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Evaluation of calix[4]arene-based chiral diphosphite ligands in Rh-catalyzed asymmetric hydrogenation of simple dehydroamino acid derivatives

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ABSTRACT

The calix[4]arene framework was readily modified to generate a number of chiral BINOL-based diphosphite ligands (**3**) capable of forming *in situ* Rh-complexes which catalyzed the asymmetric hydrogenation of model substrates methyl-(*Z*)-2-(acetamido)acrylate (**1a**) and methyl-(*Z*)-2-(acetamido)cinnamate (**1b**). The (*S*,*S*)-catalyst generated the (*R*)-product. Upper rim (R^1) and 1,3-*O*-alkylation (R^2) substitution on the calixarene strongly influenced catalyst activity and chiral induction. Optimum results were obtained when R^1 was $-C(CH_3)_3$ and R^2 was $-CH_2CH_2CH_3$ (**3b**). Under optimized conditions, **3b** hydrogenated **1a** and **1b** in 98 and 96% ee, respectively. Overall, better catalyst performance was observed for "locked" cone-conformers of **3**, with higher activity evident for the less sterically hindered **1a** (TOF up to 1300 h^{-1} at $P(H_2) = 5$ atm).

1. Introduction

Asymmetric hydrogenation of prochiral olefins by transition metal molecular catalysts are among the most important and widely used catalytic transformations [1]. The ability to generate chiral compounds efficiently using molecular hydrogen has further led to the development of several industrial applications [1,2]. Due to the ubiquitous role of chiral phosphine ligands in such systems, and the current growing demand for optically pure compounds, the further development of novel chiral phosphine and other P-based ligands is of great interest [1,3]. Among the variety of P-linkages (P–C (aromatic or aliphatic), P–O, P–N) that have been used for ligand construction [1c,3,4], phosphite-based ligands have proven to be a cost effective and versatile structural and functional motif [5,6]. Here, BINOL (BINOL = 2,2′-dihydroxy-1,1′-binaphthyl) based phosphites have generally yielded the most effective catalysts giving hydrogenation products in (often) very high enantiomeric purity.

Calixarenes are a readily modified macrocyclic family that have served as appropriate platforms for the construction of P-ligands for a range of catalytic transformations [7–9]. For phosphite-based calixarenes, application in hydroformylation catalysis has been particularly successful due to the inherently large bite angles such P-ligands form with the central metal [10], which has been found to promote formation of the desired linear aldehyde product [9]. By comparison, the use of calixarene-based P-ligands for related asymmetric hydrogenation has remained relatively unexplored [11,12]. Herein, we describe the application of several chiral diphosphite calixarene-based ligands in Rh-catalyzed asymmetric hydrogenation and evaluate their potential using methyl-(*Z*)-2-(acetamido)acrylate (**1a**) and methyl-(*Z*)-2-(acetamido)cinnamate (**1b**) as model substrates.

2. Experimental

2.1. Materials and methods

All moisture and oxygen sensitive manipulations were performed using standard Schlenk techniques under an argon atmosphere. Toluene, ether and THF were freshly distilled from metal sodium/benzophenone under argon prior to use. CH_2Cl_2 was freshly distilled from CaH_2 under argon prior to use. CH_3OH, $(CH_3)_2CHOH$, $(CH_3)_3COH$, $CH_3CO_2CH_2CH_3$ and CH_2ClCH_2Cl were distilled from CaH_2 and stored under argon. $CDCl_3$ was stored under CaH_2 and collected by cold distillation under vacuum prior to use. Solvents used in the hydrogenation reactions were degassed by three freeze-and-thaw cycles prior to use. Triethylamine and phosphorus trichloride were distilled form CaH_2 under argon. Other commercially available materials were used without further purification. Hydrogen gas (99.9999%) was obtained from Shanghai Fujiang Specialty Gases Co., Ltd. $[Rh(COD)_2BF_4]_2$

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[13], methyl-(*Z*)-2-(acetamido)acrylate (**1a**) [14], methyl-(*Z*)-2-(acetamido)cinnamate (**1b**) [15], *p-tert*-butylcalix[4]arene [16], calix[4]arene [17] and *p*-benzylcalix[4]arene [18] were synthesized according to reported procedures. ^{1}H-, ^{13}C- and ^{31}P NMR data were collected on a Varian Mercury vx 300 or 400 spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to TMS (^{1}H), $CHCl_3$ residue (^{13}C) or 85% H_3PO_4 (^{31}P). MS (MALDI) were recorded on a IonSpec 4.7 (Applied IonSpec Co.). Elemental analyses were performed on an Elementar vario EL III. Gas chromatography (GC) analysis was conducted on an Agilent Technologies 7890A instrument equipped with a Chirasil-DEX CB fused silica capillary column (df = 0.25 μm, 0.25 mm i.d., 25 m, Varian). High performance liquid chromatography (HPLC) analysis was conducted on a Waters 515 instrument equipped with a Chiralpak AD-H column (0.46 cm i.d., 25 cm L, Daicel). Optical rotations were obtained using a Jasco P-1030 polarimeter.

2.2. Synthesis of compounds

2.2.1. (S,S)-5,11,17,23-Tetra-tert-butyl-25,27-dimethoxy-26,28-bis(1,1′-binaphthyl-2,2′-dioxyphosphanyloxy)calix[4]arene (**3a**)

A hexane solution of *n*-BuLi (0.75 mL, 2.5 mol/L, 1.86 mmol) was slowly added at 0 °C to a stirred solution of *p-tert*-butyl-1,3-dimethoxycalix[4]arene [19] (630 mg, 0.93 mmol) in dried THF (30 mL) using a syringe. The reaction mixture was stirred for 2 h at RT. Subsequently, [(*S*)-(1,1′-binaphthalene-2,2′-diyl)]chlorophosphite [20] (652 mg, 1.86 mmol) in dried THF (8 mL) was added at 0 °C and the reaction mixture was stirred for 11 h at RT. After removal of the volatiles, 25 mL of CH_2Cl_2 was added to the resulting solid. LiCl was removed by filtration through a short pad of Celite and the filtrate was evaporated to dryness. The residue was subjected to flash chromatography (eluent: petroleum ether/ethyl acetate = 200/1) to afford the title compound (622 mg, 51%) as a white foamy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.98–6.34 (m, 32 H, calix-ArH and BINOL-ArH), 4.54–3.01 (m, 14 H, $ArCH_2Ar$ and OCH_3), 1.33–0.72 (m, 36 H, $C(CH_3)_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 156.08–120.81 (Ar–C), 60.75, 60.08, 57.86 (s, OCH_3), 37.80 (s, $ArCH_2Ar$), 37.13 (s, $ArCH_2Ar$), 34.12 (s, $C(CH_3)_3$), 33.65 (s, $C(CH_3)_3$), 32.43 (s, $ArCH_2Ar$), 32.15 (s, $ArCH_2Ar$), 31.65, 31.31, 31.02, 30.83, 29.70 (s, $C(CH_3)_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ = 145.99 (s, trace), 144.34 (s, trace), 143.99 (s, major), 142.31 (s), 138.18 (s). MS (MALDI): m/e 1305.6 $[M+H]^+$; 1327.5 $[M+Na]^+$. Anal. Calcd. for $C_{86}H_{82}O_8P_2$ (1305.51): C, 79.12; H, 6.33; found: C, 78.01; H, 6.58. Note that **3a** was obtained as a mixture of conformational isomers which was used without further separation for hydrogenation experiments.

