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Asymmetric enamide hydrogenation using planar-chiral cyrhetrenes

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Abstract—The catalytic asymmetric hydrogenation of α-arylenamides using catalysts prepared in situ from $[Rh(cod)_2]BF_4$ and cyrhetrenyldiphosphines was effective with a range of enamides. The corresponding acetamides were obtained with up to 93% ee.

Asymmetric hydrogenations catalyzed by transition metals continue to find widespread applications not only in academia but also in industry.[1,2] Considerable efforts have been devoted to the development of new, effective ligands, since enantioselective hydrogenation reactions are highly atom economic and give products which are important building blocks for the synthesis of biologically active compounds.

As part of our continuing studies of cyrhetrene-containing ligands for asymmetric catalysis,[3] we recently reported the synthesis of novel planar-chiral phosphines **1** (AaPhos-type), **2** and **3** bearing cyrhetrene backbones (Fig. 1).[4] Their palladium(II) and rhodium(I) complexes are highly effective catalysts for asymmetric allylic alkylation, the hydrogenation of various olefins and the Hayashi-Miyaura reaction. Herein, we describe the application of cyrhetrenes **1** in the rhodium-catalyzed asymmetric hydrogenation of α-arylenamides.[5]

Cyrhetrenes **1** were synthesized in a five-step procedure from acetylcyrhetrene (**4**) as reported earlier (Scheme 1).[4,6]

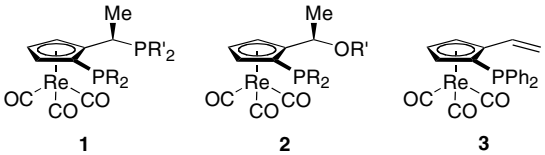

Figure 1. Planar-chiral cyrhetrenyl phosphines.

An initial screening with *N*-(1-phenylvinyl)acetamide (**6a**) as substrate revealed that the optimal conditions involved a catalyst formed in situ from 1 mol % of $[Rh(cod)_2]BF_4$ and 1.1 mol % of diphosphine **1**, ethyl acetate as solvent and a hydrogen pressure of 10 bar (Scheme 2). Use of bis(diphenylphosphino)-substituted cyrethrene **1b** led to the most enantioselective catalyst affording **7a** with 93% ee at room temperature (Table 1, entry 1).[5,7]

In order to examine the substrate scope, conversions of several substituted α-arylenamides[8] were investigated using $[Rh(cod)_2]BF_4$ and cyrhetrene **1b** as catalyst system in ethyl acetate at room temperature.[9] Enamides **6b–e** bearing either electron withdrawing substituents or electron donating ones on the aromatic ring were reduced to the corresponding acetamides **7b–e** having 85–91% ee within 24 h (Table 1, entries 2–5). Generally, a hydrogen pressure of 10 bar was applied and only in the case of (4-methoxyphenyl)enamide (**6d**) a pressure of 20 bar was necessary to achieve full conversion. *ortho*-Substitution on the aromatic ring slowed down the reaction significantly,[10] presumably due to steric congestion. Application of (2-bromophenyl)enamide (**6f**) in the hydrogenation reaction at a hydrogen pressure of 50 bar led to only 20% conversion, furnishing product **7f** with low ee (entry 6). Additional substitution on the olefin moiety was tolerated, although an increased hydrogen pressure was necessary in these cases as well. Both enamides **6g** and **6h** were applied as a mixture of *E*/*Z*-isomers in a 2:1 ratio. (4-Methylphenyl)enamide (**6g**) was hydrogenated to the corresponding acetamide **7g** with high enantioselectivity (91% ee; entry 7). In contrast, acetamide **7h** was isolated with only 68% ee (entry 8). It is known that some catalyst systems hydrogenate isomeric mixtures of *E*/*Z*-enamides with

