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Hayashi ligand-based rhodium complex in carbon monoxide and molecular hydrogen-assisted reductive amination

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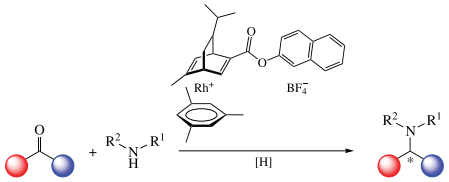
The CO- and H_2-assisted reductive amination of carbonyl compounds catalyzed by stable chiral Hayashi ligand-based rhodium complex afforded the racemic amines in moderate yields. The racemic outcome of the process results from the elimination of the chiral ligand from the catalyst under the action of hydrogen or carbon monoxide as reductants.



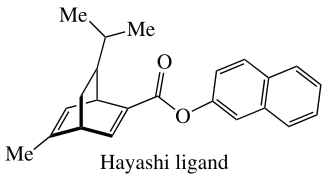
Keywords: chiral complexes, rhodium complexes, reductive amination, carbon monoxide, Hayashi ligand, diene complexes, aldehydes, ketones, amines.

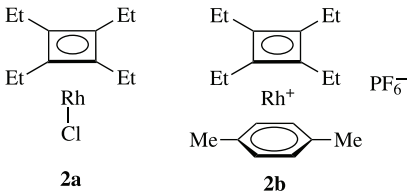
Dedicated to Professor Oleg M. Nefedov on the occasion of his 90th birthday

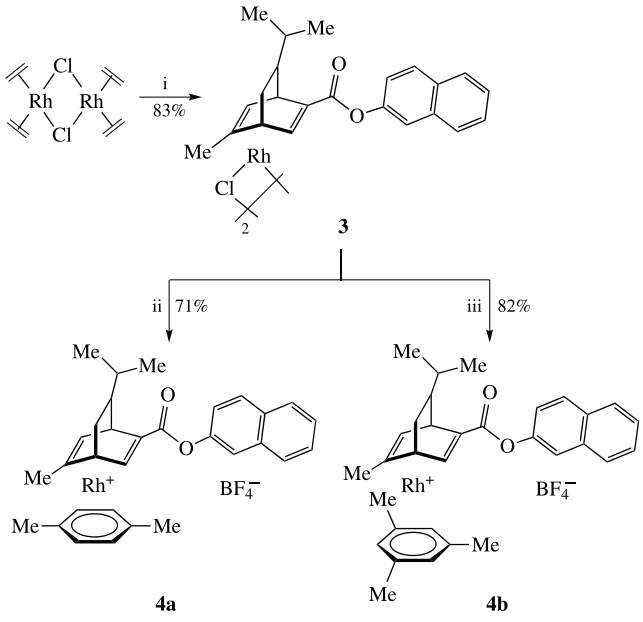
Amines are widely applied in many fields including tomography, luminescence materials, *etc*.[1–4] Asymmetric reductive amination, an essential reaction in organic chemistry,[5–9] is employed in the total synthesis of pharmaceuticals and bioactive compounds.[10–15] As has been reported by Zhang, Yin, and co-workers,[16] the vast majority of chiral catalysts for these reactions is based on phosphorus ligands.[17–19] Nevertheless, fundamental investigation of alternative catalysts and ligands,[20–24] including promising chiral diene ligands,[25–30] is of great interest. To the best of our knowledge, the catalytic activity of chiral diene complexes in reductive amination has not been reported yet.

Herein, we synthesized chiral diene complexes based on the Hayashi ligand **1** and evaluated their stability and catalytic activity in reductive amination using carbon monoxide[31–33] and hydrogen gas[19] as the reducing agents. Classical Hayashi rhodium(I) diene complexes contain chloride as counter anion.[34,35] At the same time, the catalytic activity of complexes in reductive amination may strongly depend on the nature of both ligands. For instance, the rhodium cyclobutadiene chloride complex **2a** is much less active than the rhodium cyclobutadiene complex with arene ligand **2b**.[36] Therefore, we aimed to prepare chiral rhodium complex **4a** based on the stable chiral diene ligand **1** and labile *p*-xylene ligand (Scheme 1).

Intermediate complex **3** was synthesized from rhodium chloride, (*R*)-α-phellandrene, and 2-naphthyl propiolate. Then its chloride anion was replaced with *p*-xylene to give complex **4a**. Unfortunately, complex **4a** was stable only under dry conditions since even traces of water in a solvent caused its decomposition. To solve this problem, we synthesized a similar complex **4b** with mesitylene ligand which luckily turned to be stable in the presence of air and moisture (see Scheme 1).







