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Communication

Improved Synthesis of 5,5-Diamino BINAP and Application to Asymmetric Hydrogenation†

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5,5-Diamino BINAP has been synthesized via three steps using BINAPO as starting material with high reaction yield. Present method needed only a stoichiometric quantity of nitric acid in the step of nitration of BINAPO, giving almost quantitative reaction yield. Based on 5,5-diamino BINAP, other three new BINAP derivatives have been synthesized. These modified BINAP ligands showed better catalytic properties as compared to BINAP itself in the asymmetric hydrogenation of 2-(6'-methoxyl-2'-naphthyl)acrylic acid.

Keywords BINAP, asymmetric hydrogenation, nitration

Asymmetric hydrogenation by chiral transition-metal complexes is one of the fundamental strategies for the synthesis of optically active organic compounds. Tremendous success has been achieved in the use of chiral arylphosphine ligands in Rh- and Ru-catalyzed asymmetric hydrogenation reactions.[1] Of the many diphosphine-containing catalysts reported, rhodium and ruthenium BINAP complexes have been extensively studied and several commercial processes based on these catalysts have been developed.[2] However, a major problem associated with this homogeneous catalytic system is the separation and recycling of the expensive chiral catalyst. In order to resolve this problem, several attempts to immobilize this catalytic system have been made, which include immobilization of BINAP or its metal complexes onto organic or inorganic polymer support.[3] Alternatively, new approaches based on the concept of liquid biphasic catalysis by using water or ionic liquid as a reaction medium have also been reported.[3] Because BINAP itself cannot be easily attached to a support, the modification of BINAP is usually necessary before the immobilization. Thus it is desirable to develop an efficient method for the synthesis of BINAP monomers.[4]

Recently, we have reported the synthesis of soluble polymer- or dendrimer-supported BINAP ligand by using 5,5-diamino-BINAP as the monomer,[5,6] which was prepared according to the published method.[7] These immobilized catalysts gave higher catalytic activity than that of BINAP itself.[5] However, the method described in the patent for the synthesis of 5,5-diamino-BINAP gave rather low reaction yield. To ensure the practicality of the immobilized BINAP system, we reported here an improved synthesis of 5,5-diamino BINAP via three steps using BINAPO as starting material. Present method needed only a stoichiometric quantity of nitric acid in the step of nitration of BINAPO, giving almost quantitative reaction yield. Based on 5,5-diamino BINAP, other three new BINAP derivatives have also been synthesized with the aim to further improve the catalytic activity and/or enantioselectivity via the adjustment of the electronic and steric properties of the substituents on the binaphthyl backbone of BINAP. These modified BINAP ligands showed better catalytic properties than BINAP in the asymmetric hydrogenation of 2-(6'-methoxyl-2'-naphthyl)acrylic acid.

The synthesis of 5,5-diamino-BINAP was outlined in Scheme 1. Firstly, the oxidized product BINAPO **3** was quantitatively prepared through oxidation reaction from commercially available (*R*)-BINAP. The subsequent nitration of **3** was successfully carried out using nitric acid and acetic anhydride as nitrating agent in the presence of a small amount of sulfuric acid as catalyst. Unlike the patent method which used concentrated HNO_3-H_2SO_4 as nitrating agent,[7] present method gave high selectivity and almost quantitative reaction yield. The reduction of the nitro groups with $SnCl_2$-HCl as reducing agent underwent smoothly in EtOH-H_2O (9∶1, *V*/*V*) with 95% reaction yield. Alternatively, **4** could be also hydrogenated using Pd/C as catalyst to give **5** with quantitative reaction yield. Finally, the target ligand **1** was obtained using $HSiCl_3$ as reducing agent in the presence of NEt_3 in toluene.