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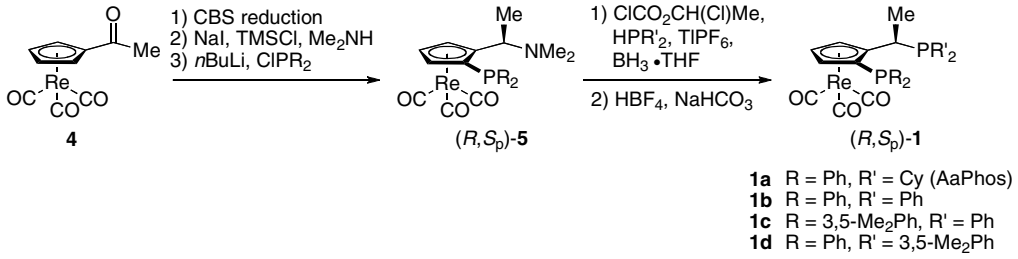
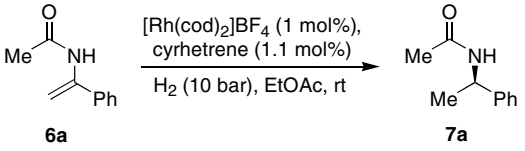


Scheme 1. Synthesis of diphosphines **1**.

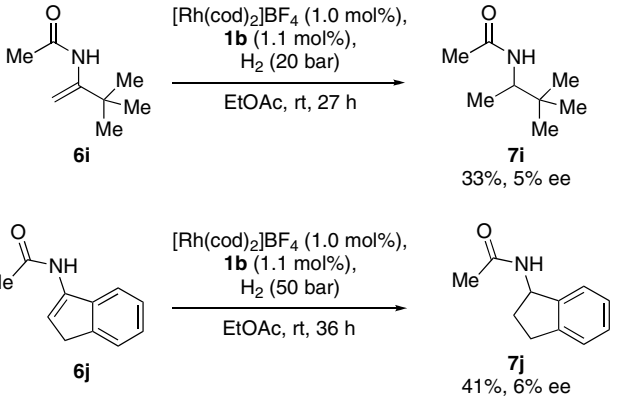


Scheme 2. Asymmetric hydrogenation of α-arylenamide **6a**.

high enantioselectivity, while others are sensitive to the configuration of the double bond.[11,12] The current system appears to be substrate dependent in this respect.

Additionally, the aliphatic enamide **6i** and the cyclic enamide **6j** were subjected to the hydrogenation (Scheme 3). Unfortunately, in both cases the enantioselectivity was low and the conversion was incomplete, even at 20 and 50 bar of hydrogen pressure, respectively. While in the former case steric bulk probably inhibited proper coordination of the substrate and therefore led to lower turnover, in the latter case the *E*-configured double bond of enamide **6i** might be the cause of the observed lack of enantioselectivity.[14]

In conclusion, AaPhos derivatives **1a**–**d** have been successfully applied in the rhodium-catalyzed asymmetric hydrogenation of various α-arylenamides **6**, which provided the corresponding acetamides **7** with up to 93% ee. Furthermore, β-substituted α-arylenamides



Scheme 3. Additional enamides examined in the asymmetric hydrogenation reaction.

could be applied, which expands the utility of the methodology. However, in some cases a *Z*-configured double bond seems to be necessary for high enantioselectivity.

Acknowledgements

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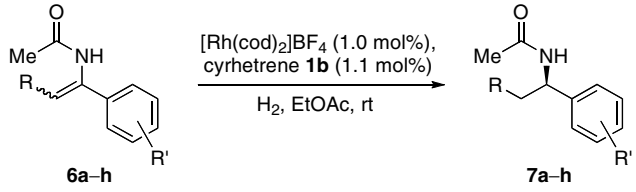
Table 1. Substrate scope of the asymmetric hydrogenation of α-arylenamides **6**



Entry	R	R′	Time (h)	$p(H_2)$ (bar)	Product	Conversion (%)	ee[a,b] (%)
1	H	H	16	10	**7a**	100	93 (*R*)
2	H	4-Cl	22	10	**7b**	100	91 (*R*)
3	H	4-CF_3	24	10	**7c**	100	89 (*R*)
4	H	4-MeO	20	20	**7d**	100	85 (*R*)
5	H	4-Me	22	10	**7e**	100	88 (*R*)
6	H	2-Br	72	50	**7f**	20	3
7[c]	Me	4-Me	20	20	**7g**	100	91 (*R*)
8[c]	Me	H	22	20	**7h**	100	68 (*R*)

[a] The enantiomeric ratios were determined by HPLC using a chiral stationary phase. See Ref. 13 for details.
[b] Absolute configurations of the products were either assigned by comparison of their optical rotation with literature data or are based on the assumption of an identical reaction pathway.
[c] An isomeric mixture of the enamide (*E*/*Z* 2:1) was employed.

by K. Deckers is appreciated, and R.T.S. thanks DFG (GRK 440) for a predoctoral stipend.

