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Grignard cross-coupling catalyzed by chiral phosphino–quincorine and phosphino–quincoridine derivatives

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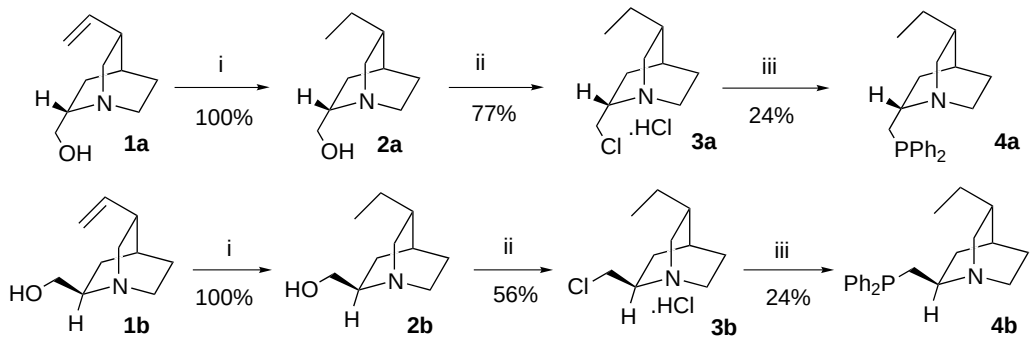
Abstract—New β-aminoalkylphosphines with a stereogenic nitrogen center have been synthesized from quincorine and quincoridine. Nickel catalysts were studied for their enantioselectivity in the asymmetric Kumada–Corriu reaction. The (2*S*,4*S*,5*R*)-2-diphenylphosphinomethyl-5-ethyl-quinuclidine–nickel complex led to e.e. of 85% for the cross-coupling of 1-phenylethylmagnesium chloride with vinyl bromide.

1. Introduction

The synthesis of optically pure isomers constitutes a major goal in the field of fine chemistry. The improvement of the enantioselectivity of asymmetric reactions involves the development of new chiral ligands, the chirality of which is carried by the carbon skeleton and/or the electronic differentiation of coordination atoms. In this latter case, the metallic center could be coordinated, either by a hard nitrogen donor or by a soft phosphorus donor. Thus amino-phosphine type ligands have been developed to lead to the preparation of numerous complexes of transition metals used in asymmetric catalysis.[1] A major interest in these ligands was their use in the synthesis of nickel complexes used for the Grignard cross-coupling reaction with aryl or vinyl halides, which has met with an unprecedented success using Kumada's aminoalkylphosphines.[2,3]

In our laboratory, we chose to illustrate this concept by the synthesis of aminophosphine ligands bearing a stereogenic nitrogen atom and to test their abilities as catalysts for asymmetric Grignard cross-coupling, also called the Kumada–Corriu reaction.[4]



Scheme 1. (i) H_2, Pd/C 10%, THF, rt, Ar; (ii) (a) HCl 33%, EtOH; (b) $SOCl_2$, $CHCl_3$, 0°C; (iii) $HPPh_2$, *tert*-BuOK, THF, reflux, Ar.

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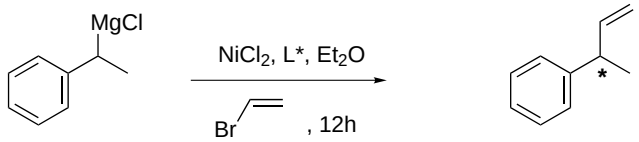
2. Results and discussion

Quincorine **1a** and quincoridine **1b** are bicyclic β-amino alcohols obtained by cleavage of the alkaloid analogues quinine and quinidine.[5,6] These fragments have four stereogenic centers each, including the stereogenic (*S*)-configured *N*-bridgehead.