2.2.2. (S,S)-5,11,17,23-Tetra-tert-butyl-25,27-dipropoxy-26,28-bis(1,1′-binaphthyl-2,2′-dioxyphosphanyloxy)calix[4]arene [9i] (**3b**)

A suspension of *p-tert*-butyl-1,3-dipropoxycalix[4]arene [21] (733 mg, 1.0 mmol) and NaH (119 mg, 60% dispension in oil, 2.98 mmol) in dried toluene (20 mL) was heated under reflux for 17 h. [(*S*)-(1,1′-Binaphthalene-2,2′-diyl)]chlorophosphite [20] (772 mg, 2.2 mmol) in dried toluene (10 mL) was added at 0 °C and the reaction mixture was stirred for 2 h at RT. The crude reaction mixture was filtered through a short pad of silica gel and washed with toluene (2× 15 mL). The filtrate was concentrated to dryness and the residue subjected to flash chromatography (eluent: petroleum ether/ethyl acetate = 90/1) to afford the title compound (454 mg, 33%) as a white foamy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 (d, ^{3}J = 8.1 Hz, 2 H, BINOL-ArH), 7.86 (d, ^{3}J = 8.7 Hz, 2 H, BINOL-ArH), 7.77 (d, ^{3}J = 8.1 Hz, 2 H, BINOL-ArH), 7.59 (d, ^{3}J = 8.7 Hz, 2 H, BINOL-ArH), 7.49 (d, ^{3}J = 8.7 Hz, 2 H, BINOL-ArH), 7.46–7.09 (m, 12 H, BINOL-ArH), 7.04 (d, ^{3}J = 8.7 Hz, 2 H, BINOL-ArH), 6.89 (d, ^{4}J = 2.4 Hz, 2 H, calix-ArH), 6.82 (d, ^{4}J = 2.4 Hz, 2 H, calix-ArH), 6.74 (d, ^{4}J = 2.4 Hz, 2 H, calix-ArH), 6.62 (d, ^{4}J = 2.4 Hz, 2 H, calix-ArH), 4.74 and 3.39 (AB system, ^{2}J = 12.9 Hz, 4 H, $ArCH_2Ar$), 4.65 and 2.95 (AB system, ^{2}J = 12.9 Hz, 4 H, $ArCH_2Ar$), 3.70–3.63 (m, 4 H, OCH_2), 1.81–1.63 (m, 4 H, OCH_2CH_2), 1.10 (s, 18 H, $C(CH_3)_3$), 1.08 (s, 18 H, $C(CH_3)_3$), 0.29 (t, ^{3}J = 7.8 Hz, 6 H, CH_2CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 137.20 (s, trace), 136.99 (s, trace), 135.87 (s), 133.00 (br s, major, cone conformational isomer), 132.86 (s), 132.48 (s, trace), 127.25 (s), 120.85 (s). Note that **3b** was obtained predominantly as the cone-conformer (ca. 90%) and was used without further separation for hydrogenation experiments.

2.2.3. (S,S)-5,11,17,23-Tetra-tert-butyl-25,27-dibutoxy-26,28-bis(1,1′-binaphthyl-2,2′-dioxyphosphanyloxy)calix[4]arene (**3c**)

A suspension of *p-tert*-butyl-1,3-dibutoxycalix[4]arene [22] (931 mg, 1.22 mmol) and NaH (122 mg, 60% dispension in oil, 3.05 mmol) in dried toluene (30 mL) was heated under reflux for 18 h. [(*S*)-(1,1′-Binaphthalene-2,2′-diyl)]chlorophosphite [20] (941 mg, 2.68 mmol) in dried toluene (15 mL) was added at 0 °C and the reaction mixture was stirred for 2 h at RT. The crude reaction mixture was filtered through a short pad of silica gel and washed with toluene (3× 15 mL). The filtrate was concentrated to ca. 5 mL. Addition of petroleum ether (50 mL) gave the title compound as colorless crystals (873 mg, 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.88 (d, ^{3}J = 8.1 Hz, 4 H, BINOL-ArH), 7.76 (d, ^{3}J = 8.1 Hz, 2 H, BINOL-ArH), 7.70 (d, ^{3}J = 9.0 Hz, 2 H, BINOL-ArH), 7.47 (d, ^{3}J = 9.0 Hz, 2 H, BINOL-ArH), 7.42–7.10 (m, 14 H, BINOL-ArH), 7.02–6.97 (m, 4 H, calix-ArH), 6.73 (d, ^{4}J = 1.8 Hz, 2 H, calix-ArH), 6.56 (d, ^{4}J = 1.8 Hz, 2 H, calix-ArH), 4.62 and 3.37 (AB system, ^{2}J = 12.9 Hz, 4 H, $ArCH_2Ar$), 4.62 and 3.11 (AB system, ^{2}J = 12.9 Hz, 4 H, $ArCH_2Ar$), 3.64–3.44 (m, 4 H, OCH_2), 1.73–1.65 (m, 4 H, OCH_2CH_2), 1.24 (s, 18 H, $C(CH_3)_3$), 0.99 (s, 18 H, $C(CH_3)_3$), 0.90–0.82 (m, 4 H, CH_2CH_3), 0.20 (t, ^{3}J = 6.6 Hz, 6 H, CH_2CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 154.18–121.90 (Ar–C), 75.51 (s, OCH_2), 33.96 (s, $C(CH_3)_3$), 33.75 (s, $C(CH_3)_3$), 32.46 (s, $ArCH_2Ar$), 31.83 (s, $ArCH_2Ar$), 31.60 (s, $C(CH_3)_3$), 31.32 (s, OCH_2CH_2), 31.28 (s, $C(CH_3)_3$), 18.35 (s, CH_2CH_3), 13.82 (s, CH_2CH_3); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ = 140.77 (br s, $P(OAr)_3$). MS (MALDI): m/e 1411.6 $[M+Na]^+$. Anal. Calcd. for $C_{92}H_{94}O_8P_2$ (1389.67): C, 79.51; H, 6.82; found: C, 79.68; H, 6.92. Only the cone-conformer for **3c** was obtained. Crystals of **3c** (colorless) suitable for X-ray diffraction were obtained by slow diffusion of petroleum ether into a solution of **3c** in toluene.

2.2.4. (S,S)-5,11,17,23-Tetra-tert-butyl-25,27-dibenzyloxy-26,28-bis(1,1′-binaphthyl-2,2′-dioxyphosphanyloxy)calix[4]arene [9j] (**3d**)

A hexane solution of *n*-BuLi (0.8 mL, 2.5 mol/L, 2.0 mmol) was slowly added at 0 °C to a stirred solution of *p-tert*-butyl-1,3-dibenzyloxycalix[4]arene [23] (828 mg, 1.0 mmol) in dried THF (30 mL) using a syringe. The reaction mixture was stirred for 2 h at RT. Subsequently, [(*S*)-(1,1′-binaphthalene-2,2′-diyl)]chlorophosphite [20] (701 mg, 2.0 mmol) in dried THF (10 mL) was added at 0 °C and the reaction mixture was stirred for 12 h at RT. After removal of the volatiles, 30 mL of CH_2Cl_2 was added to the resulting solid. LiCl was removed by filtration through a short pad of Celite and the filtrate was evaporated to dryness. The remaining residue was subjected to flash chromatography (eluent: petroleum ether/ethyl acetate = 200/1) to afford the title compound (450 mg, 31%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 (d, ^{3}J = 8.1 Hz, 2 H, BINOL-ArH), 7.71 (d, ^{3}J = 8.7 Hz, 4 H, Bn-ArH), 7.50–7.44 (m, 2 H, Bn-ArH), 7.40–7.05 (m, 26 H, Bn-ArH and BINOL-ArH), 6.69 (d, ^{4}J = 2.4 Hz, 2 H, calix-ArH), 6.62 (d, ^{4}J = 9.3 Hz, 2 H, calix-ArH), 6.44 (d, ^{4}J = 2.4 Hz, 2 H, calix-ArH), 6.35 (d, ^{4}J = 2.4 Hz, 2 H, calix-ArH), 5.11 (^{2}J = 11.7 Hz, 2 H, CH*H*Ph), 4.78

(^2J = 11.7 Hz, 2 H, C*H*HPh), 4.71 and 3.01 (AB system, ^2J = 12.9 Hz, 4 H, $ArCH_2Ar$), 4.71 and 2.60 (AB system, ^2J = 12.9 Hz, 4 H, $ArCH_2Ar$), 1.25 (s, 18 H, $C(CH_3)_3$), 0.81 (s, 18 H, $C(CH_3)_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ = 123.89 (s, $P(OAr)_3$). Only the cone-conformer for **3d** was obtained.

