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Ru(II) complexes of cyclohexane diamine and monodentate phosphorus ligands for asymmetric ketone hydrogenation

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Abstract—The incorporation of a *trans*-1,2-diaminocyclohexane in place of DPEN provides improvements in enantioselectivity to asymmetric ketone hydrogenation reactions using BrXuPHOS–Ru–diamine catalysts. Substrates containing halogenated aryl rings are particularly compatible with this catalyst, however, α-chlorinated ketones remain resistant to reduction under any conditions.

1. Introduction

Asymmetric hydrogenation (AH) of unfunctionalised ketones can be achieved in a high enantiomeric excess using complexes such as **1**, which contain a diphosphine and diamine unit. This class of ketone hydrogenation catalyst was first reported by Noyori in 1995,[1] and has since been developed by a large number of research groups worldwide.[2–4] The mechanism of catalysis is relatively well understood.[4] Catalyst **1** transfers hydrogen to the substrate through a six-centre transition state analogous to Ru(II) and Rh(III) based asymmetric transfer hydrogenation catalysts (Fig. 1). The catalyst is then regenerated by heterolytic splitting of hydrogen in a base-mediated process.[4]

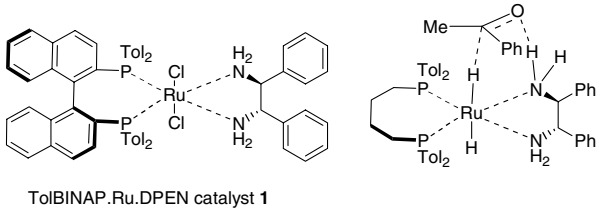
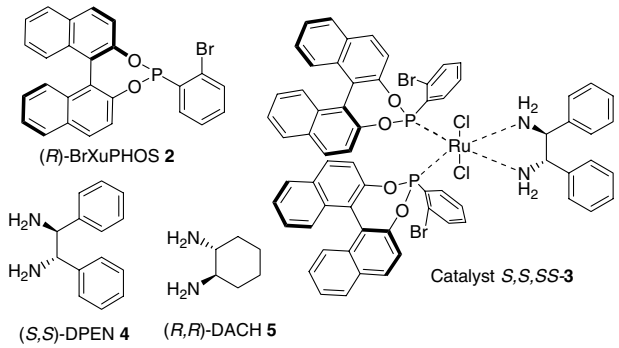


Figure 1. Mechanism of hydrogen transfer.

In recent research work in this group, we found that it was possible to employ monodentate, BINOL-derived, phosphorus donor ligands based on **2** in place of the bidentate ligand in the AH complex.[5] Phosphoramidite ligands, such as MONOPHOS, have previously been demonstrated to give comparable results to the longer-established bidentates such as BINAP in asymmetric C=C bond reduction.[6–8] However, our work was the first reported on the use of BINOL-derived monodonor ligands in Ru(II) complexes for ketone reduction. Of a series of ligands examined, the best results were obtained using the *ortho*-bromophenyl derivative BrXuPHOS **2**.[5]



Although its mechanism of action is not yet fully understood, the bromine atom appears to play an important role in the enantiocontrol of the reduction reaction. This may involve a hydrogen bonding or a dipole interaction within the catalyst structure. Using catalyst **3**, which has been determined to be the 'matched' combination, simple

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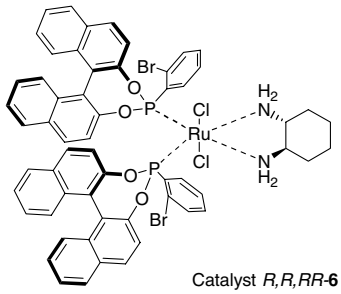
ketones can be fully hydrogenated in enantiomeric excesses of up to 99%.

