Available online at www.sciencedirect.com
ScienceDirect
C. R. Chimie 10 (2007) 213–219
COMPTES RENDUS CHIMIE
http://france.elsevier.com/direct/CRAS2C/

Full paper / Mémoire

New ligands for the RuCp*-diamine catalysed asymmetric hydrogenation of aryl ketones

Alexander Paptchikhine, Klas Källström, Pher G. Andersson*

Department of Biochemistry and Organic Chemistry, Box 576, SE-751 23 Uppsala, Sweden

Received 25 July 2006; accepted after revision 28 November 2006
Available online 17 January 2007

Abstract

New chiral diamine ligands have been synthesized and evaluated in the asymmetric Ru-catalyzed hydrogenation of prochiral aryl ketones. All catalysts showed good conversions with observed enantioselectivities ranging from moderate to good. ***To cite this article: A. Paptchikhine et al., C. R. Chimie 10 (2007).***

Résumé

De nouveaux ligands chiraux de type diamine ont été synthétisés et évalués lors de réactions d'hydrogénation asymétrique d'arylcétones prochirales catalysées par des complexes de ruthénium. L'ensemble des catalyseurs a montré de bonnes conversions, avec des énantiosélectivitiés observées bonnes à moyennes. ***Pour citer cet article : A. Paptchikhine et al., C. R. Chimie 10 (2007).***

Keywords: Diamine ligands; Hydrogenation; Asymmetric catalysis; Ruthenium

Mots-clés : Ligands de type diamine ; hydrogénation ; catalyse asymétrique ; ruthénium

1. Introduction

The growth of catalytic asymmetric synthesis has exploded in the past several decades [1] and is now arguably the most important synthetic method for the production of chiral compounds. This has made homogeneous hydrogenation of functionalized olefins one of the most studied enantioselective catalytic reactions [2a,b]; of equal practical interest is the hydrogenation of C=O and C=N bonds.

The most efficient catalysts for the hydrogenation of functionalized ketones are based on Rh- and Ru-diphosphine catalyst [3]. The method of choice for reducing unfunctionalized ketones, on the other hand, is Noyori's newly developed Ru-diphosphine/diamine catalyst system [4]. Although both Ru-diphospine/diamine complexes **1** [e.g., *P-P* = (*S*)-BINAP, *N-N* = (*S*,*S*)-1, 2-diphenylethylenediamine] and the widely used Ru–arene/diamine complex RuCl(TsDPEN)(η^6-arene)

* Corresponding author.
E-mail address: pher.andersson@biorg.uu.se (P.G. Andersson).

1631-0748/$ - see front matter © 2006 Published by Elsevier Masson SAS on behalf of Académie des sciences.
doi:10.1016/j.crci.2006.11.007

2 [TsDPEN = *N*-(*p*-toluenesulfonyl)-(*S*,*S*)-1,2-diphenylethylene-diamine] (Fig. 1) contain a characteristic NH functionality, the catalytic activity of these two catalyst systems differs tremendously.

Complexes of the type **2** are typically used in transfer hydrogenation and yet exhibit almost no reaction as hydrogenation catalysts [5], while RuCp*-1,2-diamine complexes of the type **3** do so easily.

Recently, it has been demonstrated that RuCp*-1,2-diamine complexes of the general type **3**, which are isoelectronic to the transfer hydrogenation catalyst **2** (Fig. 1), are active catalysts for the hydrogenation of ketones with H_2 as the source of hydride [6,7]. These findings are some of the few known examples of homogeneous hydrogenation catalysts that are capable of activating molecular hydrogen without having at least one phosphine ligand around the metal center [8a–d]. These studies also showed that the most active catalysts were obtained with a diamine having one tertiary and one primary amino function. Based on these reports we envisaged that the structural motif of our newly developed thiazole [9] and oxazole [10] based ligands, could serve as chiral backbones for the synthesis of new chiral diamines suitable as ligands in the asymmetric phosphine free hydrogenation of various prochiral aryl ketones. These ligands have previously been used as *N*,*P*-coordinating ligands in the Ir-catalysed asymmetric hydrogenation of olefins with great success [9,10].

2. Results and discussion

2.1. Thiazole ligand synthesis

Two thiazole amine ligands **5** and **6**, capable of forming six-membered ring chelates with transition metals were synthesized in a similar fashion, Scheme 1. Enantiomerically pure tosylates **1** and **2** were prepared as described in the literature [9]. Nucleophilic displacement by NaN_3 in DMF at 80 °C yielded the corresponding azides **3** and **4**, with less than 1% elimination product observed by ^1H NMR. Azides **3** and **4** were then reduced to their corresponding amines **5** and **6** with H_2 over Pd/C at 30 bar.