2.2.5. (S,S)-5,11,17,23-Tetra-tert-butyl-25,27-dibenzyloxy-26,28-bis(1,1′-binaphthyl-3,3′-dimethyl-2,2′-dioxyphosphanyloxy)calix[4]arene (**3e**)

A suspension of *p-tert*-butyl-1,3-dibenzyloxycalix[4]arene [23] (99.6 mg, 0.12 mmol) and NaH (15.2 mg, 60% dispension in oil, 0.38 mmol) in dried toluene (7 mL) was heated under reflux for 13 h. [(*S*)-(1,1′-binaphthalene-3,3′-dimethyl-2,2′-diyl)]chlorophosphite [24] (90.9 mg, 0.24 mmol) in dried toluene (3 mL) was added at 0 °C and the reaction mixture was stirred for 2 h at RT. The crude reaction mixture was filtered through a short pad of silica gel and washed with toluene (2× 5 mL). The filtered solution was evaporated to dryness, leading to the title compound as a pale yellow foamy solid (103.2 mg, 57%): ^1H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.52 (m, 10 H, Bn-ArH and BINOL-ArH), 7.36–7.31 (m, 10H, Bn-ArH and BINOL-ArH), 7.20–7.07 (m, 10H, BINOL-ArH), 7.04 (s, 4H, calix-ArH), 6.79 (s, 4H, calix-ArH), 5.04 (s, 4H, OCH_2Ph), 4.29 (d, ^2J = 12.8 Hz, 4 H, $ArCH_2Ar$), 3.27 (d, ^2J = 12.8 Hz, 4 H, $ArCH_2Ar$), 2.32–2.22 (m, 12 H, BINOL-$ArCH_3$), 1.29 (s, 18 H, $C(CH_3)_3$), 0.95 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 150.72–123.04 (Ar–C), 77.92 (s, OCH_2Ph), 33.91 (s, $C(CH_3)_3$), 33.79 (s, $C(CH_3)_3$), 31.70 (s, $C(CH_3)_3$), 31.42 (s, $ArCH_2Ar$), 30.99 (s, $C(CH_3)_3$), 29.69 (s, $ArCH_2Ar$), 19.72, 18.20, 18.16, 17.51, 17.29, 16.93 (s, BINOL-$ArCH_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ = 142.97 (s, major), 141.05 (s), 138.69 (s). MS (MALDI): m/e 1513.7 $[M+H]^+$. HRMS (MALDI): Calcd. for $[C_{102}H_{99}O_8P_2]^+$: 1513.681; found: 1513.680. Anal. Calcd. for $C_{102}H_{98}O_8P_2$ (1513.81): C, 80.93; H, 6.53; found: C, 78.21; H, 7.78. Note that **3e** was obtained as a mixture of conformational isomers which was used without further separation for hydrogenation experiments.

2.2.6. (S,S)-25,27-Dimethoxy-26,28-bis(1,1′-binaphthyl-2,2′-dioxyphosphanyloxy)calix[4]arene (**3f**)

A hexane solution of *n*-BuLi (0.6 mL, 1.6 mol/L, 0.972 mmol) was slowly added at 0 °C to a stirred solution of 1,3-dimethoxycalix[4]arene [25] (220 mg, 0.486 mmol) in dried toluene (20 mL), using a syringe. The reaction mixture was stirred for 2 h at RT. Subsequently, [(*S*)-(1,1′-binaphthalene-2,2′-diyl)]chlorophosphite [20] (341 mg, 0.972 mmol) in dried toluene (5 mL) was added at 0 °C and the reaction mixture was stirred for 12 h at RT. Following removal of volatiles, 15 mL of CH_2Cl_2 was added to the resulting solid. LiCl was removed by filtration through a short pad of Celite and the filtrate was evaporated to dryness. The residue was subjected to flash chromatography (eluent: petroleum ether/ethyl acetate = 20/1) to afford the title compound (172 mg, 33%) as a white solid: ^1H NMR (400 MHz in $CDCl_3$) δ = 8.16–7.24 (m, 24 H, BINOL-ArH), 7.16–6.25 (m, 12H, calix-ArH), 4.55–2.82 (m, 14 H, $ArCH_2Ar$ and OCH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 158.61–121.83 (Ar–C), 77.20, 60.96, 60.05, 58.92 (s, OCH_3), 36.37, 35.38, 31.70, 31.62, 30.29, 29.67 (s, $ArCH_2Ar$); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 148.07 (s), 145.43 (s, major), 144.80 (s). MS (MALDI): m/e 1081.3 $[M+H]^+$; 1103.3 $[M+Na]^+$. HRMS (MALDI): Calcd. for $[C_{70}H_{51}O_8P_2]^+$: 1081.3054; found: 1081.3073. Anal. Calcd. for $C_{70}H_{50}O_8P_2 \cdot 4H_2O$ (1081.09 + 72.06): C, 72.91; H, 5.07. Found: C, 70.89; H, 4.76. Note that **3f** was obtained as a mixture of conformational isomers and was used without further separation for hydrogenation experiments.

2.2.7. (S,S)-5,11,17,23-Tetra-benzyl-25,27-dibenzyloxy-26,28-bis(1,1′-binaphthyl-2,2′-dioxyphosphanyloxy)calix[4]arene (**3g**)

A suspension of *p*-benzyl-1,3-dibenzyloxycalix[4]arene [18] (93 mg, 0.096 mmol) and NaH (9.6 mg, 60% dispension in oil, 0.24 mmol) in dried toluene (7 mL) was heated under reflux for 11 h. [(*S*)-(1,1′-Binaphthalene-2,2′-diyl)]chlorophosphite [20] (67.7 mg, 0.193 mmol) in dried toluene (3 mL) was added at 0 °C and the reaction mixture was stirred for 2 h at RT. The crude reaction mixture was filtered through a short pad of silica gel and washed with toluene (2× 5 mL). The filtered solution was evaporated to dryness, leading to the title compound as a pale yellow foamy solid (90.0 mg, 59%): ^1H NMR (400 MHz, $CDCl_3$) δ = 8.00–7.81 (m, 4H, BINOL-ArH), 7.61–7.59 (m, 4H, Bn-ArH), 7.38–7.10 (m, 42H, BINOL-ArH and Bn-ArH), 6.96 (d, ^3J = 3.6 Hz, 4H, Bn-ArH), 6.81 (s, 4H, calix-ArH), 6.67 (s, 4H, calix-ArH), 4.99 (s, 4H, OCH_2Ph), 4.23 (d, ^2J = 13.2 Hz, 4 H, $ArCH_2Ar$), 3.84 (s, 4H, $ArCH_2Ph$), 3.58 (s, 4H, $ArCH_2Ph$), 3.21 (d, ^2J = 13.2 Hz, 4 H, $ArCH_2Ar$); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 151.62–126.19 (Ar–C), 78.29 (s, OCH_2Ph), 77.20 (s, OCH_2Ph), 41.23 (s, $ArCH_2Ph$), 40.94 (s, $ArCH_2Ph$), 31.54 (s, $ArCH_2Ar$); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ = 145.68 (s). MS (MALDI): m/e 1593.6 $[M+H]^+$. Anal. Calcd. for $C_{110}H_{82}O_8P_2$ (1593.77): C, 82.90; H, 5.19. Found: C, 82.53; H, 5.94. Only the cone-conformer for **3g** was obtained.