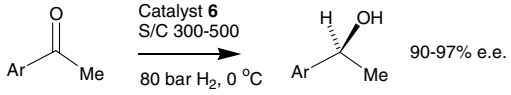
2. Results and discussion

To date, we have largely focused on the use of DPEN **4** as the diamine component, since this is readily available and widely used in related complexes. Recently, we have examined an alternative, readily available, diamine, *trans*-1,2-diaminocyclohexane **5**. In preliminary studies, we have reported the synthesis of (*R*,*R*,*RR*)- and (*S*,*S*,*RR*)-**6** and their applications to the AH of acetophenone and cyclohexyl/methyl ketone.[5] For the acetophenone reduction, a significantly improved ee of 88% (*S*) was obtained with the matched 'all-(*R*)-**6**' isomer compared to only 11.6% (*R*) for the (*S*,*S*,*RR*)-**6**. The reverse was seen for cyclohexyl/methyl ketone, with a maximum ee of only 41% using (*S*,*S*,*RR*)-**6** and 8.3% ee using (*R*,*R*,*RR*)-**6**.[5]



Catalyst *R,R,RR*-**6**

In view of the promising preliminary results obtained for the acetophenone reduction, we thought that catalyst **6** might be particularly well suited to the reduction of aryl/methyl ketones. We, therefore, carried out further studies on the reduction of aromatic ketones using (*R*,*R*,*RR*)-**6**. Our studies quickly revealed that it is a particularly good catalyst for the asymmetric reduction of halogenated ketones, including those containing fluorine, chlorine, bromine and iodine at various positions. Selected results indicating the improved activity of **6** (in comparison with **3**) are summarised in Scheme 1 and Table 1.



Scheme 1.

Although slightly higher catalyst loadings were required compared to **3**, in several cases products of a higher enantiomeric excess were obtained. In fact, **6** was more selective than **3** for all halogenated substrates other than those containing an *ortho*-substituent, for which **3** gives excellent results. Table 2 highlights the difference in enantioselectivity between the catalysts for *ortho*-bromo and *ortho*-iodo acetophenones, where **3** has the advantage. In contrast, for *meta*- and *para*-trifluoromethyl substituted acetophenones, significantly improved ees were obtained using **6**.

Fluorinated aromatic rings are important targets because they are highly represented in biologically active compounds. For example, the reduction product of *meta*-trifluoromethyl acetophenone is a building block in the synthesis of MA-20565 **7**, a wide-spectrum agricultural fungicide.[9a,b] Related trifluorinated benzyl alcohols are found in molecules such as aprepitant **8**, a drug for the treatment of chemotherapy-induced emesis.[9c] In this respect, the TsDPEN and DAC-containing catalysts are complimentary with regards to substrate compatibility.

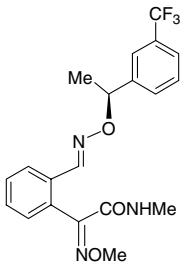
Table 1. Asymmetric hydrogenation of Aromatic ketones catalysed by (*R*,*R*,*RR*)-BrXuPHOS–Ru–DACH **6**[a]

Entry	Ar	S/C	Conv.[b] (%)	ee[c] (%)
1	C_6H_5	300	98	90 (*S*)
2	*m*-$CF_3C_6H_4$	300	100	93 (*S*)
3	*p*-$CF_3C_6H_4$	500	91	90 (*S*)
4[d]	*p*-FC_6H_4	500	100	93 (*S*)
5	*p*-ClC_6H_4	400	99	90 (*S*)
6	*m*-ClC_6H_4	400	100	90 (*S*)
7	*o*-ClC_6H_4	300	97	94 (*S*)
8	2,5-DiCH_3thienyl	300	68	91 (*S*)
9[d]	*o*-$CH_3C_6H_4$	300	100	92 (*S*)
10[d]	*o*-BrC_6H_4	300	100	97 (*S*)
11	*o*-IC_6H_4	200	100	97 (*S*)

