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An Efficient Catalyst System for the Asymmetric Transfer Hydrogenation of Ketones: Remarkably Broad Substrate Scope

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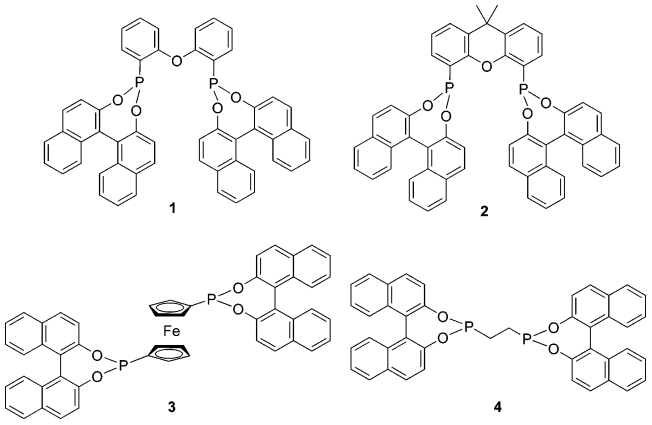
Noyori's Ru-catalyzed enantioselective hydrogenation and transfer hydrogenation of prochiral ketones constitutes a breakthrough in asymmetric transition metal catalysis.[1] Catalyst systems comprising the combination of BINAP and a chiral diamine or phosphine-free diamino ligands are effective. Nevertheless, the quest to improve this methodology continues, fueled by two challenges: to devise more readily accessible and thus cheaper ligands, and to expand the range of substrates showing high enantioselectivity. The Noyori protocols and more recent versions[2] thereof lead to high enantioselectivities (≥95% ee) for a wide variety of aryl/alkyl ketones, but purely aliphatic ketones cannot be reduced with such high selectivities. Recently, a BINAP-based catalyst system was described which is well suited for the reduction of *tert*-alkyl ketones (ees generally >96%),[3] but alkyl ketones in general were not considered. Ruthenium complexes attached to β-cyclodextrin show varying degrees of enantioselectivity in formate-based transfer hydrogenation (ee = 42−97%).[4] Tethered ruthenium catalysts constitute another notable catalyst system, leading to ee values of about 96% for aryl/alkyl ketones, in contrast to mediocre enantioselectivity in the case of alkyl/alkyl ketones (e.g., 69% ee for cyclohexyl methyl ketone).[5] Certain BINOL-derived monodentate phosphonites in combination with chiral diamines constitute yet another Ru catalyst system for the hydrogenation of aryl/alkyl ketones (ee up to 99%), but alkyl/alkyl ketones were not considered.[6] Corey's chiral borane-based hydride methodology constitutes an alternative, but again limitations arise in the case of alkyl/alkyl ketones.[7]

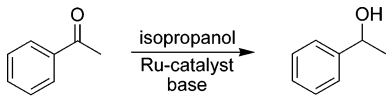
We have previously shown that BINOL-derived diphosphonites of the type **1**−**4** having different backbones are excellent ligands for asymmetric olefin hydrogenation[8a−c] and other reactions.[8d] We



now report that such ligands, specifically diphosphonite **2**,[9] are superbly suited for asymmetric transfer hydrogenation of aryl/alkyl and alkyl/alkyl ketones.[10]

In exploratory experiments, 2-propanol-based transfer hydrogenation of acetophenone **5a** was examined using $[RuCl_2(p\text{-cymene})]_2$ in the presence of ligands **1**−**4** and a base such as NaOH or potassium *tert*-butoxide. As shown in Table 1, only the xanthene-derived ligand **2** provides acceptable conversion (Table 1, entry 2). Very poor conversions with <20% ee were obtained using ligands **1**, **3**, and **4** (Table 1, entries 1, 3, and 4). Optimization of Ru/**2** showed that the ligand/Ru ratio plays a crucial role in obtaining high enantioselectivity, a ratio of about 2.5 being optimal. The nature of the base appears to be less important, KO^{t}Bu or NaOH being equally effective. Hydrogenation using H_2 is less successful.

Table 1. Screening of Ligands for the Transfer Hydrogenation of Acetophenone **5a**[a]

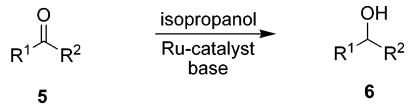


5a **6a**

entry	ligand	ligand:Ru	base	conversion (%)	ee (%)
1	**1**	1	KO^{t}Bu	5	17
2	**2**	1	KO^{t}Bu	95	54
3	**3**	1	KO^{t}Bu	10	0
4	**4**	1	KO^{t}Bu	5	5
5	**2**	2.5	KO^{t}Bu	90	93
6	**2**	3	KO^{t}Bu	85	95
7	**2**	4	KO^{t}Bu	80	97
8	**2**	6	KO^{t}Bu	45	97
9	**2**	2.5	NaOH	88	97

[a] Reaction is performed in 2-propanol for 20 h at 40 °C. Ketone **5a**: base:$[RuCl_2(p\text{-cymene})]_2$ = 200:20:1. When (*R*,*R*)-**2** is used, the product **6a** has the (*R*)-configuration.

