Enantioselective Hydrogenation

Enantioselective Hydrogenation of β-Ketoesters with Monodentate Ligands**

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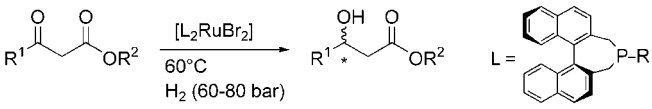
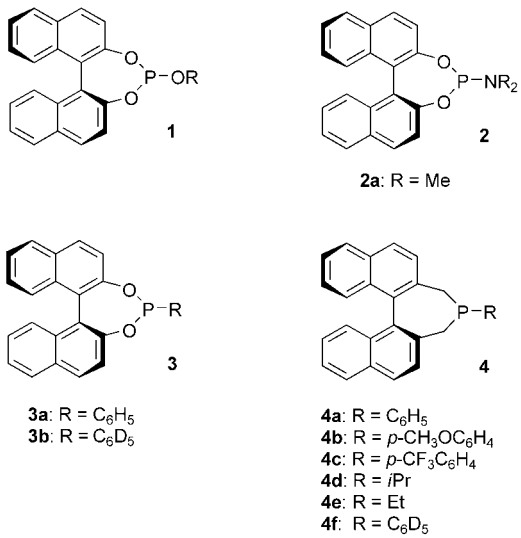
Transition-metal-catalyzed asymmetric reactions offer an efficient and elegant possibility for the synthesis of enantiomerically pure compounds.[1] Among the different catalytic methods, enantioselective hydrogenations have been used extensively in the last two decades and are likely to provide the most important access to pharmaceutical intermediates.[2] In this regard, the hydrogenation of β-ketoesters yields chiral β-hydroxyesters, which are useful building blocks for the synthesis of biologically active compounds and natural products (Scheme 1).[3]



Scheme 1. Catalytic hydrogenation of β-ketoesters **5a–c**.

Pioneering work by Noyori and co-workers established the use of binap as a highly selective ligand for this transformation.[4] More recent developments of chiral ligands were reported by the groups of Genet,[5] Weissensteiner and Spindler,[6] Imamoto,[7] Knochel,[8] Zhang,[9] and others.[10] Virtually all known ligands that induce significant enantioselectivity in the hydrogenation of β-ketoesters are optically active diphosphines.[11]

Interestingly, monodentate ligands (Scheme 2) have recently become increasingly important for catalytic asymmetric hydrogenations of amino acid precursors.[12] In this case, important contributions were made by Reetz et al. (phosphites **1**),[13] de Vries, Feringa, and co-workers (phosphoramidites **2**),[14] Pringle and co-workers (phosphonites **3**),[15] and others.[16] Parallel to the work of Zhang and Chi[17] and Gladiali and co-workers,[18] we have introduced new monodentate phosphines based on a 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine structure **4**.[19,20] Similar to phosphites and phosphoramidites, these ligands give high enantioselectivities (up to 95% *ee*) in the hydrogenation of α-dehydroamino acid methyl esters. Despite the more complicated synthesis, these ligands have advantages with regard to stability against water and other nucleophiles under typical reaction conditions. Herein we report the use of **2a**, **3a–b**, and **4a–f** in the hydrogenation of β-ketoesters. So far, these monodentate ligands have not been used for the synthesis of chiral β-hydroxyesters.



Scheme 2. Selection of recently developed monodentate ligands.

Initial studies of the influence of reaction conditions were carried out with methyl acetoacetate (**5a**) as substrate and our standard ligand 4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (**4a**). Typically the catalytic reactions were run in methanol as solvent in the presence of [Ru(cod)-(methallyl)$_2$] (1 mol%) and the ligand (2 mol%).

For full conversion within a reasonable time, the reactions had to be run under pressure (60 bar) at 60–80°C (Table 1, entries 4, 6). We were pleased to find that under these conditions, good enantioselectivities (up to 84% *ee*) were achieved. Notably, the best result was obtained at a relatively high temperature (80°C; Table 1, entry 6), which is advantageous in terms of the increased rate and selectivity of the reaction.