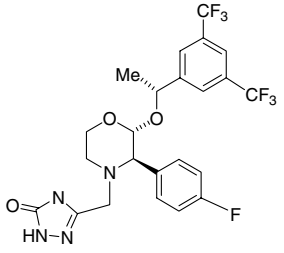
[a] Reactions were conducted in 2-propanol, B/C = 10, hydrogen pressure = 80 bar, with a 0.05 M solution of ketone in an ice bath for 8 h.
[b] Determined by GC.
[c] The ees were determined by chiral GC, and the absolute configuration determined by comparison of the sign of the specific rotation and the retention time with literature data.
[d] Time = 10 h.

Table 2. Enantioselective performance comparison between catalysts **3** and **6**

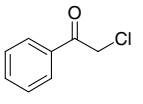
Entry	Ar	Catalyst **3**	Catalyst **6**
1	*o*-BrC_6H_4	99 (*R*)	97 (*S*)
2	*o*-IC_6H_4	99 (*R*)	97 (*S*)
3	*p*-$CF_3C_6H_4$	75 (*R*)	90 (*S*)
4	*m*-$CF_3C_6H_4$	83 (*R*)	93 (*S*)



MA-20565 **7**



Aprepitant **8**



α–chloro acetophenone **9**: no reduction under any conditions.

Whilst good ees were obtained in our reductions, the S/C ratios were lower than those typically employed using the BINAP-based catalysts,[1] and the pressures that we require are typically higher. Although substrates containing halogenated aromatic rings gave excellent results with catalyst **3**, α-halogenated substrates are significantly less reactive.

Indeed we have been unable to achieve a reduction of α-chloroacetophenone **9** under any conditions. This, coupled with the lack of any report of reduction of **9** with the Noyori-type 'diphosphine–Ru–diamine catalysts indicates that catalyst inhibition by substrate or product may be responsible. This is in some contrast to the situation with related *transfer* hydrogenation catalysts, for which α-chlorinated ketones are excellent substrates.[13] The reduction of α-chloroketones by pressure hydrogenation catalysts remains a challenging objective for ourselves and other workers in this area.

3. Conclusion

In conclusion, it has been demonstrated that a change of the diamine within BrXuPHOS complexes can deliver a significant improvement in terms of ee for certain substrates, and that the relationship between catalyst structure and enantioselectivity is a very complex one.

4. Experimental

4.1. General

NMR samples were run by Bruker DPX-300 (300 MHz), Bruker DPX-400 (400 MHz). IR spectra were obtained using a Nicolet Acatar 320 FTIR with a golden gate single reflection diamond attenuated total reflection (ATR) top plate. Optical rotations were taken using a Perkin–Elmer 241 Polarimeter. $[\alpha]_D$ values are reported as 10^{-1} deg cm^2 g^{-1}. Elemental analysis was performed by the University of Warwick analytical service. Determination of ee by HPLC analysis was performed using a Waters 501 HPLC pump, waters 486 tuneable absorbance detector, Waters 746 data module and a Daicel Chiracel OD 4.6 × 25 cm column. Determination of enantiomeric excess by was also performed using a GC (Hewlett–Packard 5890A gas chromatography, Hewlett–Packard 3396A integrator) and a GC column Cyclodextrin-β-236M-19 (CHROMPAC, 50 m). The hydrogenation reactions were conducted in a Parr high pressure autoclave (300 mL). The synthesis of (*R*,*R*,*RR*)- and (*S*,*S*,*RR*)-BrXuPHOS–Ru–DACH complexes has been reported.[5]