Although several works focused on the transformation of these building blocks to use them as novel medicinal receptors,[7–10] none mentioned their use as ligands for asymmetric catalysis. Among these derivatives, vinylic analogues of (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-2-diphenylphosphino-5-ethyl-quinuclidine (quinphos **4a** and **4b**) have been obtained by Hoffmann et al.[9] via mesylate intermediates. Using a modified synthetic route, we prepared **4a** and **4b** in four steps via chloromethyl intermediates (Scheme 1).

To avoid eventual side reactions with the vinyl functionality and to prevent potential vinyl–metal interactions during the preparation of catalysts, **1a** and **1b** were firstly hydrogenated with a Pd/C catalyst affording dihydro derivatives **2a** and **2b** quantitatively.[11] In order to exclude the possible intramolecular aziridinium ion formation,[12] the amine hydrochloride analogues were prepared with HCl in EtOH and converted into chloromethyl compounds **3a** and **3b** with $SOCl_2$ in good yields. Finally, introduction of the diphenylphosphine residue was carried out by the standard procedure using *tert*-BuOK and $HPPh_2$ in THF. Purification by chromatography afforded diastereomerically pure quinphos (2*S*,4*S*,5*R*)-**4a** and (*2R*,4*S*,5*R*)-**4b**, both in 24% yield.

Quinphos **4a** and **4b** were examined for their enantioselectivity in the cross-coupling of 1-phenylethylmagnesium chloride with vinyl bromide in the presence of nickel chloride (Scheme 2). The chiral catalysts (0.5%) were prepared in situ by mixing nickel chloride and the ligand in a 1:1 ratio. Table 1 summarizes the reaction conditions and results. At 25°C, catalyst **4a** led to better enantioselectivity than **4b**, which nevertheless gave a better conversion than **4a** (runs 1 and 3). At low temperature, despite giving a lower yield (50%), **4a** gave the product with high e.e. of 85% (run 2), close to the values obtained under the same conditions with Kumada's *tert*-leuphos (83%) or valphos (81%)[2,3] and Kellog's homomethphos (88%)[13] ligand. Thus, the nickel-(2*S*,4*S*,5*R*)quinphos **4a** complex is one of the best systems described in the literature to date.



Scheme 2.

Table 1. Nickel-catalyzed cross-coupling of 1-phenylethylmagnesium chloride with vinyl bromide

Run	Ligand	Temperature (°C)	Yield[a] (%)	E.e.[a] (%)
1	(2*S*,4*S*,5*R*)-**4a**	25	65	75 (+)
2	(2*S*,4*S*,5*R*)-**4a**	0	50	85 (+)
3	(2*R*,4*S*,5*R*)-**4b**	25	80	65 (−)

[a] Yield and enantioselectivity were determined on a β-dex (0.25 mm×60 m) column with styrene as internal standard.

3. Experimental

3.1. Reduction of vinylic function of 1a and 1b

Under Ar, at room temperature, **1a** (or **1b**) (1 g, 6 mmol) and Pd/C 10% (1 g) were maintained under H_2 (1 Bar) in THF (60 mL) for a period of 8 h. The resulting solution was filtered through Celite and the filtrate was evaporated to give pure **2a** and **2b** (100% yield) (for characterization, see Ref. 9).