The general protocol for transfer hydrogenation was applied to ketones **5a**−**q**. Table 2 shows that the catalyst system is surprisingly



5 **6**

a $R^1 = C_6H_5$; $R^2 = CH_3$
b $R1 = o\text{-}ClC_6H_4$; $R^2 = CH_3$
c $R^1 = m\text{-}MeOC_6H_4$; $R^2 = CH_3$
d $R^1 = p\text{-}MeC_6H_4$; $R^2 = CH_3$
e $R^1 = m\text{-}BrC_6H_4$; $R^2 = CH_3$
f $R^1 = p\text{-}ClC_6H_4$; $R^2 = CH_3$
g $R^1 = p\text{-}BrC_6H_4$; $R^2 = CH_3$
h $R^1 = p\text{-}CF_3C_6H_4$; $R^2 = CH_3$
i $R^1 = C_6H_5$; $R^2 = CH_2CH_3$
j R^1 = 2-naphthyl; $R^2 = CH_3$
k $R^1 = 3,5\text{-}(CF_3)_2C_6H_3$; $R^2 = CH_3$
l $R^1 = c\text{-}C_6H_{11}$; $R^2 = CH_3$
m $R^1 = CH(CH_3)_2$; $R^2 = CH_3$
n $R^1 = n\text{-}C_6H_{13}$; $R^2 = CH_3$
o $R^1 = (CH_3)_2CHCH_2$; $R^2 = CH_3$
p $R^1 = C_6H_5CH_2CH_2$; $R^2 = CH_3$
q $R^1 = n\text{-}C_4H_9$; $R^2 = CH_3$

versatile. The notoriously difficult alkyl/alkyl ketones **5l** and **5m** are reduced with essentially complete enantioselectivity (ee = 99%), which has no precedent in the literature (Table 2, entries 18 and 19). 2-Octanone **5n** is even more challenging as a substrate, yet it reacts selectively (ee = 90%; entry 20), and even **5o**−**q** lead to respectable results (entries 21−23). Some of the chiral alcohols are of industrial interest, e.g., **6k** (ee = 98%), which is an

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Table 2. Ru-Catalyzed Asymmetric Transfer Hydrogenation of Ketones **5a**−**q** Using Ligand **2**[a]

entry	ketone	base	ligand:Ru	time (h)	conversion (%)	ee (%)
1	**5a**	KO^{t}Bu	4	28	91	97
2	**5a**	NaOH	2.5	20	88	97
3	**5a**	NaOH	2.5	40	93	98
4	**5b**	NaOH	2.5	26	83	99
5	**5b**	NaOH	2.5	40	90	99
6	**5c**	NaOH	2.5	40	63	93
7	**5c**	NaOH	2.5	96	91	93
8	**5d**	NaOH	2.5	26	65	95
9	**5e**	KO^{t}Bu	4	28	100	96
10	**5e**	NaOH	2.5	16	100	96
11	**5f**	KO^{t}Bu	4	22	96	96
12	**5f**	NaOH	2.5	16	98	95
13	**5g**	NaOH	2.5	26	98	95
14	**5h**	NaOH	2.5	16	100	97
15	**5i**	NaOH	2.5	26	65	93
16	**5j**	KO^{t}Bu	4	22	56	93
17	**5k**	NaOH	2.5	6	99	98
18	**5l**	NaOH	2.5	22	97	99
19	**5m**	NaOH	2.5	22	99	99
20	**5n**	NaOH	2.5	16	96	90
21	**5o**	NaOH	2.5	40	83	79
22	**5p**	NaOH	2.5	26	97	76
23	**5q**	NaOH	2.5	26	96	82

[a] Reaction conditions as in Table 1. When (*R*,*R*)-**2** is used, the products have the (*R*)-configuration.

intermediate in the synthesis of the NK1 receptor antagonist Aprepitant (Table 2, entry 17).[11] This reduction was previously performed by the Merck group using (1*S*,2*R*)-*cis*-amino-2-indanol as the chiral ligand in a Ru-catalyzed Noyori-type process (ee = 91%), the Corey borane-based reduction leading to 93−95% ee.[11]

The present Ru-based catalyst system is the first one composed solely of P-ligands for ketone reduction with high stereoselectivity. Although detailed structural and mechanistic studies remain to be carried out, we have observed an unusual phenomenon which is worthy of mention: Upon extending the reaction time to some degree, there seems to be very little, if any, erosion of enantiopurity of the products, which may be expected due to the reversibility of transfer hydrogenation in 2-propanol.[1,2] In contrast to other transfer hydrogenation systems in which reduction needs to be terminated at the optimal time, the present system appears to be relatively insensitive in this regard. A preliminary examination of the structure of the (pre)catalyst in 2-propanol points to several Ru species.

In summary, the combination Ru/**2** constitutes the most general catalyst system for the asymmetric reduction of aryl/alkyl and alkyl/alkyl ketones known to date. Since BINOL is currently one of the cheapest chiral auxiliaries commercially available, the method is of industrial interest. Further optimization and illumination of the source of enantioselectivity are goals for the future.

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Supporting Information Available: Typical procedures for asymmetric transfer hydrogenation; complete ref 11. This material is available free of charge via the Internet at http://pubs.acs.org.

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