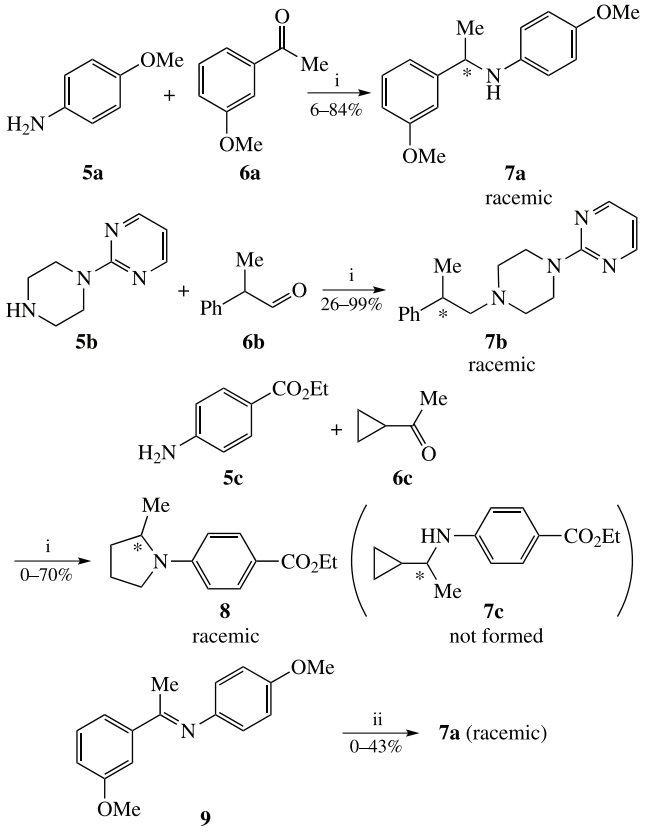
Scheme 1 *Reagents and conditions*: i, ligand **1**, CH_2Cl_2, room temperature, 1 h; ii, *p*-xylene, $AgBF_4$, CH_2Cl_2, $MeNO_2$, room temperature, 3 h; iii, mesitylene, $AgBF_4$, CH_2Cl_2, room temperature, 3 h.

The catalytic activity of complex **4b** was tested on three different model reductive amination reactions. The first reaction between primary amine **5a** and aromatic ketone **6a** should form a chiral center as a result of the direct addition of the amine at the carbonyl group (Scheme 2). This reaction proceeded in both protic and aprotic polar solvents and wide range of temperature and pressure starting from 60 °C or 10 bars (see Online Supplementary Materials). However, even under relatively mild conditions, product **7a** was racemic.

Aliphatic aldehyde **6b** contains chiral center in the α-position to the carbonyl group, so the anticipated amine may be in principle enantioenriched due to kinetic resolution or dynamic kinetic resolution (see Scheme 2). Owing to higher reactivity of aldehydes, we managed to reduce the pressure of carbon monoxide down to 1 bar and perform the reaction in a Schlenk tube. Unfortunately, even under the mildest conditions exclusively racemic product **7b** was formed. Finally, the reaction of essentially active cyclopropyl methyl ketone **6c** under all tested conditions brought about racemic pyrrolidine **8** derivative instead of expected amine **7c**, apparently, due to common ring expansion.[37]

These results inspired us to investigate the stability of the catalytic species and to perform experiments in NMR tubes at high pressure. According to the previous research,[36] one of the most active catalysts **2b** for reductive amination in carbon monoxide contains two ligands. The first cyclobutadiene ligand is stable and preserves coordination to metal under reaction conditions and stabilizes the catalytic species. In contrast, the second *p*-xylene ligand is labile and can be replaced by another ligand such as CO or amine to generate active catalytic species. We expected to observe the same pattern for catalyst **4b**, where the arene ligand (mesitylene) would be eliminated from the complex, while the chiral diene ligand **1** would stay coordinated to rhodium. Nevertheless, even though catalyst **4b** was stable in the presence of air in a 'wet' solvent at elevated temperature (90 °C) for 20 h, it was unstable in a carbon monoxide atmosphere at room temperature. Carbon monoxide substitutes not only the labile ligand mesitylene but also chiral diene **1**. Such degradation can explain the formation of exclusively racemic mixtures. Since hydrogen gas is not a strong ligand as carbon monoxide it should not substitute both ligands from complex **4b** and can keep chances for obtaining enantioenriched product. Nevertheless, complex **4b** was found to be unstable in contact with hydrogen gas, and the formation of rhodium black and the partial degradation of the complex were observed. This degradation makes it impossible to perform the chiral reduction of an imine by hydrogen gas. Even at room temperature, hydrogenation of the Schiff base **9** gives the target product **7a** as the racemate (see Scheme 2).

In conclusion, catalyst **4b** was synthesized and tested in reductive amination of different carbonyl compounds. The catalyst was found to be stable at elevated temperature (90 °C) in the presence of air and moisture. Nevertheless, elimination of the diene ligand **1** in the presence of reductive agents, such as carbon monoxide or hydrogen, leads to exclusively racemic mixtures. We believe that the stability of the ligand may be improved by steric hindrance or the introduction of additional coordination sites to the chiral diene ligand.[38] Therefore, the modified chiral diene ligands can have prospects in the future as alternative chiral ligands in reductive amination.



Scheme 2 *Reagents and conditions*: i, **5/6** = 1 : 4 (mol/mol), CO (1–30 bar), complex **4b** (5 mol%), 60–80 °C, $Pr^iOH/THF/CH_2Cl_2$ (for **5b** + **6b**), 60–90 h; ii, H_2 (3–30 bar), complex **4b** (1–4 mol%), MS 3 Å, $Pr^iOH/THF/CH_2Cl_2$/PhMe, 20–70 °C, 20–72 h.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.11.004.

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