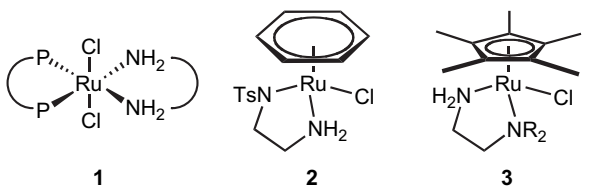
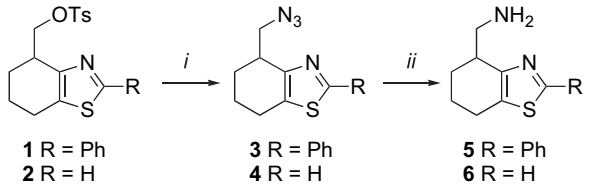


Fig. 1. General hydrogenation and transfer hydrogenation complexes.



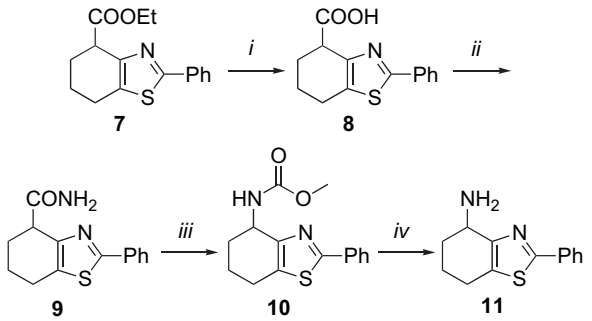
Scheme 1. Synthesis of ligands **5** and **6**. (i) NaN_3, DMF, 80 °C: **3** 73% and **4** 63%; (ii) Pd/C, H_2 (30 bar): **5** 100% and **6** 68%.

The same protocol was employed with racemic **1**; compound **3** was then resolved *via* chiral HPLC [Chiralcel OD column, hexane/isopropanol 80:20, t_R 9.51 min (*R*) and 15.1 min (*S*)] and subsequently hydrogenated giving both the optically pure enantiomers of **5**.

Compound **11** [9] was synthesized in a four-step procedure starting from racemic **7**, Scheme 2. The ester **7** was hydrolyzed to the corresponding carboxylic acid **8** and converted to amide **9** by formation of an activated ester by treatment with ammonia *in situ* [11] yielding amide **9** in high yield (97%).

Several attempts were made to convert amide **9** directly into amine **11** by Hoffmann rearrangements using general procedures such as Br_2/NaOH/H_2O [12] and Br_2/NaOEt/EtOH [13]. Unfortunately, this gave very low conversion due to the low solubility of amide **9**. A modified procedure was employed instead, using DMF as the solvent and NBS in presence of AcONa as Hoffmann rearrangement conditions to Br_2 and NaOH [14], giving **10** in 16% isolated yield.

Hydrolysis of carbamate **10** in ethanol with an excess of NaOH gave the free amine *rac*-**11**, which was resolved by chiral HPLC [Chiralcel OD, hexane/



Scheme 2. Synthesis of ligand **11**. (i) NaOH, EtOH/H_2O (6/5), reflux, 92%; (ii) $(Boc)_2O$, pyridine, NH_4HCO_3, dioxane, RT, 97%; (iii) NBS, AcONa, MeOH, DMF, 60 °C, 16%; (iv) NaOH, EtOH, reflux, 68%.

isopropanol 80:20, t_R 13.8 min (**11a**) and t_R 19.5 min (**11b**)] (Scheme 2).

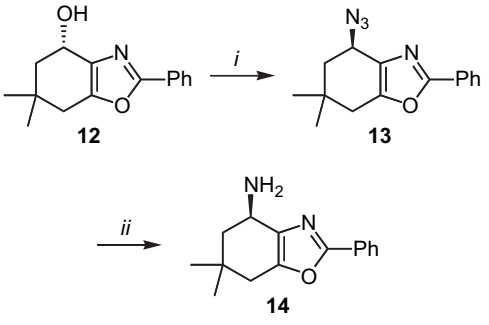
2.2. Oxazole ligand synthesis

Compound **14** was synthesized from previously reported enantiomerically pure **12** [10], Scheme 3. Alcohol **12** was converted into the corresponding azide **13**, with inversion of configuration, in 70% yield and 98% ee by a Mitsunobu reaction using diphenyl phosphoryl azide as the azide source [15]. This reaction produced 6% of elimination byproduct that could not be removed by flash chromatography but was easily removed in the next step. Azide **13** was reduced to amine **14** with H_2 over Pd/C at 30 bar, 83% isolated yield with 98% ee, Scheme 3.

2.3. Catalyst studies

In order to investigate the activity of these new ligands, we tested (*S*)-**5**, (*R*)-**6**, (−)-**11a** and (*R*)-**14** in the hydrogenations of eight different ketones of the general type ArCOR. The results are summarized in Tables 1 and 2. All reactions were run at RT for specified time and at 30 bar H_2.