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2. For overviews of phosphorous ligands for asymmetric hydrogenation, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3070; (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151.
3. Cyrhetrene is an abbreviation for η^5-cyclopentadienylrhenium(I) tricarbonyl complexes.
4. (a) Bolm, C.; Xiao, L.; Hintermann, L.; Focken, T.; Raabe, G. *Organometallics* **2004**, *23*, 2362–2369; (b) Stemmler, R. T.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 9925–9931; (c) Stemmler, R. T.; Bolm, C. *Synlett* **2007**, 1365–1370.
5. Preliminary results of the hydrogenation of enamide **6a** have been reported earlier, see Ref. 4b.
6. Analytical data for new cyrhetrene **1d**: mp: 139–142 °C (dec); $[\alpha]_D^{23}$ −143 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 1.37 (dd, $J = 6.7$, 6.2 Hz, 3H, CH_3), 1.92 (s, 6H, $2 \times ArCH_3$), 2.07 (s, 6H, $2 \times ArCH_3$), 4.29–4.43 (m, 2H, Cp-CH, CH), 4.64–4.73 (m, 1H, Cp-CH), 5.01 (dd, $J = 2.7$, 1.6 Hz, 1H, Cp-CH), 6.56 (s, 1H, Ar-CH), 6.79 (s, 1H, Ar-CH), 6.97–7.23 (m, 10H, Ar-CH), 7.41 (dt, $J = 8.0$, 1.3 Hz, 2H, Ar-CH), 7.57 (dt, $J = 8.1$, 1.7 Hz, 2H, Ar-CH); ^{13}C NMR (75 MHz, C_6D_6) δ 19.1 (CH_3), 21.2 (6C, $4 \times ArCH_3$), 29.7 (dd, $J = 21.0$, 10.3 Hz, CH), 79.6 (Cp-CH), 86.8 (d, $J = 3.9$ Hz, Cp-CH), 93.6 (d, $J = 5.0$ Hz, Cp-CH), 96.9 (dd, $J = 17.5$, 15.4 Hz, Cp-C), 122.0 (d, $J = 22.5$ Hz, Cp-C), 127.9 (Ar-CH), 128.7 (d, $J = 10.8$ Hz, 2C, Ar-CH), 128.9 (d, $J = 7.9$ Hz, 2C, Ar-CH), 129.8 (2C, Ar-CH), 130.0 (2C, Ar-CH), 130.2 (Ar-CH), 131.6 (Ar-CH), 133.2 (Ar-CH), 133.5 (Ar-CH), 133.7 (d, $J = 21.6$ Hz, 2C, Ar-CH), 134.9 ($J = 21.7$ Hz, 2C, Ar-CH), 136.9 (d, $J = 18.5$ Hz, 2C, Ar-C), 137.6 (d, $J = 7.8$ Hz, 2C, Ar-C), 138.0 (d, $J = 5.2$ Hz, 2C, Ar-C), 138.5 (d, $J = 7.3$ Hz, 2C, Ar-C); ^{31}P NMR (121 MHz, C_6D_6) δ −29.61 (d, $J = 25.4$ Hz), +11.68 (d, $J = 25.4$ Hz); IR (KBr, cm^{-1}) ν 2019, 1921, 1435, 1038, 845, 744, 695, 610, 505; MS (EI) *m*/*z* (%) 788 (M^+, 18), 786 [$(M-2)^+$, 10], 760 [$(M-CO)^+$, 100], 758 [$(M-2-CO)^+$, 64], 732 [$(M-2CO)^+$, 25], 730 [$(M-2-2CO)^+$, 15], 575 [$(M-CO-PPh_2)^+$, 60], 573 [$(M-2-CO-PPh_2)^+$, 38], 547 [$(M-PXyl_2)^+$, 16], 546 (16), 518 (14), 461 (17), 459 (11). Anal. Calcd for $C_{38}H_{35}O_3P_2Re$: C, 57.93; H, 4.48. Found: C, 57.65; H, 4.81.
7. The following enantioselectivities have been achieved: **1a** (in DCM): 87% ee; **1b** (in EtOAc): 93% ee; **1c** (in EtOAc): 77% ee; **1d** (in EtOAc): 78% ee.
8. All enamides were prepared according to reported procedures by Burk: (a) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142–5143; (b) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084–6085.