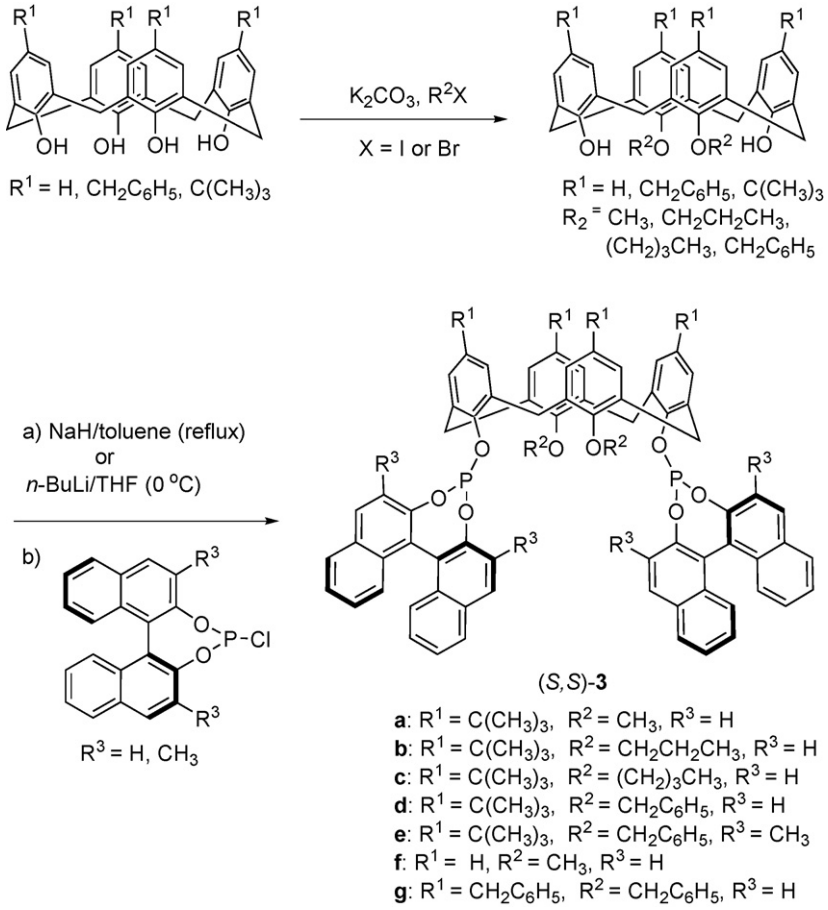
2.3. Solution studies

2.3.1. In situ [(**3**)Rh(COD)]BF_4 formation

Accurately measured amounts of (*S,S*)-**3** (11.0–15.2 mg, 10 μmol) were placed in a pre-oven-dried (120 °C) 10 mL Schlenk and the atmosphere replaced with argon. Dried $CDCl_3$ (1.0 mL) was added to obtain a 10 mM solution. To this was added 1 equiv. of $[Rh(COD)_2BF_4]$ (4.1 mg, 10 μmol) and the mixture gently stirred for 30 min. ^{31}P NMR (162 MHz, $CDCl_3$) spectra of resulting solutions were obtained after a 5 and 30 min period. Following removal of volatiles under vacuum, MS (MALDI) spectra for resulting powders were obtained. Complex, δ (ppm); m/e: (a) [(**3a**)Rh(COD)]BF_4, 120.6 (d, $J_{Rh,P}$ = 256 Hz, 95%), 117.5 (d, $J_{P,P}$ = 46 Hz, <5%), 113.6 (d, $J_{P,P}$ = 46 Hz, <5%); 1407.5 [(**3a**)Rh]$^+$; (b) [(**3b**)Rh(COD)]BF_4, 120.6 (dd, $J_{Rh,P}$ = 255 Hz, $J_{P,P}$ = 41 Hz, 5%), 119.9 (d, $J_{Rh,P}$ = 255 Hz, 85%), 117.2 (dd, $J_{Rh,P}$ = 265 Hz, $J_{P,P}$ = 43 Hz, 5%), 117.1 (d, $J_{P,P}$ = 47 Hz, <5%), 113.0 (d, $J_{P,P}$ = 47 Hz, <5%); 1463.5 [(**3b**)Rh]$^+$; (c) [(**3c**)Rh(COD)]BF_4, 120.2 (d, $J_{Rh,P}$ = 255 Hz, 90%), 117.5 (d, $J_{P,P}$ = 47 Hz, <5%), 113.5 (d, $J_{P,P}$ = 47 Hz, <5%); 1491.5 [(**3c**)Rh]$^+$; (d) [(**3d**)Rh(COD)]BF_4, 119.5 (d, $J_{Rh,P}$ = 257 Hz, 90%), 117.7 (d, $J_{P,P}$ = 46 Hz, <5%), 113.8 (d, $J_{P,P}$ = 46 Hz, <5%); 1559.5 [(**3d**)Rh]$^+$; (e) **3e**, no complex formation was observed; (f) **3f**, no complex formation was observed.

2.3.2. Evidence for in situ [(**3a**)Rh(**1b**)]BF_4 generation

Accurately measured amounts of (*S,S*)-**3** (13.1–14.6 mg, 10 μmol) were placed in a pre-oven-dried (120 °C) 10 mL Schlenk and the atmosphere replaced with argon. Dried $CDCl_3$ (1.0 mL) was added to obtain a 10 mM solution. To this was added 1 equiv. of $[Rh(COD)_2BF_4]$ (4.1 mg, 10 μmol) and the mixture gently stirred (15 min). The resulting solution was then stirred under an H_2 atmosphere (1 atm) for 15 min. ^{31}P NMR spectra were obtained under argon atm using 0.5 mL. To the remaining 0.5 mL was added an aliquot (0.5 mL) of **1b** in $CDCl_3$ (10 mM, 1 equiv./Rh) under argon. The resulting mixture was gently stirred for 30 min and the ^{31}P NMR spectrum obtained. (a) [(**3a**)Rh$(CDCl_3)_2$]BF_4 not formed, 120.0 (d, $J_{Rh,P}$ = 255 Hz, [(**3**)Rh(COD)]BF_4); no detectable change with addition of **1b**. (b) *In situ* generated [(**3b**)Rh$(CDCl_3)_2$]BF_4 not detected, 120.5 (dd, $J_{Rh,P}$ = 255 Hz, $J_{P,P}$ = 41 Hz, 10%), 119.4 (d, $J_{Rh,P}$ = 255 Hz, 15%), 117.5 (dd, $J_{Rh,P}$ = 266 Hz, $J_{P,P}$ = 43 Hz, 10%), 112.8 (d, $J_{P,P}$ = 60 Hz, 20%), 107.7 (d, $J_{P,P}$ = 60 Hz, 20%), −3.95 (s, 35%); with addition of **1b**, 126.4 (dd, $J_{Rh,P}$ = 245 Hz,



Scheme 1. Synthesis of calix[4]arene-based diphosphite ligands (**3**).