One can see that the presence of electron-donating groups, methoxy and methyl, in the *para* position of the ketone, results in reduced conversions compared to acetophenone (after 2 h). The reverse is true with the electron withdrawing chorine (Table 1, (*S*)-**5** entries 1, 2, 4 and 6), however, the highly electron withdrawing *p*-trifluoromethyl group results in only 25% conversion of the corresponding ketone (Table 1, (*S*)-**5** entry 7). Moving the electron-donating group from the *para* to the *ortho* position (Table 1, compare entries 2 and 4 with 3 and 5) resulted in a further decrease of conversion.



Scheme 3. Synthesis of ligand **14**. (i) $(PhO)_2P(O)N_3$, DEAD, Ph_3P, THF, 0 °C, 15 min, RT 1.5 h, 70%; (ii) Pd/C, isopropanol, H_2 (30 bar), 83%.

Table 1
Asymmetric Ru-catalysed hydrogenation of prochiral aryl ketones using ligands (*S*)-**5** and (*R*)-**6**

Entry	Ar	R	(*S*)-**5**[a]		(*R*)-**6**[a]	
			% Conv.[b]	% ee.[c]	% Conv.[b]	% ee.[c]
1	C_6H_5	CH_3	87	46 (*S*)	>99	14 (*R*)
2	*p*-$CH_3OC_6H_4$	CH_3	57	39 (*S*)	98	*rac*
3	*o*-$CH_3OC_6H_4$	CH_3	48	18 (*R*)	>99	16 (*R*)
4	*p*-$CH_3C_6H_4$	CH_3	61	48 (*S*)	>99	15 (*R*)
5	*o*-$CH_3C_6H_4$	CH_3	41	*rac*	>99	*rac*
6	*p*-ClC_6H_4	CH_3	98	31 (*S*)	99	15 (*R*)
7	*p*-$F_3CC_6H_4$	CH_3	25	14 (*S*)	99	15 (*R*)
8	C_6H_5	*t*-Bu	3	12 (*R*)	>99	23 (*R*)

[a] Reaction time is 2 h at 30 bar H_2 (see Section 4).
[b] Determined by ^1H NMR.
[c] Determined by chiral GC.

While, in the case of ligand **5**, there appears to be a correlation between the electronic character of the substrate substituents and conversions; there is no such obvious trend with substituents and enantioselectivities.

The ligand **6** results in a much more active catalyst, with conversions greater than 98% in 2 h, but at the expense of selectivity, Table 1. In contrast to results obtained with many transfer hydrogenation catalysts [7], increasing the steric bulk of the R group leads to an increase in stereoselectivity (*cf.* ligand **6** entries 1 and 8, Table 1). Whereas for the catalyst derived from ligand **5** the selectivity for the same substrate is inverted.

Interestingly, changing to five-membered chelating ligands, **11** and **14**, results in a more active and selective catalyst, Table 2. The ee's obtained with these catalysts follow the same pattern as we have previously reported [7].

Table 2
Asymmetric Ru-catalysed hydrogenation of prochiral aryl ketones using ligands (−)-**11a** and (*R*)-**14**

Entry	Ar	R	(−)-**11a**[a]		(*R*)-**14**[a]	
			% Conv.[b]	% ee.[c]	% Conv.[b]	% ee.[c]
1	C_6H_5	CH_3	>99	42 (*S*)	>99	43 (*S*)
2	*p*-$CH_3OC_6H_4$	CH_3	>99	57 (*S*)	>99	60 (*S*)
3	*o*-$CH_3OC_6H_4$	CH_3	>99	37 (*S*)	>99	47 (*S*)
4	*p*-$CH_3C_6H_4$	CH_3	>99	58 (*S*)	>99	60 (*S*)
5	*o*-$CH_3C_6H_4$	CH_3	>99	17 (*S*)	>99	*rac*
6	*p*-ClC_6H_4	CH_3	>99	54 (*S*)	97	63 (*S*)
7	*p*-$F_3CC_6H_4$	CH_3	>99	43 (*S*)	42	48 (*S*)
8	C_6H_5	*t*-Bu	56	78 (*S*)	61	74 (*S*)

[a] Reaction time is 0.5 h at 30 bar H_2 (see Section 4).
[b] Determined by ^1H NMR.
[c] Determined by chiral GC.

3. Conclusions

In conclusion, we have investigated the scope of the previously reported oxazole and thiazole moieties in the asymmetric hydrogenation of ketones. These newly synthesized diamine ligands are highly active in the Ru-catalysed asymmetric hydrogenation of a number of aryl ketones. We have shown in this study that a five-membered chelate is preferable over a six-membered chelate.

4. Experimental

All reactions were run using dried glassware and magnetic stirring. THF was freshly distilled under N_2 from a deep-blue solution of sodium-benzophenone ketyl prior to use. CH_2Cl_2 was freshly distilled under N_2 from powdered CaH_2 prior to use. Flash chromatography was performed using silica gel 60 Å (37–70 μm). Analytical TLC was carried out utilizing 0.25 mm precoated plates, silica gel 60 UV_{254} and spots were visualized by use of UV light and/or treatment with an ethanol solution of phosphomolybdic acid (5%) followed by heating. For NMR-spectroscopy, samples were dissolved in $CDCl_3$ and run at room temperature. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a 400-MHz spectrometer. Chemical shifts for protons are reported using the residual $CHCl_3$ as internal reference (δ 7.26). Carbon signals are referenced to the shift from the ^{13}C signal of $CDCl_3$ (δ 77.0). Mass spectra were measured at 70 eV (EI). Melting points are reported as their uncorrected values.