9. *Typical procedure for the hydrogenation of enamides* **6**: $[Rh(cod)_2]BF_4$ (2.0 mg, 5.0 μmol, 1.0 mol %) and cyrhetrene **1b** (4.0 mg, 5.5 μmol, 1.1 mol %) were placed in a vial under argon, dissolved in ethyl acetate (0.4 mL) and stirred at room temperature for 20 min. A solution of enamide **6a** (81 mg, 0.50 mmol) in ethyl acetate (0.4 mL) was added, and the vial was placed into an argon-filled 100 mL autoclave. The autoclave was sealed, purged with hydrogen (3×10 bar) and finally pressurized to 10 bar. The reaction mixture was stirred for 16 h, after which full conversion of the starting material was achieved as indicated by TLC analysis (pentane/ethyl acetate 1:3). The solution was filtered through a short plug of silica gel (elution with ethyl acetate) and concentrated. *N*-(1-Phenylethyl)acetamide (**7a**) was isolated as pale yellow solid (81 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, $J = 6.9$ Hz, 3H), 1.99 (s, 3H), 5.13 (dq, $J = 7.4$, 6.9 Hz, 1H), 5.64 (br s, 1H, NH), 7.25–7.37 (m, 5H). The enantiomeric ratio was determined by chiral GC using a FS Cyclodex β-I/P capillary column (25 m × 0.2 mm), with H_2 as the carrier gas; 49.4 min (minor), 50.7 min (major).
10. *ortho*-Substituted α-arylenamides are generally challenging substrates in the hydrogenation reaction, and they often lead to low enantiomeric excesses of the corresponding acetamides. The influence of *ortho*-substitutents has been studied, and alternative modes of coordination of the enamide, which are competitive in the case of *ortho*-substituted α-arylenamides, were suggested by Imamoto: Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268–5276.
11. For examples of insensitive catalyst systems see: (a) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142–5143; (b) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590–9593; (c) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871–5874; (d) Zeng, Q.-H.; Hu, X.-P.; Duan, Z.-C.; Liang, X.-M.; Zheng, Z. *J. Org. Chem.* **2006**, *71*, 393–396.
12. For an example of a catalyst system sensitive to the configuration of the enamide-double bond see: Imamoto, T.; Oohara, N.; Takahashi, H. *Synthesis* **2004**, 1353–1358.
13. The enantiomeric ratios were determined by HPLC or GC using a chiral stationary phase [HPLC: Daicel Chiralcel columns, GC: FS-Cyclodex β I/P (25 m × 0.2 mm)]. The separation conditions for compounds **7b**–**j** are as follows: Acetamide **7b**: AS, heptane/2-PrOH 90:10, 1.0 mL/min, 220 nm, 22.6 min (minor), 25.9 min (major); **7c**: AS, heptane/2-PrOH 90:10, 1.0 mL/min, 205 nm, 15.5 min (minor), 17.8 min (major); **7d**: OD, heptane/2-PrOH 90:10, 1.0 mL/min, 220 nm, 9.7 min (major), 11.4 min (minor); **7e**: AD-H, heptane/2-PrOH 95:5, 0.6 mL/min, 220 nm, 16.9 min (major), 22.4 min (minor); **7f**: AD-H, heptane/2-PrOH 90:10, 0.6 mL/min, 220 nm, 9.4 min (major), 11.1 min (minor); **7g**: OD-H, heptane/2-PrOH 95:5, 0.55 mL/min, 220 nm, 16.6 min (major), 19.7 min (minor); **7h**: OD-H, heptane/2-PrOH 90:10, 0.55 mL/min, 220 nm, 17.9 min (major), 20.6 min (minor); **7i**: FS-Cyclodex β I/P, 80 kPa H_2, 80.4 min (minor), 81.0 min (major); **7j**: OD-H, Heptan/2-PrOH 90:10, 0.55 mL/min, 210 nm, 28.2 min (minor), 33.3 min (major).
14. Presumably, the *Z*-isomer of α-arylenamides is hydrogenated more selectively, which was also observed by Imamoto using the DiSquareP*/Rh(I) catalyst system, see Ref. 12.