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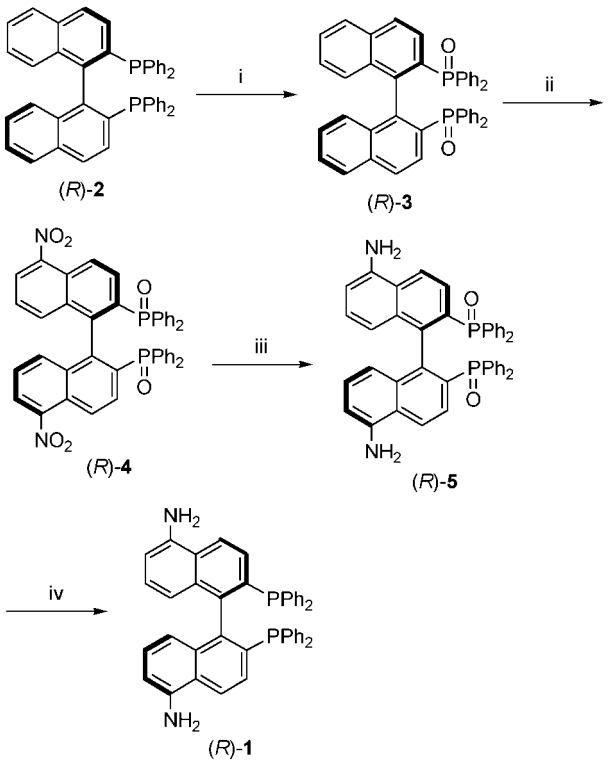
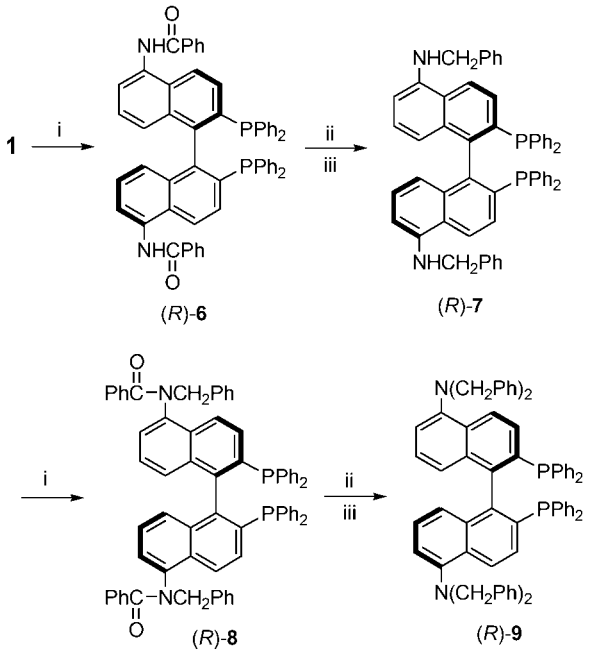
Scheme 1



Reagents and conditions: (i) 30% H_2O_2, THF, quantitative yield; (ii) HNO_3-Ac_2O, H_2SO_4, −20 to −5 ℃, 98.0% yield; (iii) $SnCl_2$-HCl, EtOH-H_2O (9∶1, *V*/*V*), 40—60 ℃, 95% yield; or Pd/C, EtOH, 5.05×10^6 Pa H_2, quantitative yield; (iv) $HSiCl_3$-NEt_3, toluene, refluxing, 90% yield.

In order to further improve the reactivity and enantioselectivity, several BINAP derivatives bearing different substituents on the four-phenyl rings have been synthesized and applied to asymmetric hydrogenation.[8] However, in sharp contrast to the modification on the phenyl ring, few examples of modified BINAP on the binaphthyl backbone have been reported.[6] With 5,5-diamino-BINAP on hand, we synthesized four BINAP derivatives via acylation and alkylation of the amino groups (Scheme 2). 5,5-dibenzoylamino BINAP **6** was easily synthesized by reacting **1** with benzoyl chloride in the presence of pyridine according to the published procedure.[9] Reduction of **6** by BH_3-THF at room temperature gave the BH_3-protected 5,5-dibenzylamino BINAP (BH_3-**7**), which was deprotected by an excess of DABCO (triethylenediamine) in toluene at 60 ℃ to produce **7**. Similarly, compound **7** reacted with benzoyl chloride in the presence of pyridine to give *N*,*N*-dibenzyl-5,5-dibenzoylamino BINAP **8** with quantitative yield. **8** was then reduced by BH_3-THF followed by deprotection with DABCO to give 5,5-bis(*N*,*N*-dibenzyl)amino BINAP **9** with high reaction yield. All four BINAP derivatives were further purified by recrystallization or flash chromatography and characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and MS.[10] These modified BINAP ligands except for **8** gave well-resolved ^{1}H NMR spectra consistent with their structures. While ^{1}H NMR spectra of **8** were more complicated, and its ^{31}P NMR spectra also showed two sets of doublet peaks and other two singlet peaks, which indicated the formation of enamide isomers of **8** in solution.