4.1.1. General experimental procedure for the asymmetric hydrogenation catalysed by (*R*,*R*,*RR*)-BrXuPHOS–Ru–DACH. In an oven dried round-bottomed flask (250 mL), acetophenone (293 mg, 2.4414 mmol) and $(CH_3)_3COK$ (9.1 mg, 0.08138 mmol, 3.3 mol%) were dissolved in dry and degassed 2-propanol (50 mL). (*R*,*R*,*RR*)-BrXuPHOS–Ru–DACH (10 mg, 0.008138 mmol, 0.33 mol %) was dissolved in anhydrous CH_2Cl_2 (2 mL), and the mixture transferred into the above reaction solution under argon. The mixture was degassed by three vacuum-filling argon cycles and then quickly transferred into the autoclave. The reaction mixture was purged with hydrogen 18 times, and finally the hydrogen was introduced to 80 bar. The reaction mixture was stirred vigorously in an ice bath for 8 h. The mixture was filtered through a pad of silica gel and the pad was washed with a 50% solution of ethyl acetate in hexane (150 mL). The filtrate was concentrated under reduced pressure to afford the reduction product. Purification by flash chromatography was applied when appropriate.

4.1.2. (*S*)-(−)-1-Phenylethanol. Conversion and the enantiomeric excess of the product were respectively determined to be of 98% and 90% by chiral GC analysis. $[\alpha]_D^{28} = -45.0$ (*c* 0.10, CH_2Cl_2) {lit.[10] $[\alpha]_D^{23} = +48.6$ (*c* 1.0, CH_2Cl_2), 96% ee (*R*)}, 90.0% ee (*R*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 115$ °C, $P = 15$ psi, (*R*)-isomer 13.8 min, (*S*)-isomer 14.3 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32$–7.24 (4H, m, Ar–*H*), 7.21–7.16 (1H, m, Ar–*H*), 4.76 (1H, q, *J* 6.4 Hz, HOC*H*), 4.40 (1H, br s, O*H*), 1.40 (3H, d, *J* 6.6 Hz, HOCHCH_3).

4.1.3. (*S*)-(−)-1-(3′-Trifluoromethylphenyl)ethanol. The conversion and the enantiomeric excess of the product were respectively determined to be of 100% and 93% by chiral GC analysis. $[\alpha]_D^{20} = -24.0$ (*c* 0.24, MeOH) {lit.[10] $[\alpha]_D^{22} = -28.4$ (*c* 1.26, MeOH), >99% ee (*S*)}, 93.0% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 120$ °C, $P = 15$ psi, (*R*)-isomer 15.0 min, (*S*)-isomer 15.8 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.59$ (1H, s, Ar–*H*), 7.48 (2H, t, *J* 7.5 Hz, Ar–*H*), 7.40 (1H, t, *J* 7.7 Hz, Ar–*H*), 4.84 (1H, q, *J* 6.6 Hz, HOC*H*), 3.35 (1H, br s, O*H*), 1.41 (3H, d, *J* 6.6 Hz, HOCHCH_3).

4.1.4. (*S*)-(−)-1-(4′-Trifluoromethylphenyl)ethanol. The conversion and the enantiomeric excess of the product were respectively determined to be of 91% and 90% by chiral GC analysis. $[\alpha]_D^{22} = -22.3$ (*c* 0.62, MeOH) {lit.[11] $[\alpha]_D^{22} = -28.1$ (*c* 1.13, MeOH), >99% ee (*S*)}, 90.0% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 140$ °C, $P = 15$ psi, (*R*)-isomer 8.3 min, (*S*)-isomer 8.7 min). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.57$ (2H, d, *J* 8.0 Hz, Ar–*H*), 7.44 (2H, d, *J* 8.3 Hz, Ar–*H*), 4.90 (1H, q, *J* 5.0 Hz, HOC*H*), 2.70 (1H, d, *J* 2.8 Hz, O*H*), 1.46 (3H, d, *J* 6.5 Hz, HOCHCH_3).