$J_{P,P}$ = 91 Hz, 35%), 124.9 (dd, $J_{Rh,P}$ = 246 Hz, $J_{P,P}$ = 91 Hz, 35%), 119.9 (dd, $J_{Rh,P}$ = 262 Hz, $J_{P,P}$ = 40 Hz, 5%), 119.2 (d, $J_{Rh,P}$ = 255 Hz, 10%), 117.2 (dd, $J_{Rh,P}$ = 264 Hz, $J_{P,P}$ = 42 Hz, 5%), 113.9 (d, $J_{P,P}$ = 56 Hz, 5%), 109.1 (d, $J_{P,P}$ = 56 Hz, 5%). (c) *In situ* generated [(**3c**)Rh($CDCl_3$)$_2$]BF_4, 121.7 (d, $J_{Rh,P}$ = 353 Hz, ca. 20%); with addition of **1b**, 126.1 (dd, $J_{Rh,P}$ = 249 Hz, $J_{P,P}$ = 96 Hz, 30%), 124.7 (dd, $J_{Rh,P}$ = 248 Hz, $J_{P,P}$ = 96 Hz, 30%); 121.5 (d, $J_{Rh,P}$ = 354 Hz, 5%), 119.4 (d, $J_{Rh,P}$ = 255 Hz, 25%). (d) *In situ* generated [(**3d**)Rh($CDCl_3$)$_2$]BF_4, 122.8 (s, ca. 10%); no significant change with addition of **1b**.

2.4. Hydrogenations

2.4.1. Typical procedure for [Rh(COD)$_2$BF$_4$]/**3**-catalyzed asymmetric hydrogenation using (S,S)-**3b** is given

Accurately weighed amounts of Rh(COD)$_2$BF$_4$ (1.2 mg, 3 μmol) and (*S*,*S*)-**3b** (6.1 mg, 4.5 μmol) were placed in a pre-oven-dried glass autoclave containing a magnetic stirring bar. The mixture was placed under high vacuum for at least 20 min before purging with Ar. Degassed CH_2Cl_2 (1 mL) was added, the solution stirred for 2–5 min, and then a solution of prochiral olefin (**1a**, 128.8 mg, 0.9 mmol; **1b**, 65.8 mg, 0.3 mmol) in 2 mL of degassed CH_2Cl_2 was added under an Ar atmosphere. H_2 was introduced under 3 atm pressure with several quick release–fill cycles before being set to 5 atm pressure. The solution was vigorously stirred at 30 °C. Following the designated reaction time, H_2 was released and the volatiles removed under vacuum. The residue was dissolved in ether and passed through a short pad of silica gel. Following removal of the solvent under vacuum, the conversion was determined by ^{1}H NMR analysis and the enantiomeric excess (ee%) value obtained by chiral GC or HPLC. (*R*)-*N*-Acetylalanine methyl ester (**2a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.15 (brs, 1 H), 4.66–4.56 (m, 1 H), 3.76 (s, 3 H), 2.03 (s, 3 H), 1.41 (d, ^3J = 7.2 Hz, 3 H); GC (Chirasil-DEX CB column) *P* = 12.0 psi, *T* = 180 °C, t_R of (*S*)-**2a** = 17.29 min, t_R of (*R*)-**2a** = 17.53 min; $[\alpha]_D^{25} = -9.6°$ (c 1, $CHCl_3$) [Lit. [26] $[\alpha]_D^{25} = -9.2°$ (c 1, $CHCl_3$) for (*R*)-enantiomer]. (*R*)-*N*-acetyl-3-phenylalanine methyl ester (**2b**): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32–7.22 (m, 3 H), 7.10–7.08 (m, 2 H), 6.03 (d, ^3J = 6.0 Hz, 1 H), 4.92–4.86 (m, 1 H), 3.73 (s, 3 H), 3.19–3.05 (m, 2 H), 1.99 (s, 3 H); HPLC (Chiralcel AD-H 250 column) hexane:isopropanol = 90:10, flow rate = 0.7 mL/min, UV detection at 214 nm, t_R of (*R*)-**2b** = 10.48 min, t_R of (*S*)-**2b** = 15.21 min; $[\alpha]_D^{25} = -13.4°$ (c 1, MeOH) [Lit. [26] $[\alpha]_D^{25} = -15.8°$ (c 1, MeOH) for (*R*)-enantiomer].

2.4.2. Hydrogenation profiles

Hydrogenations were conducted in a glass autoclave equipped with a sampling needle connected to a three-way stop valve as previously described [27]. This experimental set-up allowed for samples to be taken from the reaction mixture under an H_2 atmosphere. Accurately weighed amounts of Rh(COD)$_2$BF$_4$ (typically 2.4 mg, 6 μmol) and (*S*,*S*)-**3** (11.7–14.3 mg, 9 μmol) were placed in the autoclave containing a magnetic stirring bar. The mixture was placed under high vacuum for at least 20 min before purging with Ar. Degassed CH_2Cl_2 (2 mL) was added, the solution stirred for 20 min, and then a solution of **1a** (typically 257.6 mg, 1.8 mmol) or **1b** (typically 131.5 mg, 0.6 mmol) in 4 mL of degassed CH_2Cl_2 was added under an Ar atmosphere such that the desired Rh: **3**:**1** ratio was obtained. If needed, the autoclave was placed in a pre-warmed oil-bath set at the desired reaction temperature. H_2 was introduced under 7 atm pressure with several quick release–fill cycles before being set to 5 atm pressure. Stirring and

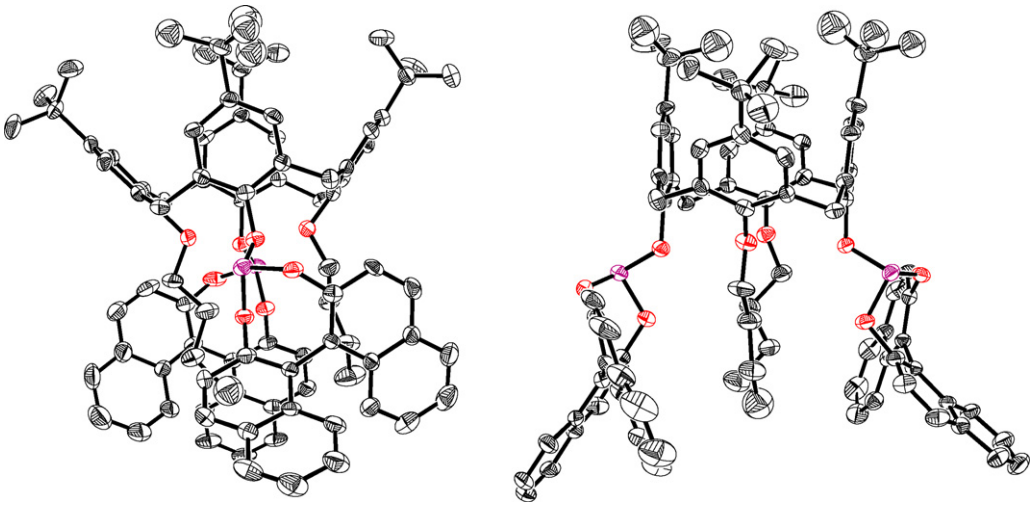


Fig. 1. Crystal structure of calix[4]arene-based chiral diphosphite ligand **3c**. Hydrogen atoms are omitted for clarity (C, black; O, red; P, purple). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

timing (t = 0 min) were immediately commenced. Reaction samples were obtained (2 drops into an ether-filled GC sample tube) at specified time-intervals (t), and the extent of substrate consumption and ee of (*R*)-**2** determined by GC or HPLC. Conditions: [$Rh(COD)_2BF_4$] = 1.0 mM; [(*S*,*S*)-**3**] = 1.5 mM; [**1a**] = 0.3 M (S/C = 300) or [**1b**] = 0.1 M (S/C = 100); $P(H_2)$ = 5 atm; T = 30 °C; V_T = 6 mL, solvent = CH_2Cl_2.

