Ruthenium-catalysed asymmetric hydrogenation of ketones using QUINAPHOS as the ligand

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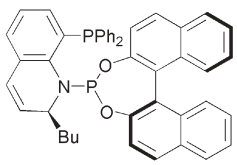
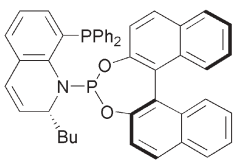
Received (in Cambridge, UK) 13th April 2005, Accepted 18th May 2005
First published as an Advance Article on the web 9th June 2005
DOI: 10.1039/b505195a

Highly enantioselective ruthenium-catalysed hydrogenation of aromatic ketones is achieved with (R_a,S_C)-QUINAPHOS in the presence of achiral and chiral diamines as co-catalysts.

Asymmetric hydrogenation of ketones is an extremely useful synthetic route to chiral alcohols. In contrast to functionalised ketones in which a secondary coordination to the metal centre enhances the reactivity and facilitates the transfer of the chiral information, unfunctionalised ketones are much more challenging substrates.[1,2] It was not until the introduction of [(diphosphine)$RuCl_2$(diamine)] as catalyst systems[3] that this method gained an important place in the tool-box of the organic chemist. Notably, the most effective ligands for this transformation such as BINAP and its derivatives, PennPhos, DIOP, BDDP and BICP are C_2-symmetric.[1] Very recently, it was shown that monodentate phosphonites can serve as excellent ligands for asymmetric hydrogenation of ketones.[4] In some cases, an enhancement of the stereoselectivity was observed by using C_1-symmetric diamines[5] or achiral thioamines[6] as co-catalysts.



(R_a,S_C)-QUINAPHOS, (R_a,S_C)-**1**



(R_a,R_C)-QUINAPHOS, (R_a,R_C)-**1**

Recently, we introduced QUINAPHOS **1**, a phosphine–phosphoramidite ligand based on the 1,2-dihydroquinoline backbone.[7] This bidentate ligand[8] with two dissimilar phosphorous donors was originally designed for rhodium catalysed asymmetric hydroformylation. Indeed, QUINAPHOS accomplished the asymmetric hydroformylation of styrene with good enantioselectivities (*ee* up to 74%) and remarkable regioselectivities (>96%). At the same time, high activities as well as high enantioselectivities have been achieved in the hydrogenation of dimethyl itaconate and methyl 2-acetoamidoacrylate (ee up to 99.4% and 97.8%, respectively; TOF > 35 000 h^{-1} for dimethyl itaconate).[7] A strong cooperative effect of the two elements of chirality in these two applications was observed. Whereas (R_a,S_C)-**1** was the preferred ligand for hydroformylation, the (R_a,R_C) diastereomer works best in C=C hydrogenation.

We want to disclose here a further application of QUINAPHOS in asymmetric catalysis, namely the highly enantioselective Ru-catalysed hydrogenation of unfunctionalised ketones. Selected catalytic runs are summarised in Table 1. As benchmark substrates, acetophenone **2a**, 4-fluoro-acetophenone **2b** and 4-methoxyacetophenone **2c** have been chosen. The catalyst was prepared *in situ* from $[RuCl_2(C_6H_6)]_2$, the ligand, a diamine co-catalyst, and sodium *tert*-butoxide as activator following the procedure described by Genov and Ager.[6] In a first series of experiments (entries 1–8), ethylendiamine **4** was used as the co-catalyst. Using (R_a,R_C)-**1**, 1-phenylethanol **3a** was obtained with moderate conversion (45%) and an ee of 65% under standard reaction conditions† (entry 1). By increasing the amount of base from 4 mol% to 10 mol% almost quantitative conversion was achieved with the same ee (entry 2). By using (R_a,S_C)-**1** as the ligand under otherwise identical conditions, the hydrogenation of **2a** was accomplished with similar conversion but with a significantly higher ee of 80% (entry 3). Remarkably, an opposite absolute configuration of the alcohol was found (*R vs. S*; entry 3 *vs.* entry 2) indicating that the transfer of the chiral information from the ligand to the substrate is mainly controlled by the stereocenter in the dihydroquinoline backbone. The same level of enantioselectivity is retained also using a S/C of 5000. After 18 h, 31% conversion was achieved which corresponds to an average TOF of 86 h^{-1} (entry 4). An optimisation of the reaction parameters towards higher catalyst activity was not pursued at this stage of the investigation.