The ee's of synthesized compounds were determined by chiral chromatography on either a Chiralcel OD-H or Chiralpak AS-H column (4.6 × 250 mm), using hexane/isopropanol as mobile phase. The ees of hydrogenated ketones were determined by chiral GC on CP-Chirasil-Dex column with 15 psi N_2 as carrier gas and FID detection [7].

4.1. General procedure for the preparation of compounds **3** and **4**

4.1.1. (R/S)-4-(Azidomethyl)-2-phenyl-4,5,6,7-tetrahydrobenzo[d]thiazole (**3**)

Compound *rac*-**1** (4.80 g, 12.0 mmol, 1.0 eq) and NaN_3 (1.17 g, 18.0 mmol, 1.5 eq) were suspended in DMF (20 mL) and heated slowly in oil bath to 80 °C over 1 h. Temperature was kept at 80 °C for 5 h until no starting material was detected by TLC (pentane/EtOAc 75:25). Water (30 mL) and Et_2O (100 mL) were added. After separating the aqueous layer, the organic phase was washed with water (5 × 30 mL), dried (Na_2SO_4) and evaporated under vacuum to give 2.69 g of crude azide **3**. After flash chromatography on silica (pentane/EtOAc 95:5) 2.38 g (73%) of pure azide **3** was obtained as a colourless oil. Separation on semi-preparative Chiralcel OD column [hexane/isopropanol 80:20, t_R 9.51 min (*R*) and 15.1 min (*S*)] afforded two enantiomers as clear oils with >99% ee; $R_f = 0.58$ (pentane/EtOAc 90:10); $[\alpha]_D^{23}$ +113.5 (*S*) enantiomer (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 2936, 2860, 2099, 1541, 1502, 1463, 1267, 979, 762 and 689 cm^{-1}; ^1H NMR δ: 1.73–1.88 (m, 2H, CH_2), 1.92–2.13 (m, 2H, CH_2), 2.79–2.84 (m, 2H, $CH_2C{=}C$), 3.15 (m, 1H, $CHCH_2N_3$), 3.60 (dd, $J = 12.1$, 8.3 Hz, 1H, CH_2N_3), 3.92 (dd, $J = 12.1$, 3.9 Hz, 1H, CH_2N_3), 7.34–7.45 (m, 3H, *o*/*p*-CH), 7.86–7.94 (m, 2H, *m*-CH); ^{13}C NMR δ: 21.4, 23.7, 26.5, 37.5, 54.9, 126.2, 128.8, 129.6, 131.4, 133.9, 151.0, 164.9; MS (EI) (*m*/*z*) (rel. intensity) 271 (MH^+, 100%), 270 (M, 14%), 215 (15%), 214 (69%), 213 (17%), 212 (10%) and 111 (13%).

4.1.2. (R)-4-(Azidomethyl)-4,5,6,7-tetrahydrobenzo[d]thiazole (**4**)

Prepared from enantiomerically pure (*S*)-**2**. Colourless oil, 63%; >99% ee; $R_f = 0.56$ (pentane/EtOAc 75:25); $[\alpha]_D^{22}$ +8.80 (*c* 0.83, $CHCl_3$); IR (neat) ν_{max} 2941, 2864, 2102, 1543, 1450, 1418, 1274 and 909 cm^{-1}; ^1H NMR δ: 1.70–1.90 (m, 2H, CH_2), 1.91–2.12 (m, 2H, CH_2), 2.77–2.84 (m, 2H, $CH_2C{=}C$), 3.14 (m, 1H, $CHCH_2N_3$), 3.58 (dd, $J = 12.1$, 8.0 Hz, 1H, CH_2N_3), 3.82 (dd, $J = 12.1$, 3.9 Hz, 1H, CH_2N_3), 8.59 (s, 1H, CH=N); ^{13}C NMR δ: 21.4, 23.5, 26.5, 37.3, 54.8, 131.0, 149.8, 150.6; MS (EI) (*m*/*z*) (rel. intensity) 195 (MH^+, 100%) and 138 (10%).

4.2. General procedure for the preparation of compounds **5** and **6**

4.2.1. (S)-(2-Phenyl-4,5,6,7-tetrahydrobenzo[d]thiazol-4-yl)methanamine (**5**)

To a solution of (*S*)-**3** (0.16 g, 0.60 mmol) in EtOAc (3 mL) was added Pd/C (10%) (10 mg, 0.6%).