Next we focused our attention on the influence of different ligands in the hydrogenation of methyl acetoacetate (**5a**). Apart from the phenyl ligand **4a**, the *p*-methoxyphenyl derivative **4b**, the *p*-trifluoromethylphenyl derivative **4c**, the isopropyl derivative **4d**, the ethyl derivative **4e**, and the deuterated phenyl derivative **4f** were used (Table 2). All ligands **4a–f** were prepared in good yields by straightforward Grignard reaction of 1-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine with the corresponding aryl and alkyl halides.[21] Furthermore, monodentate state-of-the-art ligands

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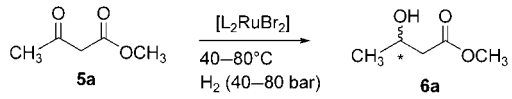
Table 1: Hydrogenation of **5a** in the presence of [Ru(cod)(methallyl)$_2$]/**4a**.[a]



5a **6a**

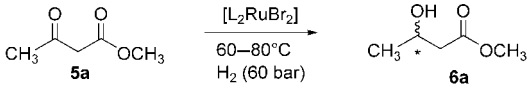
Entry	Solvent	*t* [h]	*p* [bar]	*T* [°C]	Conversion [%]	*ee* [%]
1	MeOH	16	20	60	25	53 (*R*)
2	MeOH	16	40	60	46	68 (*R*)
3	MeOH	16	60	60	51	74 (*R*)
4	MeOH	16	80	60	95	69 (*R*)
5	MeOH	16	60	40	28	34 (*R*)
6	MeOH	16	60	80	95	84 (*R*)
7	acetone	16	60	60	4	5 (*R*)
8	toluene	16	60	60	1	2 (*S*)
9	THF	16	60	60	<1	8 (*R*)

[a] Conditions: solvent (20 mL), **5a** (3.8 mmol), [Ru(cod(methallyl)$_2$] (38 μmol), **4a** (76 μmol).

from other groups such as (*R*)-monophos (**2a**) and the Pringle ligand **3a** were applied.[22]

Importantly, in the presence of the monodentate phosphonate and phosphoramidite, only low enantioselectivity was observed (10–28% *ee*; Table 2, entries 1,2). More surprisingly, the structurally analogous phosphonate **3a** gave a significantly lower enantioselectivity than **4a**. In this case, the formal exchange of two oxygen atoms by sterically similar CH_2 groups led to an increase in enantioselectivity from 28% (*S*) to 84% (*R*) (Table 2, entries 2,4). This clearly demonstrates the importance of electronic effects for achieving high selectivity in the test reaction. These findings inspired us to study the effect of variations of substituents on the phenyl group in **4a** more closely.

Table 2: Hydrogenation of **5a** in the presence of different ligands.[a]



5a **6a**

Entry	Ligand	*t* [h]	*T* [°C]	Conversion [%]	*ee* [%]
1	**2a**	16	80	85	10 (*S*)
2	**3a**	16	60	>99	28 (*S*)
3	**3b**	16	60	>99	56 (*S*)
4	**4a**	16	80	95	84 (*R*)
5	**4b**	48	80	98	93 (*R*)
6	**4b**	16	80	>99	92 (*R*)
7	**4c**	16	80	>99	51 (*R*)
8	**4d**	16	60	>99	60 (*R*)
9	**4e**	16	60	96	10 (*R*)
10	**4e**	16	80	95	64 (*R*)
11	**4f**	16	80	95	59 (*R*)

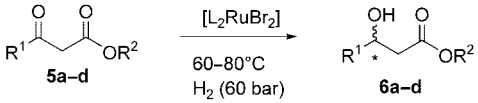
[a] Conditions: methanol (20 mL), **5a** (3.8 mmol), [Ru(cod)(methallyl)$_2$] (38 μmol), **4a–f**, **2a**, or **3a,b** (76 μmol), 60 bar.

Among the different ligands, **4b** gave the highest enantioselectivity (up to 93% *ee*) (Table 2, entry 5). Only the introduction of electron-donating (*p*-methoxy) groups at C4 of the phenyl ring led to a slight increase in selectivity. One of the smallest structural variations possible within the ligand is the exchange of hydrogen by deuterium atoms. We were curious to see if this minor change also influences the enantioselectivity. Thus, the pentadeuterated ligand **4f** was prepared in good yield by a similar method to that described above. A comparison of **4a** and **4f** under identical reaction conditions led to (*R*)-methyl 3-hydroxybutyrate in >95% yield with 84 and 59% *ee*, respectively.

This is, to the best of our knowledge, the first example of an isotope influence on the stereoselectivity of catalytic asymmetric reactions. Because of this finding, we also compared the hydrogenation reaction in the presence of **3a** and its deuterated analogue **3b**. In this case, we noted even an increase in the selectivity upon substitution of the hydrogen atoms with deuterium atoms (28 versus 56% *ee*, respectively; Table 2, entries 2,3). As the mechanism for the ruthenium-catalyzed asymmetric hydrogenation of β-ketoesters is still vague,[23] we do not have a clear rational explanation for the observed change in *ee* values. We believe that the phenyl ring also coordinates to the metal center during the catalytic cycle and therefore affects the outcome of the reaction. A comparison of catalytic reactions with the deuterated ligand **4f** in the presence of methanol (**5a**: 64% *ee*) and deuterated methanol (**5a**: 73% *ee*) demonstrates that deuteration of the solvent also influences the selectivity of the model reaction. Finally we applied ligands **4a**,**b**,**f** in the hydrogenation of different β-ketoesters (Table 3).