3. Results and discussion

3.1. Synthesis and structure of calix[4]arene-based bisphosphite ligands (*3*)

The known BINOL-derived calix[4]arene-diphosphite ligands **3b** and **3d**, and previously unreported **3a**, **3c** and **3e**–**g** were prepared following known calixarene alkylation and phosphorylation methods, Scheme 1 [18–25]. Addition of (*S*)- or (*R*)-(1,1′-binaphthalene-2,2′-diyl)chlorophosphite to appropriately distally *O*-dialkylated calixarene precursors in the presence of a base (NaH or *n*-BuLi) led to the desired diphosphites **3** in typically 30–60% yields. More sterically hindered calixarenes were obtained predominantly as the cone-conformer while conformationally flexible macrocycles resulted in a mixture of (undetermined) isomers. For the former, ^{1}H NMR spectra exhibited two distinct AB patterns for the bridging diastereotopic methylene protons, consistent with C_2-symmetry, and a single (broadened) resonance in ^{31}P NMR spectra (δ 123.9–145.4 ppm). Diffusion of petroleum ether into a toluene solution of **3c** yielded appropriate crystals for solid-state structural elucidation [28]. As shown in Fig. 1, the calixarene framework adopts a flattened cone structure whereby the less sterically hindered *O*-butyl groups are pushed inwards towards the calixarene axis in accordance with previously reported crystal structures for closely related calix[4]arene diphosphites [9i,j].

3.2. In situ generation of catalytically relevant complexes

Formation of Rh/**3** complexes was monitored *in situ* by mixing $CDCl_3$ solutions of **3** (10 mM) with $Rh(COD)_2BF_4$ (1 equiv.). For **3a**–**d**, ^{31}P NMR spectra of resulting mixtures showed a predominant doublet centered at δ 119.5–120.6 ppm ($J_{Rh,P}$ = 255–257 Hz) even after only 5 min. Similarly, two AB systems were observed for the bridging diastereotopic methylene protons. Accordingly, the calixarene-diphosphite ligands adopt a cone-configuration which chelates the Rh-metal resulting in a (time averaged) *pseudo*-C_2 complex [29]. Resonances consistent with formation of other complexes were only present in minor amounts (ca. 5%). Even highly flexible **3a** gave a single isomer in 95% yield (δ 120.6, d, $J_{Rh,P}$ = 256 Hz). Importantly, MS spectra of resulting solids following removal of volatiles were consistent with [(**3a**–**d**)Rh(COD)]BF_4 formation ([(**3a**–**d**)Rh]$^+$, 1407.5–1559.5 m/e). For **3e** and **3f**, no complex formation was detected under the same conditions.

Fig. 2 shows the ^{31}P NMR spectrum for *in situ* formed [(**3c**)Rh(COD)]$^+$ following partial hydrogenation of COD (1 atm, 15 min) and addition of **1b** (1 equiv.) [30]. The resonances centered at 121.7 (d, $J_{Rh,P}$ = 353 Hz) and 126.1 (dd, $J_{Rh,P}$ = 249 Hz, $J_{P,P}$ = 96 Hz), 124.7 (dd, $J_{Rh,P}$ = 248 Hz, $J_{P,P}$ = 96 Hz) are tentatively assigned as [(**3c**)Rh($CDCl_3$)$_2$]$^+$ and [(**3c**)Rh(**1b**)]$^+$, respectively [30]. Similarly, the same procedure for [(**3b**)Rh(COD)]$^+$ yielded [(**3c**)Rh(**1b**)]$^+$ with resonances at 126.4 (dd, $J_{Rh,P}$ = 245 Hz, $J_{P,P}$ = 91 Hz) and 124.9 (dd, $J_{Rh,P}$ = 246 Hz, $J_{P,P}$ = 91 Hz). For [(**3a**)Rh(COD)]$^+$ no hydrogenation of COD was apparent after addition of H_2 (15 or 60 min, 1 atm), while addition of **1b** (1 or 5 equiv.) to *in situ* generated [(**3d**)Rh($CDCl_3$)$_2$]$^+$ did not generate the corresponding [(**3d**)Rh(**1b**)]$^+$ complex. Thus, the observed solution behavior of Rh/**3** complexes varied significantly depending on the R^1- and R^2-substituents in **3**.

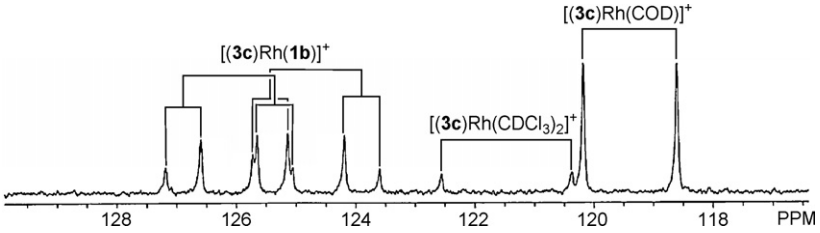
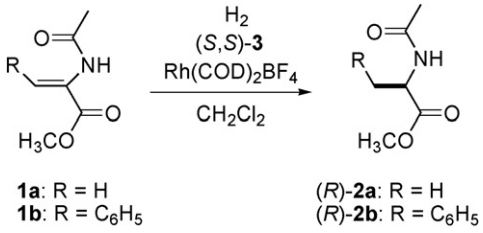


Fig. 2. ^{31}P NMR spectrum following partial hydrogenation of COD in [(**3c**)Rh(COD)]$^+$ (1 atm, 15 min) and addition of **1b** (1 equiv.).



Scheme 2. Asymmetric hydrogenation of methyl-(*Z*)-2-(acetamido)acrylate (**1a**) and methyl-(*Z*)-2-(acetamido)cinnamate (**1b**) catalyzed by *in situ* generated catalysts comprised of $[Rh(COD)_2BF_4]$ and calix[4]arene-based chiral diphosphite ligands [(*S*,*S*)-**3**].

3.3. Catalytic performance

The synthesized calix[4]arene-1,3-diphosphites (**3**) were trialed as chiral ligands in the Rh-catalyzed asymmetric hydrogenation of **1a** and **1b** (conditions: $[Rh(COD)_2BF_4]$ = 1.0 mM; [(*S*,*S*)-**3**] = 1.5 mM; [**1a**] = 0.3 M or [**1b**] = 0.1 M; $P(H_2)$ = 5 atm; T = 30 °C; V_T = 3 mL, solvent = CH_2Cl_2) [31]. The active catalyst was generated *in situ* from $Rh(COD)_2BF_4$ and corresponding (*S*,*S*)-**3** as obtained without further separation of conformational isomers (where applicable), Scheme 2. Both the catalyst activity and extent of chiral induction were influenced by the substituents on the calixarene backbone (R^1 and R^2). Furthermore, the catalytic performance showed some substrate dependence with overall better results obtained for the less sterically hindered **1a**. The (*S*,*S*)-catalyst generated the (*R*)-product as expected from corresponding BINOL-based monophosphite [5] and related bidentate phosphite [6,11,32] Rh-catalyzed hydrogenation systems.

