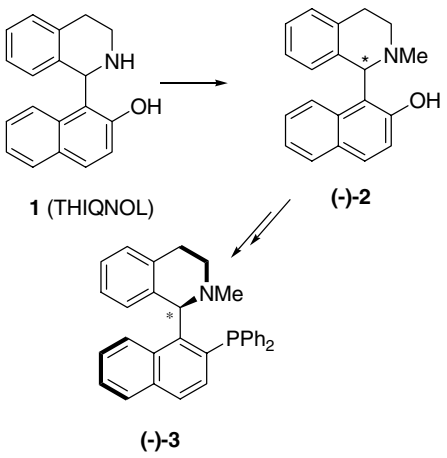


Fig. 1.

Recently, we have designed and synthesized a new class of chiral compounds, 1-naphtholyl tetrahydroisoquinolines, including the lead compound 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (THIQNOL) (**1**) as chiral ligands for asymmetric synthesis and other applications.[6,7] Subsequently, we have prepared a new chiral amino phosphine ligand (*S*, a*R*)-**3** from methylated THIQNOL **2**, which was resolved by L-tartaric acid efficiently

* Corresponding author. Tel.: +1 514 398 8457; fax: +1 514 398 3797.
E-mail address: cj.li@mcgill.ca (C.-J. Li).

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.126



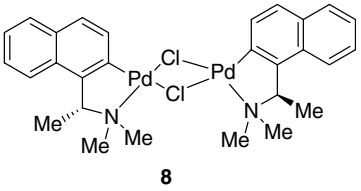
Scheme 1.

(Scheme 1). The asymmetric induction property of the ligand in asymmetric allylic alkylation reaction has also been investigated: the reaction gave good yields and up to 78% ee of the desired product.[3]

On the other hand, unlike **3**, the QUINAP ligand (Fig. 1, **a**) bears an sp^2 nitrogen. To have a direct analogy to the QUINAP ligand, we envisioned that proper modifications of THIQNOL will give us a new class of ligands: chiral dihydroisoquinoline derivatives such as dihydro-QUINOL (**4**) and dihydro-QUINAP (**5**) (Scheme 2).

Initially, we planned to convert the secondary amine **1** to imine **4** directly under oxidative conditions. Subsequent triflation and phosphination could yield the new imine–phosphine ligand **5**.

Unfortunately, oxidation of THIQNOL (**1**) by using various oxidants such as $KMnO_4$, DDQ, or IBX could not afford the desired product **4**, with the decomposition of the starting material in each case. We reasoned that the existence of the naphthol group had interfered with the oxidation of the amine group. Thus, we decided to switch the order of oxidation and triflate formation. However, an immediate challenge is the selective triflate formation at the less reactive hydroxyl group in the presence of the more reactive amine group. After many experiments, we found that such a selective triflation of the naphthol could be performed by using 4-nitrophenyl trifluoromethanesulfonate to give the desired product **6** in almost quantitative yield.[8] Then, oxidation of triflate **6** can be done readily by using either DDQ or IBX to give imine triflate **7**. Finally, using a combination of Zn and Ph_2PCl catalyzed by $Ni(PPh_3)_2Cl_2$[9] generated the dihydro-QUINAP **5**, albeit the yield is quite low prior to the optimization of the reaction conditions (Scheme 3). With this compound in hand, various attempts were made to resolve the racemic phosphine **5**. Although the palladium complex **8**, derived from (*S*)-(+)-dimethyl(phenylethyl) amine, has been successfully utilized for the resolutions of QUINAP derivatives,[10] we were unable to resolve dihydro-QUINAP **5** by the same method, possibly due to its racemization during the resolution.



