Bidentate Camphane Phosphine Phosphinites as Ligands in Asymmetric Hydrogenation of α-Dehydroamino Acids

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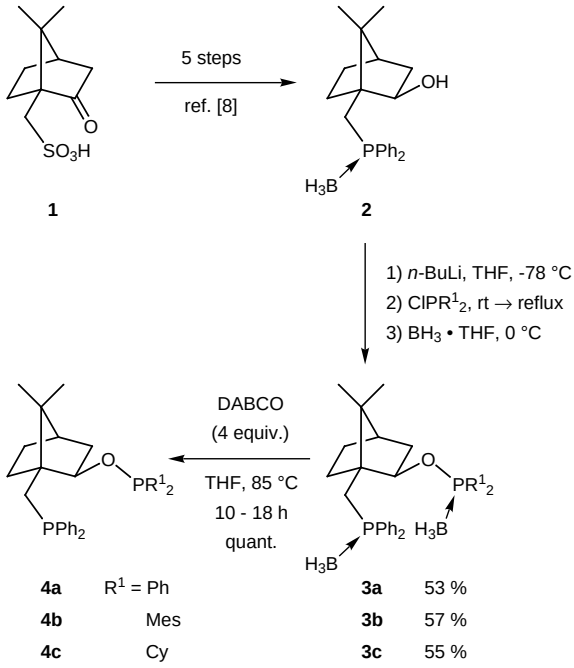
Dedicated to Prof. L. F. Tietze, Universität Göttingen, on the occasion of his 60th birthday.

Abstract: The rhodium(I) catalyzed asymmetric hydrogenation of methyl (*Z*)-*N*-acetamido cinnamates **5a**–**c** in the presence of camphor-derived phosphine phosphinites **4a**–**c** gave the corresponding phenyl alanine derivatives **6a**–**c** with good enantioselectivities (up to 89% ee) and high conversions.

Key words: hydrogenation, rhodium, asymmetric synthesis, amino acids, phosphines

The asymmetric hydrogenation of α-dehydroamino acids is one of the most successful catalytic reactions and over the last decade a plethora of novel ligands has been developed for this purpose.[1] Whereas the majority of the work in this area involves bidentate phosphine, phosphite and phosphinite ligands, several results indicated that mixed phosphine phosphite[2] or aminophosphine phosphinite ligands[3,4] are equally or even better suited for such catalytic reactions. This is in accordance with the proposal by Achiwa, that two different donor sites can a priori lead to a better match of the intermediates determining reactivity and selectivity.[5] In contrast to phosphine phosphites and aminophosphine phosphinites, the corresponding phosphine phosphinites have only been rarely exploited.[6] This is surprising, because Saito reported excellent stereoselectivities and improved *n*/*iso* ratios in hydroformylations using binaphthyl-derived phosphine phosphinites as compared to the diphosphines.[7] In addition, Börner observed promising activities and selectivities of Rh(I) diphosphinite complexes in asymmetric hydrogenations of imines[8] and enamines.[9] Recently, we obtained the novel bisboranato camphane phosphine phosphinite **3a** by a 6-step synthesis from (*1S*)-(+)-camphorsulfonic acid **1**.[10] We were thus interested whether the corresponding borane-free ligand **4a** (Scheme 1) can be used in hydrogenation reactions. Furthermore, we wanted to explore modifications of the phosphinite moiety. The preliminary results are reported below.

In order to study the electronic and steric effects of the phosphinite moiety of **4**, three different ligands **4a**–**c** were prepared according to our previously described procedure



Scheme 1

using hydroxyphosphine **2** as a common intermediate.[10] Treatment of **2** with *n*-BuLi, followed by addition of the corresponding chlorophosphine and subsequent borylation yielded compounds **3a**–**c** in 53–57%. Removal of the borane groups from **3** was achieved by treatment with 4 equivalents of 1,4-diazabicyclo[2.2.0]octane (DABCO) in THF giving the desired ligands **4a**–**c**,[11] which were directly used for hydrogenation experiments. As shown in Scheme 2 and the Table treatment of methyl (*Z*)-*N*-acetamidocinnamate **5a** with 0.5 mol% of $[Rh(COD)]_2OTf$ and 0.6 mol% of phosphine phosphinite ligand **4a** in MeOH at ambient temperature under 5 atm of hydrogen resulted in clean formation of the (*S*)-configurated phenylalanine derivative **6a** with good enantioselectivity (81% ee, entry 1).[12] However, when using 4-methyl-substituted cinnamate **5b**, the conversion dropped down dramatically to 20% (entry 2). With 4-bromo-substituted cinnamate **5c** again quantitative conversion together with high enantioselectivity was achieved (entry 3). In order to avoid such large variations of the reaction rate, the solvent was changed