The hydrogenation of substrate **2b** bearing an electron withdrawing group proceeded more slowly with both diastereomers of QUINAPHOS leading to conversions between 32 and 34% after 16 h. With this substrate, (R_a,R_C)-**1** and (R_a,S_C)-**1** led to similar enantioselectivities (albeit with opposite sign) of 69% (*S*) and 73% (*R*), respectively (entries 5 and 6).

The hydrogenation of 4-methoxy-substituted acetophenone **2c** carried out in the presence of (R_a,R_C)-**1** afforded **3c** with 65% conversion and an ee of 67% (*S*) (entry 7), whereas full conversion and an ee of 86% (*R*) resulted by using (R_a,S_C)-**1** (entry 8). For comparison, the hydrogenation of 1-acetonaphthone with the system (*S*)-BINAP–ethylendiamine affords the corresponding alcohol with an ee of only 57% (*R*).[9] More recently, enantioselectivities in the same range of those obtained with (R_a,S_C)-**1/4** have been reported for a system comprising an achiral thioamine and BICP.[6]

In the next set of experiments the chiral diamine (*S*,*S*)-**5** was used as a co-catalyst (entries 9–14). Full conversion was obtained in all cases, indicating that the amine has a pronounced influence on reactivity *and* selectivity. The combination (R_a,R_C)–**1**/(*S*,*S*)-**5** afforded **3a** almost as a racemic mixture (entry 9). The value of 6% ee (*R*) obtained in this experiment reflects two opposite contributions. On one side, the system chiral phosphorous ligand/achiral diamine (R_a,R_C)-**1/4** led to **3a** with 65% ee (*S*)

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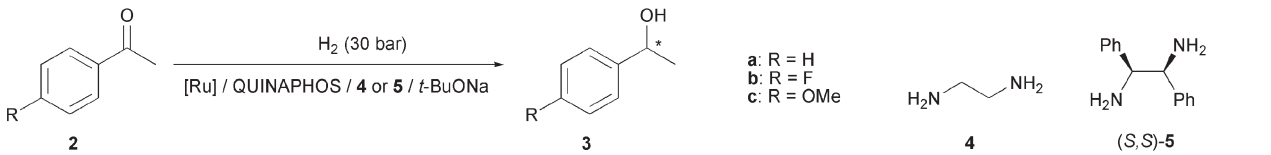
Table 1 Asymmetric hydrogenation of acetophenones[a]



No.	Substrate	Ligand	Diamine	*Cv*. (%)	Ee[b] (%)
1[c]	**2a**	(R_a,R_C)-QUINAPHOS	**4**	45	65 (*S*)
2	**2a**	(R_a,R_C)-QUINAPHOS	**4**	91	65 (*S*)
3	**2a**	(R_a,S_C)-QUINAPHOS	**4**	90	80 (*R*)
4[d]	**2a**	(R_a,S_C)-QUINAPHOS	**4**	31	82 (*R*)
5	**2b**	(R_a,R_C)-QUINAPHOS	**4**	32	69 (*S*)
6	**2b**	(R_a,S_C)-QUINAPHOS	**4**	34	73 (*R*)
7	**2c**	(R_a,R_C)-QUINAPHOS	**4**	65	67 (*S*)
8	**2c**	(R_a,S_C)-QUINAPHOS	**4**	>99	86 (*R*)
9	**2a**	(R_a,R_C)-QUINAPHOS	(*S*,*S*)-**5**	>99	6 (*R*)
10	**2a**	(S_a,R_C)-QUINAPHOS	(*S*,*S*)-**5**	>99	36 (*S*)
11	**2a**	(S_a,S_C)-QUINAPHOS	(*S*,*S*)-**5**	>99	75 (*R*)
12	**2a**	(R_a,S_C)-QUINAPHOS	(*S*,*S*)-**5**	>99	94 (*R*)
13	**2b**	(R_a,S_C)-QUINAPHOS	(*S*,*S*)-**5**	>99	94 (*R*)
14	**2c**	(R_a,S_C)-QUINAPHOS	(*S*,*S*)-**5**	>99	94 (*R*)

[a] See footnote 1. [b] The ee values were determined by GC on a Lipodex E for **3a** and **3b** and on a Ivadex 7 for **3c**. [c] *t*-BuONa 4 mol%. [d] [Ru] = 0.02 mol%, *t*-BuONa = 4 mol%, *t* = 18 h.