The reaction vessel was placed in high-pressure equipment and charged with H_2 (30 bar) and stirred overnight (reduction is complete after several hours). After filtering through Celite the solids were washed with Et_2O. The solution was evaporated under vacuum to give 0.15 g (quantitative) of amine **5** as a yellowish oil; $R_f = 0.51$ (methanol/Et_3N 80:20); $[\alpha]_D^{22.7}$ +66.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3365, 3293, 3062, 2933,

2861, 2214, 1598, 1581, 1538, 1462, 1336, 1313, 977, 910, 763, 732 and 690 cm^{-1}; ^1H NMR δ: 1.55–1.86 (m, 4H, CH_2, NH_2), 1.89–2.04 (m, 2H, CH_2), 2.71–2.81 (m, 2H, $CH_2C{=}C$), 2.86 (m, 1H, $CHC{=}C$), 2.93 (dd, $J = 12.4$, 5.8 Hz, 1H, CH_2NH_2), 3.06 (dd, $J = 12.3$, 6.0 Hz, 1H, CH_2NH_2), 7.30–7.43 (m, 3H, *o*/*p*-CH), 7.83–7.91 (m, 2H, *m*-CH); ^{13}C NMR δ: 21.7, 23.7, 26.7, 40.5, 46.8, 126.0, 128.6, 129.3, 130.1, 133.9, 153.5, 164.3; MS (EI) (*m*/*z*) (rel. intensity) 245 (MH^+, 51%), 244 (M, 10%), 216 (19%), 215 (100%), 214 (66%) and 121 (17%).

4.2.2. (R)-(4,5,6,7-Tetrahydrobenzo[d] thiazol-4-yl)methanamine (**6**)

Yellowish oil, 68%; $R_f = 0.48$ (methanol/Et_3N 80:20); $[\alpha]_D^{24.2}$ +34.5 (*c* 1.3, $CHCl_3$); IR (neat) ν_{max} 3391, 2935, 1634 and 1415 cm^{-1}; ^1H NMR δ: 1.52 (br s, 2H, NH_2), 1.61–1.85 (m, 2H, $CH_2CHC{=}C$), 1.91–2.04 (m, 2H, $CH_2CH_2C{=}C$), 2.70–2.82 (m, 2H, $CH_2C{=}C$), 2.88 (m, 1H, $CHC{=}C$), 2.95 (dd, $J = 12.3$, 6.1 Hz, 1H, CH_2NH_2), 3.06 (dd, $J = 12.3$, 5.5 Hz, 1H, CH_2NH_2), 8.57 (t, $J = 0.7$, 1H Hz, $CH{=}N$); ^{13}C NMR δ: 21.7, 23.6, 26.7, 40.4, 46.5, 129.8, 149.5, 153.0; MS (EI) (*m*/*z*) (rel. intensity) 169 (MH^+, 9%), 140 (13%), 139 (88%), 138 (100%), 111 (15%) and 77 (12%).

4.3. Procedures for the preparation of compounds **8–14**

4.3.1. 2-Phenyl-4,5,6,7-tetrahydrobenzo[d] thiazole-4-carboxylic acid (**8**)

To a solution of thiazole ester **7** (12.68 g, 46.1 mmol, 1.0 eq) in 96% ethanol (60 mL) was added 2 M NaOH (50 mL, 0.10 mol NaOH, 2.2 eq) and the reaction mixture was refluxed for 1 h. After evaporation of ethanol, water (200 mL) and CH_2Cl_2 (200 mL) were added. The aqueous phase was acidified with conc. HCl to pH approx. 5. After separating the organic layer, the aqueous layer was extracted several times with CH_2Cl_2 (4 × 100 mL), restoring the pH to 5 after each extraction. The combined organic extracts were dried (Na_2SO_4) and evaporated under vacuum to give 10.99 g (92%) of carboxylic acid **8** as a white solid. mp 156.9–159.8 °C; $R_f = 0.28$ (pentane/AcOH 80:20); IR (KBr) ν_{max} 3050, 2945, 2863, 1948, 1735, 1700, 1550, 1500, 1462, 1394, 1261, 1222, 1177, 981, 860 and 761 cm^{-1}; ^1H NMR δ: 1.84 (m, 1H, CH_2), 1.97–2.20 (m, 2H, CH_2), 2.35 (m, 1H, CH_2), 2.72–2.84 (m, 2H, CH_2), 3.85 (m, 1H, CH), 7.38–7.48 (m, 3H, *o*/*p*-CH), 7.79–7.89 (m, 2H, *m*-CH), 12.2 (br s, 1H, COOH); ^{13}C NMR δ: 22.1, 23.5, 25.1, 42.0, 126.3, 129.1, 130.6, 131.8, 132.4, 146.4, 166.2, 172.3; MS (EI) (*m*/*z*) (rel. intensity) 261 (MH^+, 25%), 260 (M, 100%), 215 (51%) and 214 (42%).