Scheme 2

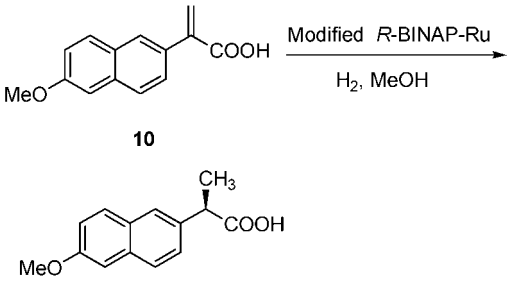


Reagents and conditions: (i) PhCOCl, pyridine, CH_2Cl_2, 0 ℃—r.t., quantitative yield; (ii) BH_3-THF, THF, r.t. to 60 ℃; (iii) DABCO, toluene, 40—50 ℃.

The ruthenium catalysts of these modified BINAP ligands were prepared *in situ* via reaction of BINAP derivatives with $[RuCl_2(cymene)]_2$ (cymene: isopropyltoluene) in a methanol-toluene mixed solvent system according to the published method.[8] Their catalytic efficiency was evaluated by choosing asymmetric hydrogenation of 2-(6'-methoxyl-2'-naphthyl)acrylic acid as the model reaction. As shown in Table 1, all modified BINAP ligands gave higher catalytic activity than BINAP (Entries 1—6). For example, the hydrogenation of 2-(6'-methoxyl-2'-naphthyl)acrylic acid **10** using [Ru(**7**)(cymene)Cl]Cl as catalyst with a substrate/ catalyst molar ratio of 200 and under 6.76×10^6 Pa H_2 at r.t. gave 85% conversion in 30 min. When using [Ru(BINAP)(cymene)Cl]Cl as catalyst, the same reaction under otherwise identical conditions gave only 30% conversion. This substituent effect was probably due to the introduction of the electron-donating amine or amide groups into the binaphthyl backbone of BINAP, which favored the formation of metal hydride species during the catalytic reaction. The BINAP with the more electron-donating amine groups gave faster rate than those with amide groups, further indicating that the electronic feature of the substituents of BINAP influenced the activity of the reaction. When the reaction was carried out at low temperature and higher H_2 pressure, all the modified BINAP ligands gave complete conversion in 8 h with high enantioselectivity up to

97.2% (Entries 7—12), which are higher than that of BINAP (94.4% *ee*).

Table 1 Asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid **10** catalyzed by modified Ru-BINAP and Ru-BINAP catalysts[a]



Entry	Ligand	Temp./℃	Time/h	Conv.[b]/%	TOF[c]/h^{-1}	*ee*[b]/%
1	BINAP	r.t.	0.5	30	118	89.1
2	**1**	r.t.	0.5	75	302	91.5
3	**6**	r.t.	0.5	47	187	92.6
4	**7**	r.t.	0.5	85	341	92.4
5	**8**	r.t.	0.5	50	200	92.1
6	**9**	r.t.	0.5	71	283	92.2
7	**1**	1—2	8	100	—	94.7
8	**6**	1—2	8	100	—	96.2
9	**7**	1—2	8	100	—	94.8
10	**8**	1—2	8	100	—	97.2
11	**9**	1—2	8	100	—	95.6
12	BINAP	1—2	8	100	—	94.4

[a] Hydrogenations were carried out in 0.032 mol·L^{-1} (0.063 mmol of **10**) solution of methanol under the following reaction conditions: substrate/catalyst=200 (molar ratio); NEt_3/substrate=1∶1 (molar ratio); H_2 pressure=6.76×10^6 Pa except for Entries 7—12 (1.08×10^7 Pa); r.t. [b] Determined by HPLC analysis using a SUMICHIRAL OA-2500 column. [c] Average TOF calculated over the quoted reaction time.