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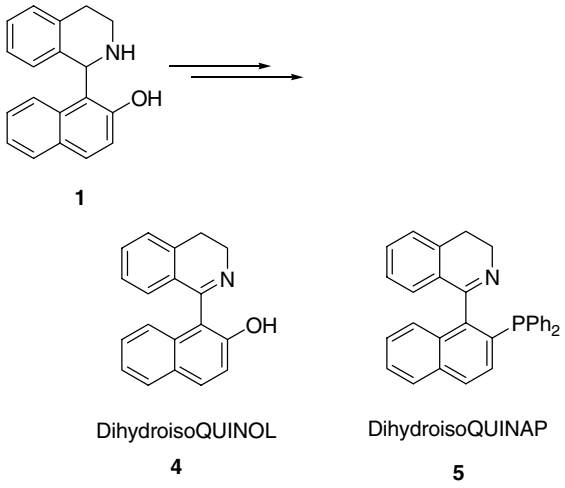
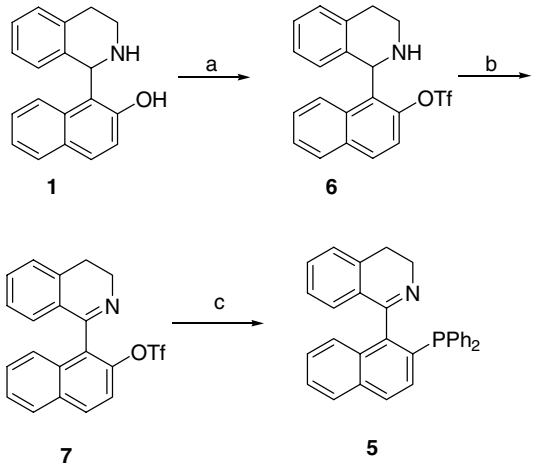
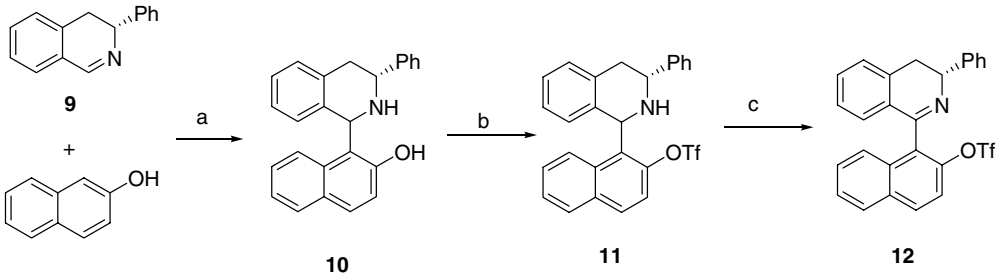
To overcome this problem, we decided to install a chirality adjacent to the nitrogen and to use an optically pure starting material. It was reported that optically active dihydroisoquinoline **9** could be synthesized readily through a modified Bischler–Napieralski procedure[11] from diphenylethylamine, which is resolved with (+)-tartaric acid.[12] The (−)-enantiomer of **9** was shown by Nakazaki[13] to have the *R* absolute stereochemistry.



Scheme 2.



Scheme 3. (a) Reagents and conditions: 4-Nitrophenyl trifluoromethanesulfonate, K_2CO_3, DMF, rt, 92%; (b) 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), CH_2Cl_2, rt, 87%; (c) Ph_2PCl, $NiCl_2(PPh_3)_2$, Zn, DMF, 110 °C, 12 h, 27%.

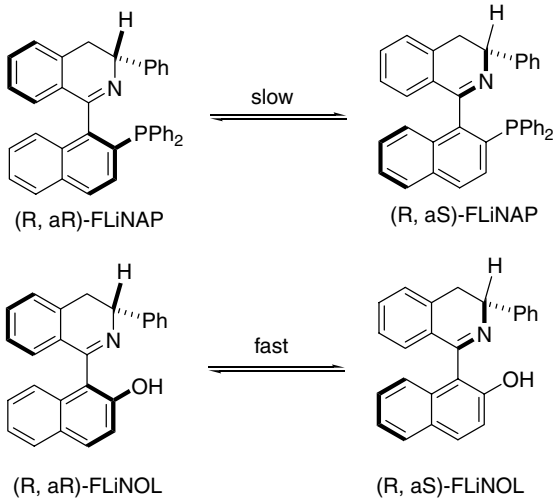


Scheme 4. Reagents and conditions: (a) neat, 80 °C, 76%; (b) 4-nitrophenyl trifluoromethanesulfonate, K_2CO_3, DMF, rt, 91%; (c) DDQ, DCM, 0 °C, 85%.