Better activity and selectivity was obtained using non-conformationally flexible calixarenes which ensures a "locked" cone conformation, Table 1. Thus, hydrogenation of **1a** catalyzed by Rh/**3a–d** yielded (*R*)-**2a** quantitatively in up to 98% (5–16 h) enantiomeric excess (ee), while flexible **3f** showed mediocre catalytic activity [33]. Even in the presence of 3 equiv of **3f**, only 46% (16 h) and 12% (23 h) conversions were obtained for hydrogenation of **1a** and **1b**, respectively. The reduced activity may reflect the poor chelating ability for **3f** (see Section 3.2).

Table 1
Asymmetric hydrogenation of methyl-(*Z*)-2-(acetamido)acrylate (**1a**) and methyl-(*Z*)-2-(acetamido)cinnamate (**1b**) catalyzed by *in situ* generated catalysts comprised of $[Rh(COD)_2BF_4]$ and chiral calix[4]arene-based bidentate phosphite ligands (**3**)[a].

Entry	Ligand	Substrate	Time (h)	Conv.[b] (%)	ee[c] (%) (config)[d]
1	(*S*,*S*)-**3a**[e]	**1a**	16	100	85 (*R*)
2[f]	(*S*,*S*)-**3a**[e]	**1b**	14	100	72 (*R*)
3	(*S*,*S*)-**3b**[e]	**1a**	11	100	98 (*R*)
4	(*S*,*S*)-**3b**[e]	**1b**	10	100	96 (*R*)
5	(*S*,*S*)-**3c**	**1a**	10	100	93 (*R*)
6	(*S*,*S*)-**3c**	**1b**	21	68	64 (*R*)
7	(*S*,*S*)-**3d**	**1a**	16	100	95 (*R*)
8	(*S*,*S*)-**3d**	**1b**	15	100	76 (*R*)
9[f]	(*S*,*S*)-**3e**[e]	**1a**	48	100	16 (*R*)
10[f]	(*S*,*S*)-**3e**[e]	**1b**	48	100	23 (*S*)
11[f]	(*S*,*S*)-**3f**[e]	**1a**	16	46	91 (*R*)
12[f]	(*S*,*S*)-**3f**[e]	**1b**	23	12	31 (*R*)
13	(*S*,*S*)-**3g**	**1a**	15	100	74 (*R*)
14	(*S*,*S*)-**3g**	**1b**	17	100	61 (*R*)

[a] Conditions: $[Rh(COD)_2BF_4]$ = 1.0 mM; [**3**] = 1.5 mM; [**1a**] = 0.3 M (S/C = 300) or [**1b**] = 0.1 M (S/C = 100); $P(H_2)$ = 5 atm; T = 30 °C; V_T = 3 mL, CH_2Cl_2 solvent.
[b] Isolated yield, conversion determined by ^1H NMR.
[c] Enantiomeric excess (ee) determined by chiral GC or HPLC.
[d] Absolute configuration (config) determined from $[\alpha]_D$ measurement.
[e] Mixture of conformational isomers.
[f] 3 equiv. of (*S*,*S*)-**3** used.

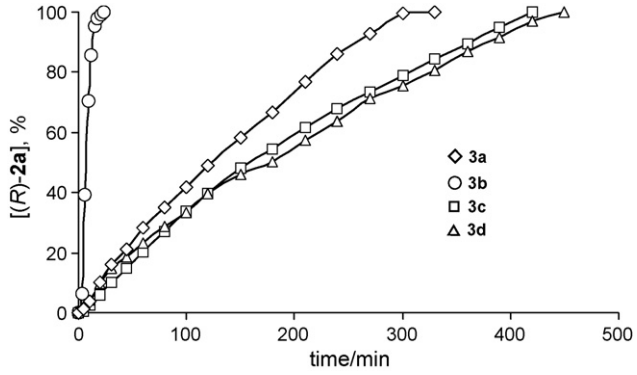


Fig. 3. Reaction profiles for the asymmetric hydrogenation of methyl-(*Z*)-2-(acetamido)acrylate (**1a**) catalyzed by *in situ* generated catalysts comprised of $[Rh(COD)_2BF_4]$ and calix[4]arene-based chiral diphosphite ligands [(*S*,*S*)-**3a–d**]. Conditions: $[Rh(COD)_2BF_4]$ = 1.0 mM; [(*S*,*S*)-**3a–d**] = 1.5 mM; [**1a**] = 0.3 M; $P(H_2)$ = 5 atm; T = 30 °C; CH_2Cl_2 solvent.

The *O*-alkyl substituent R^2 similarly exerts an influence on catalytic performance. Accordingly, hydrogenation of **1a** proceeded with quantitative yields (5–16 h) in 85, 98, 93, and 95% ee for **3a–d**, respectively. The effects were more obvious for more sterically demanding **1b**. While the *O*-$CH_2CH_2CH_3$ (**3b**) substituted diphosphite calixarene yielded (*R*)-**2b** in 96% ee, *O*-$(CH_2)_3CH_3$ (**3c**) and *O*-$CH_2C_6H_5$ (**3d**) gave (*R*)-**2b** in considerably lower ee, 64 and 76%, respectively. The steric effects are not straightforward, however, with the less sterically hindered *O*-CH_3 (**3a**) similarly yielding (*R*)-**2b** in low ee (72%). Catalyst activity was also influenced by the R^2 substituent. Hydrogenation of **1b** by Rh/**3c** only gave 68% conversion after 21 h (entry 6, Table 1). Fig. 3 contrasts reaction profiles for hydrogenation of **1a** catalyzed by Rh/**3a–d** systems (conditions: $[Rh(COD)_2BF_4]$ = 1.0 mM; [(*S*,*S*)-**3a–d**] = 1.5 mM; [**1a**] = 0.3 M; $P(H_2)$ = 5 atm; T = 30 °C; V_T = 6 mL, solvent = CH_2Cl_2). The hydrogenation rates for **3a**, **3c** and **3d** are considerably lower than for **3b** under these conditions, while the latter exhibited a turn-over-frequency (TOF) [34] of ca. 1300 h^{-1} (5 atm). Thus, optimum catalytic performance is obtained when the R^2 group is $-CH_2CH_2CH_3$. Such variation on reactivity and selectivity have been previously observed for related hydroformylation systems [9j,32].

Although the principle function of the upper rim *para*-substituent R^1 is to minimize conformational freedom, an influence on enantioselectivity was also observed. Thus, Rh/**3g** catalyzed hydrogenation yielded (*R*)-**2a** and -**2b** in lower 74% (cf. 95% for **3d**) and 61% (cf. 76% for **3d**) ee, respectively. Here, the added flexibility of the P-ligand resulting from *para*-benzyl substitution may account for the difference. However, electronic effects cannot be ruled out. Hydrogenation of **1b** with related bulky monophosphite ligands have been shown to yield product with lower ee values [5c].

Modification of the BINOL-backbone resulted in considerably lower activity and loss of chiral induction. Thus, AH of **1a** with the Rh/**3e** system gave (*R*)-**2a** in only 16% ee, while hydrogenation of **1b** resulted in a reversal of the product chirality yielding (*S*)-**2b** in only 23% ee. Moreover, the system required 3 equiv. of **3e** and long reaction times for high conversions reflecting the lower Rh-chelating ability of this ligand (see Section 3.2).

Typical reaction profiles for the optimum *O*-propyl calixarene Rh/**3b** system are shown in Fig. 4 (conditions: $[Rh(COD)_2BF_4]$ = 1.0 mM; [(*S*,*S*)-**3b**] = 1.5 mM; [**1a**] = 0.3 M or [**1b**] = 0.1 M; $P(H_2)$ = 5 atm; T = 30 °C; V_T = 6 mL, solvent = CH_2Cl_2). The hydrogenation proceeded smoothly following a short incubation period without formation of any side products yielding (*R*)-**2a** in 98% ee with a maximum TOF of 1300 h^{-1}, and (*R*)-**2b** in 96% ee with a TOF of 250 h^{-1}. Product (*R*)-**2** was generated in near constant enantioselectivity throughout the hydrogenation for both systems.