In general, all substrates were hydrogenated with excellent conversion and yield. The best selectivities were obtained

Table 3: Hydrogenation of different β-ketoesters **5a–d**.[a]



5a–d **6a–d**

Entry	4	5	R^1	R^2	*t* [h]	*T* [°C]	Yield [%]	*ee* [%]
1	**a**	**a**	Me	Me	16	80	95	84 (*R*)
2	**a**	**b**	Et	Me	16	80	97	86 (*R*)
3	**a**	**c**	CH_2Cl	Et	24	80	81	13 (*S*)
4	**a**	**d**	C_6H_5	Et	16	80	>99	73 (*S*)
5	**b**	**a**	Me	Me	16	80	97	92 (*R*)
6	**b**	**a**	Me	Me	8	100	99	93 (*R*)
7	**b**	**a**	Me	Me	8	120	96	93 (*R*)
8	**b**	**b**	Et	Me	16	80	99	94 (*R*)
9	**b**	**b**	Et	Me	8	100	99	95 (*R*)
10	**b**	**b**	Et	Me	8	120	99	94 (*R*)
11	**b**	**c**	CH_2Cl	Et	16	80	98	6 (*S*)[b]
12	**b**	**c**	CH_2Cl	Et	8	100	73	23 (*S*)[b]
13	**b**	**c**	CH_2Cl	Et	8	120	77	38 (*S*)[b]
14	**b**	**d**	C_6H_5	Et	16	80	>99	94 (*S*)[b]
15	**b**	**d**	C_6H_5	Et	8	100	99	95 (*S*)[b]
16	**b**	**d**	C_6H_5	Et	8	120	99	91 (*S*)[b]
17	**f**	**a**	Me	Me	48	60	98	64 (*R*)
18	**f**	**a**	Me	Me	16	80	95	59 (*R*)
19	**f**	**b**	Et	Me	16	80	99	78 (*R*)
20	**f**	**c**	CH_2Cl	Et	16	80	97	9 (*S*)[b]
21	**f**	**d**	C_6H_5	Et	16	80	>99[c]	64 (*S*)[b]

[a] Conditions: solvent (20 mL), **5** (3.8 mmol), [Ru(cod)(methallyl)$_2$] (38 μmol), **4a,b,f** (76 μmol) 60 bar; methanol was used as a solvent for methyl esters and ethanol for ethyl esters. [b] Owing to the change in priority of the substituents, the configuration of the stereocenter is changed. [c] Conversion; reaction run at 80 bar pressure of H_2.

by using the 4-methoxyphenyl-substituted dinaphthophosphepine ligand **4b** at temperatures of 100–120 °C. Whereas 3-oxobutyrate and 3-oxopentanoate gave enantioselectivities of 93–95 % *ee*, the 4-chloro-3-oxobutyrate led only to 38 % *ee*.[24] The phenyl-substituted β-ketoester gave up to 95 % *ee*. In agreement with the previous findings, the deuterated ligand **4f** showed a significantly different selectivity than that of ligand **4a** in every hydrogenation. Hence, the observed deuterium effect on the selectivity seems to be general for this type of reaction.

In conclusion, we have shown for the first time that monodentate phosphine ligands can be used efficiently for the ruthenium-catalyzed hydrogenation of β-ketoesters. The catalysts are remarkably temperature-tolerant: Enantioselectivities of up to 95 % *ee* were possible, even at 100–120 °C. A comparison of **4a** with structurally related **2a** and **3a** demonstrates the superiority of phosphines over phosphites, phosphonates, and phosphoramidites. Interestingly, the use of deuterated phenyl compounds **3b** and **4f** led to the observation of an isotope effect on the enantioselectivity of the reaction, which may be of interest to asymmetric reactions in general.

Experimental Section

Unless otherwise noted, all chemicals are commercially available and were used without further purification. The β-ketoesters **5a**–**d** were distilled under an argon atmosphere. Products were fully characterized (b.p., IR, MS, elemental analysis, NMR).