Without any solvent, 2-naphthol was coupled with the chiral imine **9** to afford product **10** in high yield. Then, selective triflation of the phenol group generated **11** in 91% yield. The secondary amine in **11** was then oxidized by DDQ to afford the key intermediate **12** (Scheme 4). Further studies showed that the chiral axis of triflate **12** could rotate freely in solution.

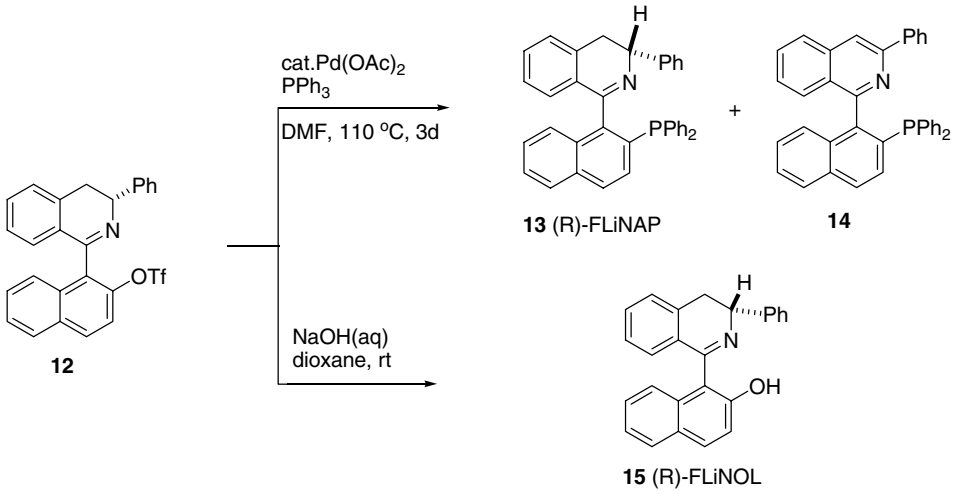
When we applied the nickel-catalyzed method (used in synthesizing compound **5**) to triflate **12**, no phosphine product was obtained. Then, it was found that the palladium-catalyzed phosphination of aryl triflates **12** by using triphenylphosphine provided the imine–phosphine ligand **13** (FLiNAP) in 18% yield (unoptimized) (Scheme 5).[14] At the same time, ca. 25% of phenyl-substituted QUINAP **14** was also obtained, however, with complete racemization. Hydrolysis of triflate **12** at room temperature by using NaOH in aq dioxane afforded new imine naphthol ligand **15** (FLiNOL) in 63% yield (Scheme 5).

As there exist two chiral elements (a chiral axis and a chiral center) in both FLiNAP (**13**) and FLiNOL (**15**), there are two possible diastereomers in each case. We found that the two diastereomers of **13** are relatively more stable and can be separated by chromatography in pure forms. However, the purified diastereomer interchange slowly with the other diastereomer overtime. On the other hand, the two diastereomers of **15** interchange rapidly at room temperature and could not be separated in diastereomerically pure forms (Scheme 6).



Scheme 6.

In summary, we have designed and synthesized a new class of chiral imine–phosphine ligands and chiral imine–phenol ligands.[15] The corresponding 3-phenyl substituted derivatives FLiNAP and FLiNOL were obtained in optically pure forms. The chiral centers in these compounds



Scheme 5.

appears fixed whereas the chiral axes are flexible. Further studies regarding their complex formation with various transition-metals and applications in asymmetric catalysis are in progress in our laboratory.

Acknowledgments

We are grateful to the Canada Research Chair (Tier I) foundation (to C.-J.L.), the CFI, and NSERC, for support of our research.

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