4.3.2. 2-Phenyl-4,5,6,7-tetrahydrobenzo[d] thiazole-4-carboxamide (**9**)

To a solution of compound **8** (10.31 g, 39.8 mmol, 1.0 eq) in dioxane (100 mL) was added pyridine (2 mL, 24.8 mmol, 0.62 eq), $(Boc)_2O$ (12.06 g, 55.3 mmol, 1.4 eq) and NH_4HCO_3 (3.98 g, 50.3 mmol, 1.3 eq). Solution was stirred overnight (after several hours the amide starts to precipitate). Most of the dioxane was evaporated under vacuum and water (20 mL) was added. The solids were filtered on a Buchner funnel, washed with water (40 mL) and dried in exicator to give 9.92 g (96.5%) of amide **9** as a fine white powder. mp 177.4–181.9 °C; $R_f = 0.15$ (pentane/AcOH 80:20); IR (KBr) ν_{max} 3387, 3164, 2946, 1683, 1616, 1545, 1376, 1172, 973, 881, 775, 692 and 570 cm^{-1}; ^1H NMR δ: 1.84–2.03 (m, 3H, 2 × CH_2CH_2CHCO and CH_2CHCO), 2.45 (m, 1H, CH_2CHCO), 2.70–2.88 (m, 2H, $CH_2C{=}C$), 3.77 (m, 1H, CHCO), 5.75 (br s, 1H, NH_2), 7.21–7.48 (m, 4H, *o*/*p*-CH and NH_2), 7.78–7.92 (m, 2H, *m*-CH); ^{13}C NMR δ: 21.4, 23.7, 24.6, 42.1, 126.2, 128.9, 129.9, 131.9, 133.4, 148.2, 165.4, 174.0; MS (EI) (*m*/*z*) (rel. intensity) 259 (MH^+, 25%), 258 (M, 100%), 216 (15%), 215 (82%), 214 (88%), 213 (49%), 212 (13%), 180 (16%), 121 (20%), 111 (18%), 104 (15%) and 77 (14%).

4.3.3. Methyl 2-phenyl-4,5,6,7-tetrahydrobenzo[d]-thiazol-4-ylcarbamate (**10**)

Compound **9** (1.00 g, 3.87 mmol, 1.0 eq) and AcONa (0.95 g, 12 mmol, 3.0 eq) were suspended in DMF (15 mL). Methanol (3.1 mL, 76 mmol, 20 eq) was added and suspension was immersed into ice bath whereby a solution of NBS (0.76 g, 4.3 mmol, 1.1 eq) in DMF (3 mL) was added dropwise. The suspension was heated slowly in oil bath to 60 °C over 2 h. After cooling, the solution was neutralised by 5% $NaHCO_3$ (10 mL) and extracted by Et_2O (50 mL). The organic phase was washed with water (3 × 10 mL), dried (Na_2SO_4) and evaporated under vacuum to give 0.785 g of crude material. Recrystallization from CH_2Cl_2:pentane gave 0.17 g (16%) pure thiazole carbamate **10** as fine white powder. mp 150.7–157.0 °C; $R_f = 0.26$ (pentane/EtOAc 75:25); IR (KBr) ν_{max} 3282, 2949, 2248, 1706, 1545, 1464, 1337, 1253, 1192, 1071, 977, 909, 766, 733 and 692 cm^{-1}; ^1H NMR δ: 1.69–1.87 (m, 2H, CH_2CH_2CHNH), 1.93 (m, 1H, CH_2), 2.08 (m, 1H, CH_2), 2.47–2.72 (m, 2H, CH_2),

3.71 (s, 3H, CH_3), 4.81 (m, 1H, C*H*NH), 5.84 (br s, 1H, NH), 7.30–7.44 (m, 3H, *o*/*p*-CH), 7.74–7.88 (m, 2H, *m*-CH); ^{13}C NMR δ: 19.8, 23.4, 29.8, 47.9, 51.9, 126.3, 128.7, 129.7, 133.0, 133.5, 149.9, 156.6, 165.3; MS (EI) (*m*/*z*) (rel. intensity) 290 (20%), 289 (MH^+, 100%), 288 (M, 33%), 230 (16%), 229 (84%), 214 (24%), 213 (62%), 212 (20%) and 180 (14%).

4.3.4. (R/S)-2-Phenyl-4,5,6,7-tetrahydrobenzo[d] thiazol-4-amine (**11**)