In summary, a practical improved method for the synthesis of 5,5-diamino BINAP via three steps by using BINAPO as starting material has been described. The present method only needed a stoichiometric quantity of nitric acid in the step of nitration of BINAPO and offered almost quantitative reaction yield. Based on 5,5-diamino BINAP, other three new BINAP derivatives have also been prepared. Their catalytic activity was examined for Ru-catalyzed asymmetric hydrogenation of 2-(6'-methoxyl-2'-naphthyl)acrylic acid. It was found that these modified BINAP ligands showed better catalytic properties than BINAP. Further application of these modified BINAP ligands in other reactions is currently in progress.

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10 (*R*)-**7**: $[\alpha]_D^{20}$ +105.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.46 (s, 4H), 4.71 (s, 2H), 6.35 (d, *J*=8.41 Hz, 2H), 6.54 (d, *J*=7.59 Hz, 2H), 6.84 (t, *J*=8.22 Hz, 2H), 7.05—7.47 (m, 32H), 7.88 (d, *J*=8.72 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 48.77, 105.76, 117.94, 119.97, 123.10, 126.54, 127.40, 127.79, 127.89, 127.92, 127.95, 127.98, 128.21, 128.71, 129.61, 132.77, 132.87, 132.97, 133.84, 133.95, 134.06, 134.16, 134.21, 134.26, 135.09, 135.15, 137.85, 137.97, 138.10, 139.13, 143.06, 146.46, 146.88; ^{31}P NMR ($CDCl_3$) δ: −17.1; MS (ESI) *m/z* (%): 833.0 ($[M+H]^+$).

(*R*)-**8**: $[\alpha]_D^{20}$ +100.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.52—4.66 (m, 2H), 5.75—6.71 (m, 9H), 6.83—7.51 (m, 41H), 7.89 (t, *J*=8.52 Hz, 1H), 8.04 (t, *J*=8.61 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 53.4, 122.87, 122.96, 124.57, 124.79, 124.89, 127.09, 127.41, 127.55, 127.62, 127.74, 127.93, 128.01, 128.22, 128.32, 128.39, 128.42, 128.59, 128.70, 129.10, 129.31, 129.38, 129.56, 130.21, 130.28, 131.16, 131.49, 132.54, 132.63, 132.73, 132.89, 133.05, 134.35, 134.57, 134.68, 134.73, 134.95, 136.28, 136.32, 136.53, 137.26, 137.42, 138.63, 138.73, 171.29, 171.65; ^{31}P NMR ($CDCl_3$) δ: −16.64, −16.26 (d, *J*=13.93 Hz), −15.60 (d, *J*=14.09 Hz), −15.36; MS (ESI) *m/z* (%): 1041.1 ($[M+H]^+$).

(*R*)-**9**: $[\alpha]_D^{20}$ +125.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.21—4.36 (m, 8H), 6.47 (d, *J*=8.4 Hz, 2H), 6.64 (t, *J*=8.21 Hz, 2H), 6.75 (d, *J*=7.24 Hz, 2H), 6.99—7.02 (m, 8H), 7.14—7.31 (m, 32H), 7.47 (m, *J*=8.69 Hz, 2H), 8.56 (d, *J*=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 57.10, 99.55, 118.85, 123.26, 123.72, 124.98, 126.98, 127.50, 127.97, 128.08, 128.17, 128.30, 128.73, 129.49, 129.88, 132.84, 132.93, 133.03, 134.46, 134.57, 134.68, 135.62, 137.16, 138.19, 138.50, 145.45, 145.85, 147.29; ^{31}P NMR ($CDCl_3$) δ: −15.91; MS (ESI) *m/z* (%): 1013.2 ($[M+H]^+$).

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