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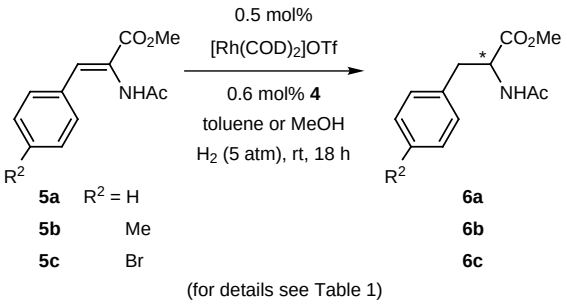
from MeOH to toluene. Indeed, the conversion for **5b** to **6b** could be considerably improved to 60% (entry 5). Concerning the enantioselectivities the use of toluene led to an overall increase of the ee values (entries 4–6) irrespective of the *para*-substituent of the cinnamates **5a**–**c**. This solvent effect was rather unexpected because kinetic studies and ^{103}Rh NMR experiments by Heller and Baumann indicated that aromatic solvents inhibit the catalytic activity of cationic Rh(I) diphosphine complexes due to η^6-complex formation.[13] When dimesitylphosphinite **4b** was employed for the hydrogenations, quantitative conversions were obtained in all cases (entries 7–9). The enantioselectivities were in the same range as compared to diphenylphosphinite **4a**. The most surprising outcome was the reversal of the configuration, when dicyclohexylphosphinite **4c** was used instead (entries 10–12). A similar reversal of configuration was observed by Pizzano in hydrogenations of dimethyl itaconate upon replacement of phenyl by alkyl groups in the phosphine phosphite ligand.[14] According to mechanistic studies by Ruiz, Claver[2a,b] and Landis[15] we propose that the different steric bulkiness of diarylphosphites **4a**,**b** and dicyclohexylphosphite **4c** results in the preferred formation of different diastereomeric Rh(enamide)$(H)_2$ complexes and thus yields opposite enantiomers of **6**.



Scheme 2

In conclusion, the enantioselectivities obtained with ligands **4a**–**c** in Rh(I)-catalyzed hydrogenations of methyl (*Z*)-*N*-acetylamidocinnamates **5a**–**c** compare well to the selectivities reported by Chan for an aminophosphine phosphinite ligand derived from ketopinic acid.[3] Comparison with spiro diphosphinites[16] and phosphine phosphites[2] indicates however, that further reduction of the conformational flexibility of ligands **4** is required in order to further optimize the enantioselectivity.

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Table Catalytic Hydrogenations of Methyl (*Z*)-*N*-Acetamido Cinnamates **5a**–**c** in the Presence of Phosphine Phosphinites **4a**–**c**[a]

Entry	**4**	R^1	**5**	R^2	Solvent	**6**	Conv. [%][b]	% ee	Config.[c]
(1)	**a**	Ph	**a**	H	MeOH	**a**	100	81	(*S*)
(2)	**a**	Ph	**b**	Me	MeOH	**b**	20	73	(*S*)
(3)	**a**	Ph	**c**	Br	MeOH	**c**	100	82	(*S*)
(4)	**a**	Ph	**a**	H	toluene	**a**	100	85	(*S*)
(5)	**a**	Ph	**b**	Me	toluene	**b**	60	85	(*S*)
(6)	**a**	Ph	**c**	Br	toluene	**c**	100	87	(*S*)
(7)	**b**	Mes	**a**	H	toluene	**a**	100	89	(*S*)
(8)	**b**	Mes	**b**	Me	toluene	**b**	100	85	(*S*)
(9)	**b**	Mes	**c**	Br	toluene	**c**	100	87	(*S*)
(10)	**c**	Cy	**a**	H	toluene	**a**	100	50	(*R*)
(11)	**c**	Cy	**b**	Me	toluene	**b**	93	34	(*R*)
(12)	**c**	Cy	**c**	Br	toluene	**c**	98	29	(*R*)

[a] Reaction conditions: 0.3 mmol of α-dehydroamino acid **4**, 1.5 μmol of $[Rh(COD)_2]OTf$, 1.8 μmol of ligand **4**, 1.3 mL of solvent, 5 bar H_2, r.t., 18 h.
[b] Conversions were determined by capillary GC using a Chrompac CP-SilCB WCOT column, length 25 m, initial temperature 100 °C, rate 10 °C/min, final temperature 300 °C, carrier gas: He.
[c] Enantioselectivities were determined by HPLC using a Chiracel OD column with hexane/2-propanol (80:20) as solvent, flow 1 mL/min, detection at λ = 220 nm.

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(11) Selected spectroscopic data of phosphine phosphinite ligands:
4a: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.72 (s, 3 H), 0.75–0.85 (m, 1 H), 0.94–1.05 (m, 1 H), 1.10 (s, 3 H), 1.34–1.45 (m, 1 H), 1.52–1.59 (m, 2 H), 1.79 (d, 1 H), 2.12 (d, broad, *J* = 13.8 Hz, 1 H), 2.12 (dd, *J* = 13.8/5.0 Hz, 1 H), 2.27 (d, *J* = 15.0 Hz, 1 H), 4.32 (t, *J* = 7.5 Hz, 1 H), 6.95–7.54 (m, 20 H); ^{31}P NMR (202 MHz, $CDCl_3$): δ = –24.0 (s), 112.2 (s).
4b: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.71 (s, 3 H), 0.71–0.82 (m, 2 H), 0.92–1.00 (m, 1 H), 1.11 (s, 3 H), 1.36–1.42 (m, 1 H), 1.53–1.59 (m, 2 H), 1.83 (d, broad, *J* = 13.8 Hz, 1 H), 2.05 (s, 6 H), 2.11 (dd, *J* = 13.8/5.0 Hz, 1 H), 2.20 (s, 6 H), 2.26 (d, *J* = 15.0 Hz, 1 H), 4.25 (t, *J* = 7.5 Hz, 1 H), 6.72 (s, 1 H), 6.84 (s, 1 H), 6.94–7.51 (m, 14 H); ^{31}P NMR (202 MHz, $CDCl_3$): δ = –23.9 (s), 112.9 (s).
4c: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.73 (s, 3 H), 0.73–0.85 (m, 2 H), 0.98 (s, 3 H), 0.90–1.85 (m, 28 H), 2.10 (dd, *J* = 13.8/5.0 Hz, 1 H), 2.33 (d, *J* = 13.8 Hz, 1 H), 3.90 (t, *J* = 7.5 Hz, 1 H), 7.05–7.55 (m, 10 H); ^{31}P NMR (202 MHz, $CDCl_3$): δ = –25.7 (s), 143.1 (s).

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