3.2. Synthesis of 3a and 3b

A solution of alcohol **2a** or **2b** (0.9 g, 5.3 mmol) in ethanol (10 mL) was added to a solution of 37% hydrochloric acid (4 mL) in ethanol (10 mL). After stirring the mixture for 30 min, the solvent and the excess acid were removed under reduced pressure. Thionyl chloride (1 mL) was then added to a solution of the amine hydrochloride in $CHCl_3$ (10 mL) at 0°C. After stirring the mixture for 2 h under reflux, the solvent was removed and the residue dissolved in ethanol (2 mL). Dropwise addition of Et_2O provided white crystals which were collected by filtration. Drying under vacuum at 50°C over P_2O_5 gave pure **3a** or **3b** in 56 and 81%, respectively. **3a**: ES-MS (ES^+): 188.0 ($[M+H]^+$); 411.2 ($[2M+HCl+H]^+$); (ES^-): 258.0 ($[M+Cl]^-$); 296.0 ($[M+HCl+Cl]^-$). ^1H NMR ($CDCl_3$): 0.82 (t, 3H, $J=$ 7.1); 1.4–2.2 (m, 8H); 2.8–4.0 (m, 7H); 11.89 (s, 1H). ^{13}C NMR ($CDCl_3$): 11.5; 24.3; 24.6; 26.6; 34.9; 41.6; 43.5; 55.6; 57.4. **3b**: ES-MS (ES^+): 188.0 ($[M+H]^+$); 411.2 ($[2M+HCl+H]^+$); (ES^-): 258.0 ($[M+Cl]^-$); 296.0 ($[M+HCl+Cl]^-$). ^1H NMR ($CDCl_3$): 0.92 (t, 3H, $J=$ 7.1); 1.3–2.2 (m, 8H); 2.7–4.4 (m, 7H); 12.28 (s, 1H). ^{13}C NMR ($CDCl_3$): 11.4; 23.9; 24.5; 24.8; 24.9; 35.2; 42.7; 48.5; 48.6; 57.5.

3.3. Synthesis of quinphos 4a and 4b

To a suspension of *tert*-BuOK (11.5 mmol) in anhydrous THF (20 mL) was added diphenylphosphine (2.2 mmol). After stirring the mixture for 30 min at room temperature, amine hydrochloride salts **3a** or **3b** (0.5 g, 2.2 mmol) were added to the red solution. The reaction mixture was heated under reflux until the total disappearance of the color. After evaporation of the solvent, aqueous HCl (10%, 10 mL) was added to the residue. The aqueous layer was extracted with toluene, neutralized with 10% NaOH and then extracted with toluene. The organic layer was rinsed with brine, dried with Na_2SO_4 and evaporated. Purification by filtration through alumina led to pure **4a** and **4b** as colorless oils in 24% yield. **4a**: $[\alpha]_D^{25}=+15.9$ ($c=1$, THF). ES-MS

(ES$^+$): 338.2.0 ([M+H]$^+$). ^{31}P ($CDCl_3$): −22.0. ^{1}H NMR ($CDCl_3$): 0.75 (t, br, 3H); 1.0–3.2 (m, 15H); 7.2–7.7 (m, 10H); ^{13}C NMR ($CDCl_3$): 11.9; 25.7; 26.9; (d, $J=5$); 29.2; 29.7 (d, $J=7$); 37.4 (d, $J=12$); 37.9; 48.7 (d, $J=11$); 48.9 (d, $J=17$); 128.4; 128.5; 128.6; 132.7; 132.9. **4b**: $[\alpha]_D^{25}=-16.2$ ($c=1$, THF). ES-MS (ES$^+$): 338.2.0 ([M+H]$^+$). ^{31}P ($CDCl_3$): −22.0. ^{1}H NMR ($CDCl_3$): 0.87 (t, br, 3H); 1.0–1.8 (m, 9H); 2.0–3.0 (m, 6H); 7.2–7.6 (m, 10H); ^{13}C NMR ($CDCl_3$): 12.1; 25.8; 26.5; (d, $J=5$); 27.3; 29.6 (d, $J=7$); 35.1 (d, $J=12$); 37.9; 49.1 (d, $J=11$); 53.4 (d, $J=17$); 128.3; 128.4; 128.5; 133.0; 133.1.

3.4. Typical Kumada–Corriu reaction

Under Ar, vinyl bromide (20 mmol) and 1-phenylethylmagnesium chloride (40 mmol) were successively added to a solution of anhydrous $NiCl_2$ (0.1 mmol) and chiral quinphos (0.1 mmol) in ether (40 mL) at −78°C. The mixture was kept at 0°C for 12 h and hydrolyzed with aqueous HCl (10%). The organic layer was extracted with ether, washed with saturated Na_2CO_3 solution and dried over anhydrous Na_2SO_4.

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