4.1.5. (*S*)-(−)-1-(2′-Bromophenyl)ethanol. The conversion and the enantiomeric excess of the product were respectively determined to be of 100% and 97% by chiral GC analysis. $[\alpha]_D^{26} = -54.5$ (*c* 0.2, $CHCl_3$) {lit.[11] $[\alpha]_D^{24} = -54.6$ (*c* 1.23, $CHCl_3$), 99% ee (*S*)}, 97.0% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 165$ °C, $P = 15$ psi, (*R*)-isomer 9.1 min, (*S*)-isomer 9.7 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (1H, dd, *J* 1.7 Hz, *J* 7.7 Hz, Ar–*H*), 7.46 (1H, dd, *J* 1.32 Hz, *J* 7.9 Hz, Ar–*H*), 7.32–7.26 (1H, m, Ar–H), 7.10–7.05 (1H, m, Ar–H), 5.17 (1H, dq, J_{Br-H} 3.0 Hz, *J* 6.4 Hz, HOC*H*), 2.98 (1H, d, *J* 2.8 Hz, O*H*), 1.41 (3H, d, *J* 6.4 Hz, HOCHCH_3).

4.1.6. (*S*)-(−)-1-(2′-Iodophenyl)ethanol. The conversion and the enantiomeric excess of the product were respectively determined to be of 100% and 97.0% by chiral GC analysis. $[\alpha]_D^{29} = -41.3$ (*c* 0.20, $CHCl_3$) {lit.[12] $[\alpha]_D^{24} = +37.7$ (*c* 0.934, $CHCl_3$), 86% ee (*R*)}, 97.0% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 180$ °C, $P = 15$ psi, (*R*)-isomer 9.1 min, (*S*)-isomer 9.7 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.79$ (1H, d, *J* 7.7 Hz, Ar–*H*), 7.55 (1H, dd, *J* 1.7 Hz, *J* 7.7 Hz, Ar–

H), 7.37 (1H, td, *J* 1.1 Hz, *J* 7.7 Hz, Ar–*H*), 6.96 (1H, td, *J* 1.7 Hz, *J* 7.5 Hz, Ar–*H*), 5.06 (1H, q, *J* 6.21 Hz, HOC*H*), 2.15 (1H, br s, O*H*), 1.45 (3H, d, *J* 6.4 Hz, HOCHCH_3).

4.1.7. (*S*)-(−)-1-(4′-Fluorophenyl)ethanol. The conversion and the enantiomeric excess of the product were respectively determined to be of 100% and 93% by chiral GC analysis. $[\alpha]_D^{30} = -29.3$ (*c* 0.22, CH_3OH) (lit.[11] $[\alpha]_D^{25} = -37.7$ (*c* 0.931, CH_3OH), 99% ee (*S*)), 93% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 120$ °C, $P = 15$ psi, (*R*)-isomer 13.5 min, (*S*)-isomer 14.2 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.29$ (2H, dd, *J* 6.0 Hz, *J* 8.7 Hz, Ar–*H*), 6.97 (2H, m, Ar–*H*), 4.79 (1H, q, *J* 6.4 Hz, HOC*H*), 3.93 (1H, br s, O*H*), 1.41 (3H, d, *J* 6.4 Hz, HOCHCH_3).

4.1.8. (*S*)-(−)-1-(4′-Chlorophenyl)ethanol. The conversion and the enantiomeric excess of the product were, respectively, determined to be of 99% and 90% by chiral GC analysis. $[\alpha]_D^{29} = -37.8$ (*c* 0.30, ether) {lit.[11] $[\alpha]_D^{25} = -49.0$ (*c* 1.84, ether), 99% ee (*S*)}, 90% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 150$ °C, $P = 15$ psi, (*R*)-isomer 11.9 min, (*S*)-isomer 12.3 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23$–7.21 (2H, m, Ar–H), 7.16–7.13 (2H, m, Ar–H), 4.68 (1H, q, *J* 6.4 Hz, HOC*H*), 3.86 (1H, br s, O*H*), 1.33 (3H, d, *J* 6.4 Hz, HOCHCH_3).