(entry 1). On the other side, an ee value of 75% (*R*) in the hydrogenation of 1-acetonaphthone has been reported for the system achiral phosphine (PPh_3)/(*S*,*S*)-**5**.[9] This indicates that two inductions are "cancelled" almost in an additive way in the mixed system.

In order to gain a comprehensive picture of matching and mismatching effects, all possible stereoisomers of QUINAPHOS were tested in combination with (*S*,*S*)-**5**. The catalyst system based on (S_a,R_C)-**1**/(*S*,*S*)-**5** resulted in 36% ee of the *S* enantiomer (entry 10). This low enantioselectivity is again the result of combining the intrinsic (*S*)-selectivity of the phosphorous ligand with the (*R*)-selectivity of the diamine. Indeed, an increase in selectivity from 65% (*cf*. entry 1) to 75% (*R*) (entry 11) was observed upon matching the (*R*)-selective ligand (S_a,S_C)-**1** with (*S*,*S*)-**5**.

Finally, the optimum match was identified for the pair (R_a,S_C)-**1**/(*S*,*S*)-**5**. This combination allowed the hydrogenation of **2a** with an enantioselectivity as high as 94% (*R*) (entry 12). Similarly, substrates **2b** and **2c** were converted quantitatively to the corresponding alcohols with an ee of 94% (entries 13 and 14).

All applications of QUINAPHOS-type ligands show a marked interplay between the stereocenter and the axial chirality and the two diasteromers often show very different catalytic results.[7,8] Interestingly, (R_a,R_C)-**1** is the diastereomer of choice for rhodium catalysed asymmetric hydrogenation of C=C double bonds,[7] whereas (R_a,S_C)-**1** proved to be superior for ruthenium catalysed hydrogenation of C=O double bonds. The performance of the ligand with the preferred stereochemical relation in C=O hydrogenation can be improved further by the choice of the chiral co-catalyst. It is noteworthy, however, that the intrinsic enantioselectivity of QUINAPHOS is already quite high (up to 86% ee) and hence, the difference in ee between the achiral diamine **4** and the chiral co-catalyst **5** is considerably smaller than for other ligand systems. In the case of (*S*)-BINAP, for instance, the enantioselectivity in the hydrogenation of 1-acetonaphthone increases from 57% (*R*) to 97% (*R*) when **4** is replaced with (*S*,*S*)-**5** as the co-catalyst.[9]

In summary, we have shown that QUINAPHOS ligands can lead to very high enantioselectivities in the Ru-catalysed hydrogenation of ketones. The chirality of the carbon center in the ligand backbone is of particular importance for the asymmetric induction offering an obvious target for further optimisation. The remarkable performance of Quinoline-based chiral phosphoramidites in a broad range of enantioselective reactions[7,8] suggests that this ligand framework provides a particularly suitable arrangement for stereochemical induction ("privileged" ligand).[10]

Financial support from the Deutsche Forschungsgemeinschaft (SFB 380) is gratefully acknowledged.

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Notes and references

† Procedure for the preparation of the precatalyst:[6] A mixture of QUINAPHOS (27.6 mg, 0.04 mmol) and $[RuCl_2(C_6H_6)]_2$ (10.0 mg, 0.02 mmol) was dissolved in anhydrous DMF (5 mL) and stirred at 110 °C for 30 min. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) and the resulting solution was diluted with CH_3OH to a final volume of 10 mL. General procedure for asymmetric hydrogenation: A stainless-steel autoclave (*V* = 13 mL) equipped with a magnetic stirring bar was charged under an inert atmosphere with substrate **2a–c** (2 mmol), a freshly prepared precatalyst solution (1 mL, 4×10^{-3} mmol), a methanol solution of the diamine (0.4 mL, 0.1 M), and a methanol solution of *t*-BuONa (2 mL, 0.1 M). Molar ratio: substrate : [Ru] : diamine : base = 500 : 1 : 10 : 50. The autoclave was pressurised with H_2 (30 bar) and stirred at rt for 16 h. The reaction mixture was filtered over a short pad of SiO_2 and analysed *via* GC and NMR.

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