Table 2
Asymmetric hydrogenation of methyl-(*Z*)-2-(acetamido)acrylate (**1a**) and methyl-(*Z*)-2-(acetamido)cinnamate (**1b**) with *in situ* generated catalysts comprised of [$Rh(COD)_2BF_4$] and chiral calix[4]arene-based bidentate phosphite ligands (**3d** or **3b**)[a].

Entry	Ligand	Substrate	S/C	Pressure (atm)	Temperature (°C)	Time (h)	Conv.[b] (%)	ee[c] (%) (config)[d]
1	(*S*,*S*)-**3d**	**1a**	300	5	20	2	25	97 (*R*)
2	(*S*,*S*)-**3d**	**1a**	300	5	30	2	40	96 (*R*)
3	(*S*,*S*)-**3d**	**1a**	300	5	50	2	76	96 (*R*)
4	(*S*,*S*)-**3d**	**1a**	1000	5	30	12	41	95 (*R*)
5	(*S*,*S*)-**3d**	**1a**	1000	5	50	12	100	94 (*R*)
6	(*S*,*S*)-**3d**	**1a**	300	2	30	13	100	97 (*R*)
7	(*S*,*S*)-**3d**	**1a**	300	8	30	5	100	95 (*R*)
8	(*S*,*S*)-**3d**	**1a**	300	16	30	4	100	93 (*R*)
9	(*S*,*S*)-**3b**	**1b**	100	5	20	2	100	94 (*R*)
10	(*S*,*S*)-**3b**	**1b**	100	5	30	2	100	96 (*R*)
11	(*S*,*S*)-**3b**	**1b**	100	5	50	2	100	97 (*R*)
12	(*S*,*S*)-**3b**	**1b**	1000	5	50	18	86	92 (*R*)
13	(*S*,*S*)-**3b**	**1b**	100	2	30	11	100	98 (*R*)
14	(*S*,*S*)-**3b**	**1b**	100	8	30	1.5	100	93 (*R*)
15	(*S*,*S*)-**3b**	**1b**	100	16	30	1	100	92 (*R*)

[a] Conditions: [$Rh(COD)_2BF_4$] = 1.0 mM; [**3d**] = 1.5 mM; [**3b**] = 1.5 mM (mixture of conformational isomers); [**1a**] = 0.3 or 1.0 M; [**1b**] = 0.1 or 1.0 M; V_T = 3 mL, CH_2Cl_2 solvent.
[b] Isolated yield, conversion determined by ^{1}HNMR.
[c] Enantiomeric excess (ee) determined by chiral GC or HPLC.
[d] Absolute configuration (config) determined from $[\alpha]_D$ measurement.

Such results are comparable with other phosphite-based ligands [5,6,12a,32], but cannot compete with the best bisphosphine ligands available in terms of overall efficiency [1,26,35].

The catalysis proceeded best using CH_2Cl_2 (or CH_2ClCH_2Cl) as solvent. Thus, although hydrogenation was quantitative in CH_2Cl_2 (98% ee), only 8–30% conversion (69–85% ee) was obtained in protic solvents (MeOH, *i*-PrOH, *t*-BuOH), while 13–48% (57–88% ee) was managed in other non-protic solvents (THF, Et_2O, EtOAc, toluene) (conditions: [$Rh(COD)_2BF_4$] = 1.0 mM; [(*S*,*S*)-**3b**] = 1.5 mM; [**1b**] = 0.1 M; $P(H_2)$ = 5 atm; T = 30 °C; V (solvent) = 3 mL). Table 2 summarizes the influence of reaction parameters on the overall catalysis during hydrogenation of **1a** and **1b** with *in situ* formed Rh/**3d** and Rh/**3b**, respectively. Significantly, the enantioselectivity showed a small dependence on hydrogen pressure with better ee values obtained at lower pressures. Thus, (*R*)-**2a** was obtained in 97% ee at 2 atm and 93% ee at 16 atm under otherwise identical conditions ([$Rh(COD)_2BF_4$] = 1.0 mM; [(*S*,*S*)-**3b** or **3d**] = 1.5 mM; [**1a**] = 0.3 M or [**1b**] = 0.1 M; T = 30 °C; V_T = 3 mL, solvent = CH_2Cl_2), while the ee% dropped from 98 to 92% over the same range for (*R*)-**2b**. A relatively small drop in enantioselectivity was observed for hydrogenation of **1a** with increasing temperature, 97% (20 °C) and 96% (50 °C), while the ee% increased for **1b** from 94 to 97% in going from 20 to 50 °C. Such findings are consistent with Halpern kinetics involving concurrent and competitive reaction pathways for the two possible diastereomeric intermediates [30a,36]. The enhanced catalyst activity at higher temperature (50 °C) allowed for 100 and 86% conversions for **1a** (12 h) and **1b** (18 h), respectively, at a substrate-to-catalyst (S/C) molar ratio of 1000 (0.1 mol% catalyst loading).

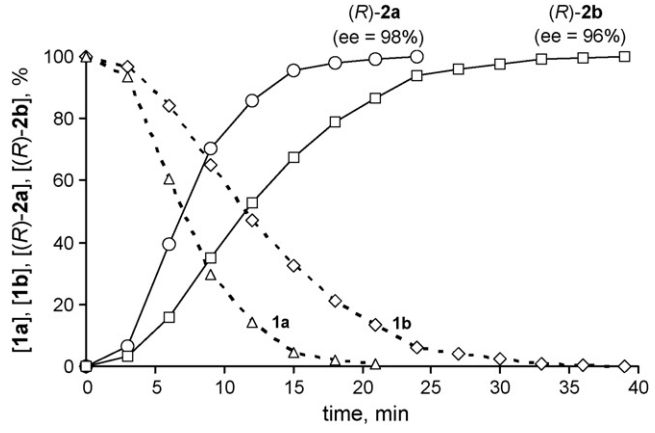


Fig. 4. Reaction profiles for the asymmetric hydrogenation of methyl-(*Z*)-2-(acetamido)acrylate (**1a**) and methyl-(*Z*)-2-(acetamido)cinnamate (**1b**) catalyzed by *in situ* generated catalyst comprised of [$Rh(COD)_2BF_4$] and (*S*,*S*)-**3b**. Conditions: [$Rh(COD)_2BF_4$] = 1.0 mM; [(*S*,*S*)-**3b**] = 1.5 mM; [**1a**] = 0.3 M (S/C = 300); [**1b**] = 0.1 M (S/C = 100); $P(H_2)$ = 5 atm; T = 30 °C; CH_2Cl_2 solvent.

4. Conclusions

The readily modified calix[4]arene framework allowed for facile generation of a number of chiral diphosphite functionalized ligands capable of forming *in situ* Rh-complexes which catalyzed the asymmetric hydrogenation of methyl acetamidoacrylate (**1a**) and the corresponding cinnamate (**1b**). The upper rim (R^1) and 1,3-*O*-alkylation (R^2) substituents strongly influenced the catalyst activity and chiral induction with optimum results obtained when R^1 was $-C(CH_3)_3$ and R^2 was $-CH_2CH_2CH_3$ (**3b**). Under optimized conditions, the **3b**/Rh system yielded (*R*)-**2a** in up to 98% ee with a TOF of 1300 h^{-1} (5 atm), and (*R*)-**2b** in 96% ee with a TOF of 250 h^{-1} (5 atm).

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