4.1.9. (*S*)-(−)-1-(3′-Chlorophenyl)ethanol. The conversion and the enantiomeric excess of the product were respectively determined to be of 100% and 90% by chiral GC analysis. $[\alpha]_D^{31} = -24.1$ (*c* 0.56, $CHCl_3$) {lit.[11] $[\alpha]_D^{25} = -43.5$ (*c* 1.08, $CHCl_3$), 99% ee (*S*)}, 90% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 150$ °C, $P = 15$ psi, (*R*)-isomer 12.5 min, (*S*)-isomer 12.8 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$ (1H, s, Ar–*H*), 7.20–7.15 (2H, m, Ar–*H*), 7.14–7.10 (1H, m, Ar–*H*), 4.70 (1H, q, *J* 6.4 Hz, HOC*H*), 3.71 (1H, br s, O*H*), 1.35 (3H, d, *J* 6.6 Hz, HOCHCH_3).

4.1.10. (*S*)-(−)-1-(2′-Chlorophenyl)ethanol. The conversion and the enantiomeric excess of the product were, respectively, determined to be of 97% and 94% by chiral GC analysis. $[\alpha]_D^{29} = -32.9$ (*c* 0.22, $CHCl_3$) {lit.[11] $[\alpha]_D^{25} = -62.7$ (*c* 0.894, $CHCl_3$), 99% ee (*S*)}, 94% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 150$ °C, $P = 15$ psi, (*R*)-isomer 9.8 min, (*S*)-isomer 10.5 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$ (1H, dd, *J* 1.9 Hz, *J* 7.7 Hz, Ar–*H*), 7.18–7.09 (2H, m, Ar–H), 7.05–7.00 (1H, m, Ar–H), 5.11 (1H, dq, *J* 3.0 Hz, *J* 6.2 Hz, HOC*H*), 3.87 (1H, d, *J* 3.2 Hz, O*H*), 1.29 (3H, d, *J* 6.4 Hz, HOCHCH_3).

4.1.11. (*S*)-(−)-1-(2′-Methylphenyl)ethanol. The conversion and the enantiomeric excess of the product were respectively determined to be of 100% and 92% by chiral GC analysis. $[\alpha]_D^{24} = -75.0$ (*c* 0.15, EtOH) {lit.[11] $[\alpha]_D^{25} = -64.3$ (*c* 1.04, EtOH), >99% ee (*S*)}, 95% ee (*S*) by GC (Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 125$ °C, $P = 15$ psi, (*R*)-isomer 17.0 min, (*S*)-isomer 18.9 min). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39$ (1H, dd, *J* 1.5 Hz, *J* 7.4 Hz, Ar–*H*), 7.15–7.00 (3H, m, Ar–*H*), 4.90 (1H, q, *J* 6.4 Hz, HOC*H*), 3.47 (1H, s, O*H*), 2.20 (3H, s, Ar–CH_3), 1.30 (3H, d, *J* 6.4 Hz, HOCHCH_3).

4.1.12. (*S*)-(−)-1-(2,5-Dimethyl-3-thienyl)ethanol. The conversion and the enantiomeric excess of the product were, respectively, determined to be of 68.0% and 91.3% by chiral GC analysis.[5] $[\alpha]_D^{28} = -16.4$ (*c* 0.30, $CHCl_3$) 91% ee (*S*) by GC (column, Cyclodextrin-β-236M-19 (CHROMPAC, 50 m), $T = 145$ °C, $P = 15$ psi, (*R*)-isomer 10.6 min, (*S*)-isomer 11.0 min). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.64$ (1H, s, thienyl-*H*), 4.82 (1H, q, *J* = 6.5 Hz, HOC*H*CH_3), 2.41 (1H, d, *J* = 3.3 Hz, CHO*H*), 2.37 (3H, s, thienyl-CH_3), 2.31 (3H, s, thienyl-CH_3), 1.39 (3H, d, *J* = 6.3 Hz, HOCHCH_3).

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