Compound **10** (63 mg, 0.22 mmol, 1.0 eq) and NaOH (94 mg, 2.4 mmol, 11 eq) were dissolved in 96% ethanol (5 mL) and refluxed for 2 h. After evaporation of the solvent in vacuum, the residue was dissolved in water/Et_2O (5:5 mL) and acidified with conc. HCl until pH < 1. After vigorous stirring and removal of the organic phase, the aqueous phase was basified with 2 M NaOH solution until pH > 12 and extracted by CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under vacuum to give 34 mg (68%) amine **11** as a colourless oil that crystallised on standing. mp 146.8–149.6 °C (racemic). Amine was separated on a semi-preparative Chiralcel OD column (hexane/isopropanol 80:20) to give two enantiomers **11a** (t_R 13.8) and **11b** (t_R 19.5), >99% ee; R_f = 0.58 (methanol/Et_3N 95:5); $[\alpha]_D^{23.6}$ −78.1 (*c* 0.75, $CHCl_3$) **11a**; $[\alpha]_D^{23.7}$ +67.4 (*c* 0.75, $CHCl_3$) **11b**; IR (KBr) ν_{max} 3327, 3056, 2943, 1690, 1465, 1203, 1171, 1127, 976, 828, 798, 760 and 689 cm^{-1}; ^{1}H NMR δ: 1.64–1.86 (m, 2H, CH_2CH$_2$C=C), 1.96 (m, 1H, CH_2CHNH$_2$), 2.14 (m, 1H, CH_2CHNH$_2$), 2.72 (ddd, *J* = 12.2, 5.7, 1.5 Hz, 2H, CH_2C=C), 3.90 (br s, 2H, NH_2), 4.17 (m, 1H, C*H*NH$_2$), 7.27–7.47 (m, 3H, *o*/*p*-CH), 7.74–7.93 (m, 2H, *m*-CH); ^{13}C NMR δ: 20.7, 23.6, 31.2, 47.8, 126.3, 128.8; MS (EI) (*m*/*z*) (rel. intensity) 232 (MH^+, 16%), 231 (M, 100%), 230 (17%), 229 (37%), 215 (11%), 214 (36%), 213 (91%), 203 (15%), 202 (85%), 201 (24%), 175 (27%), 121 (18%).

4.3.5. (R)-6,6-Dimethyl-2-phenyl-4,5,6,7-tetrahydrobenzo[d]oxazol-4-azide (**13**)

Compound **12** (1.00 g, 4.11 mmol, 1.0 eq) and triphenyl phosphine (1.29 g, 4.92 mmol, 1.2 eq) were dissolved in dry THF (15 mL) and cooled to 0 °C. Diphenyl phosphoryl azide (1.06 mL, 4.92 mmol, 1.2 eq) and 85% DEAD (0.93 mL, 5.0 mmol, 1.2 eq) were added and the solution was stirred for 10 min at 0 °C and then for 1.5 h at RT. The solvent was evaporated under vacuum and the residue was chromatographed on a silica column (Et_2O/pentane 10:90) to give 0.77 g (70%) of crude azide as a colourless oil, containing 6% of elimination product (^{1}H NMR) that could not be separated. Product was used as is in the next step. R_f = 0.47 (pentane/Et_2O 90:10); HPLC: Chiralcel OD-H column (4.6 × 250 mm), hexane/isopropanol 80:20, 0.5 mL/min, t_R 9.31 min minor (*S*) and 13.2 min major (*R*), 98% ee; $[\alpha]_D^{23.3}$ −30.2 (*c* 1.42, $CHCl_3$); IR (neat) ν_{max} 2958, 2929, 2871, 2098, 1646, 1553, 1488, 1449, 1253, 1058, 1025, 921, 775, 710 and 693 cm^{-1}; ^{1}H NMR δ: 1.03 (s, 3H, Me), 1.17 (s, 3H, Me), 1.68 (dd, *J* = 13.5, 7.9 Hz, 1H, CH_2CHN$_3$), 1.95 (ddd, *J* = 13.4, 5.9 Hz, 1.1, 1H, CH_2CHN$_3$), 2.46 (ddd, *J* = 16.6, 1.6, 1.1 Hz, 1H, CH_2C=C), 2.58 (dd, *J* = 16.6, 2.1 Hz, 1H, CH_2C=C), 4.75 (ddt, *J* = 7.8, 6.0, 1.7 Hz, 1H, CHN$_3$), 7.36–7.46 (m, 3H, *m*/*p*-CH), 7.97–8.06 (m, 2H, *o*-CH); ^{13}C NMR δ: 26.8, 29.8, 32.6, 35.2, 42.2, 53.6, 126.1, 127.4, 128.5, 130.0, 132.5, 148.5, 161.1; MS (EI) (*m*/*z*) (rel. intensity) 269 (MH^+, 35%), 268 (M, 12%), 227 (21%) and 226 (100%).

4.3.6. (R)-6,6-Dimethyl-2-phenyl-4,5,6,7-tetrahydrobenzo[d]oxazol-4-amine (**14**)