General procedure: in situ preparation of ruthenium catalyst:[5] $[Ru(cod)(methallyl)_2]$ (0.038 mmol) and ligand **2a**, **3**, or **4** (0.076 mmol) were placed in a dried 25-mL Schlenk tube under an argon atmosphere, and anhydrous and degassed acetone (5 mL) was added. After the dropwise addition of a solution of HBr in methanol (0.33 mL, 0.29 M) a brown precipitate was formed. Stirring was then continued over 30 min, the solvent was removed in vacuo, and methanol (20 mL) or ethanol (for substrates **5c** and **5d**) was added.

Asymmetric hydrogenation of β-ketoesters **5a**–**d**: Catalytic hydrogenation experiments were carried out in a Parr stainless-steel autoclave (100 mL). In a typical experiment, the autoclave was charged with a mixture of the catalyst $[L_2RuBr_2]$ prepared in situ and **5a** (3.80 mmol) in methanol (20 mL) under a stream of argon. The autoclave was stirred under 40–80 bar pressure of hydrogen at 60–120 °C for 16–48 h. The autoclave was cooled to room temperature, and the hydrogen was released. The reaction mixture was filtered over silica gel, and the enantiomeric excess was determined by GC (Lipodex E) or HPLC (Chiracel OD-H). Most of the hydrogenation products have been described previously. Methyl 3-hydroxybutyrate (**6a**): GC (25 m Lipodex E, 95 °C isothermal): $t_r = 4.9$ (*S*), 5.7 min (*R*); methyl 3-hydroxyvalerate (**6b**): GC (25 m Lipodex E, 85 °C isothermal): $t_r = 10.9$ (*S*), 11.6 min (*R*); ethyl 3-hydroxy-4-chlorobutyrate (**6c**): GC (25 m Lipodex E, 95 °C isothermal): $t_r = 20.4$ (*R*), 20.6 min (*S*); ethyl 3-hydroxy-3-phenylpropionate (**6d**): HPLC (OD-H, hexane/ethanol 95:5, 0.5 mL min^{-1}), $t_r = 10.1$ (*S*), 11.5 min (*R*).

6a: B.p. 63–66 °C/10 Torr; IR (KBr): $\tilde{\nu} = 3439$ br, 3140 w, 2974 w, 2967 m, 2937 m, 1737 br vs, 1439 vs, 1410 s, 1377 s, 1298 s, 1269 s, 1195 s, 1178 s, 1170 w, 1126 w, 1089 w, 1082 w, 946 s, 886 s, 862 m, 719 m, 598 m, 593 s, 475 cm^{-1} w; MS (70 eV): *m*/*z* (%): 103 (16) $[M-Me]^+$, 100 (3) $[M-OH]^+$, 87 (16) $[M-OMe]^+$, 85 (5), 74 (50), 71 (26), 61 (12), 59 (10) $[COOCH_3]^+$, 45 (55) $[CHOHCH_3]^+$, 43 (100), 42 (26), 31 (14) $[CH_3O]^+$, 29 (17), 15 (21); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.10$–4.06 (m, 1H; CH), 3.58 (s, 3H; OCH_3), 3.30 (s, 1H; OH), 2.34 (m, 2H; CH_2), 1.11 ppm (d, $J = 6.3$ Hz, 3H; CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 173.2$ (CO), 64.2 (C-OH), 51.7 (CH_3O), 43.0 (CH_2), 22.7 ppm (CH_3); elemental analysis: calcd (%) for $C_5H_{10}O_3$ (118.17): C 59.15, H 8.54; found: C 59.01, H 8.59.

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Keywords: β-ketoesters · asymmetric catalysis · hydrogenation · ruthenium

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[20] These ligands are commercially available from Degussa AG/ Catalyst and Initiators.
[21] Importantly, an alternative synthesis of ligand **4a** by double metallation of 2,2′-dimethylbinaphthyl with *n*-butyl lithium in the presence of tetramethylethylenediamine (TMEDA) and direct quenching with commercially available dichlorophenylphosphane gave the corresponding ligand with only 80–95% purity (impurities: lithium salts and organic by-products). This decreased purity led to a lower enantioselectivity in the reduction of **5a** and the product was obtained with opposite absolute configuration. We do not know currently which impurity is responsible for the different outcome. In this respect, it is also interesting that the addition of lithium and magnesium salts influences the enantioselectivity of the reduction of **5a** in the presence of **4a** by 5–10%.
[22] We also tried phosphites similar to the Reetz ligand in β-ketoester hydrogenation, but these ligands did not prove to be stable under our conditions (80–120°C, methanol).
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[24] In the case of **5c**, dehydrochlorination was observed as a side reaction at higher temperature.