Compound **13** (0.43 g, 1.6 mmol) was dissolved in isopropanol (4 mL) followed by addition of Pd/C (10%) (0.10 g, 2.3%); the vial was placed in the high-pressure equipment and charged with H_2 (50 bar) and stirred for 14 h at RT. The solution was filtered through Celite and evaporated. Et_2O (20 mL) and water (20 mL) were added and the solution was acidified by conc. HCl until pH < 1; after vigorous stirring and removal of the organic phase the aqueous phase was washed with another portion of Et_2O (10 mL). The aqueous phase was basified with conc. NaOH (aq) until pH > 12, extracted with $CHCl_3$ (2 × 20 mL), the combined organic phase was dried (Na_2SO_4) and the solvent was removed under vacuum to give 0.33 g (83%) of amine **14** as a yellowish oil. R_f = 0.61 (methanol/Et_3N 95:5); HPLC: Chiralpak AS-H column (4.6 × 250 mm), hexane/isopropanol 95:5, 0.5 mL/min, t_R 17.4 min minor (*S*) and 21.69 min major (*R*), 98% ee; IR (neat) ν_{max} 3362, 2956, 1645, 1550, 1486, 1449, 1388, 1367, 1285, 1062, 1025, 775, 727, 700 and 693 cm^{-1}; ^{1}H NMR δ: 1.00 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.36 (dd, *J* = 13.0, 9.7 Hz, 1H, CH_2CNH$_2$), 1.77 (brs, 2H, NH_2), 1.91 (ddd, *J* = 13.0, 5.7 Hz, 1.6, 1H, CH_2CNH$_2$), 2.44 (dt, *J* = 16.3, 1.6 Hz, 1H, CH_2C = C), 2.55 (dd, *J* = 16.3, 2.6 Hz, 1H, CH_2C=C), 3.90 (dddd, *J* = 9.9, 5.7, 2.7, 1.6 Hz, 1H, C*H*NH$_2$), 7.33–7.47 (m, 3H, *m*/*p*-CH), 7.93–8.03 (m, 2H, *o*-CH); ^{13}C NMR δ: 26.1, 31.5, 32.9, 35.9, 44.4, 47.3, 126.2, 128.2, 128.9, 130.0, 138.2, 146.7, 161.0; MS (EI) (*m*/*z*) (rel. intensity) 243 (MH^+, 13%), 242 (M, 15%), 226 (13%), 225 (13%), 189 (71%), 187 (16%), 186 (100%), 171 (25%), 158 (14%), 104 (13%) and 77 (15%).

4.4. General procedure for hydrogenations

A Schlenk tube was charged with appropriate diamino ligand (0.0190 mmol), Ru-complex $[Cp^*RuCl]_4$ (0.00475 mmol) and 3 mL isopropanol, under N_2 atmosphere. The solution was stirred at RT for 30 min; 0.110 M solution of ^tBuOK in isopropanol (0.170 mL, 0.0190 mmol) and substrate (1.90 mmol) was added. The reaction mixture was loaded *via* a syringe into N_2 filled test tube containing a stirring bar. Syringe was washed with isopropanol (1 mL) and the solvent was combined with reaction mixture. Test tube was placed in the high-pressure equipment and purged several times with H_2 and a pressure of 30 bar of H_2 was applied for specified time. The pressure was released and solution was first evaporated under reduced pressure, diluted by Et_2O (1 mL) filtered through a short plug of silica, and the plug was washed with Et_2O (3 mL). The combined solvent was evaporated under vacuum and residue was analysed by ^1H NMR ($CDCl_3$) for the conversion and chiral GC (Et_2O) for the ee.

References

[1] E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis, vols. I and II, Springer, Berlin, 1999.

[2] (a) T. Ohkuma, M. Kitamura, R. Noyori, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley-VCH, New York, 2000, p. 1;
(b) H.U. Blaser, F. Spindler, M. Studer, Appl. Catal., A: Gen. 221 (2001) 119.

[3] For a recent review see: R. Noyori, M. Kitamura, T. Ohkuma Proc. Natl Acad. Sci. USA 101 (2004) 5356.

[4] (a) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 117 (1995) 2675;
(b) T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 117 (1995) 10417;
(c) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A.F. England, T. Ikariya, R. Noyori, Angew. Chem., Int. Ed. Engl. 37 (1998) 1703;
(d) T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, J. Am. Chem. Soc. 122 (2000) 6510;
(e) T. Ohkuma, M. Koizumo, K. Muniz, G. Hilt, C. Kabuto, R. Noyori, J. Am. Chem. Soc. 124 (2002) 6508.

[5] K. Haack, J.S. Hashigushi, A. Fujii, T. Ikariya, R. Noyori, Angew. Chem., Int. Ed. Engl. 36 (1997) 285.

[6] M. Ito, M. Hirakawa, K. Murata, T. Ikariya, Organometallics 20 (2001) 379.

[7] C. Hedberg, K. Källström, P.I. Arvidsson, P. Brandt, P.G. Andersson, J. Am. Chem. Soc. 127 (2005) 15083.

[8] (a) Y. Blum, D. Czarkie, Y. Rahamim, Y. Shvo, Organometallics 4 (1985) 1459;
(b) C. Vicente, G.B. Shulpin, B. Moreno, S. Sabo-Étienne, B. Chaudret, J. Mol. Catal. A: Chem. 98 (1995) L5;
(c) H. Huang, T. Okuno, K. Tsuda, M. Yoshimura, M. Kitamura, J. Am. Chem. Soc. 128 (2006) 8716;
(d) I. Karamé, M. Jahjah, A. Messaoudi, M.L. Tommasino, M. Lemaire, Tetrahedron: Asymmetry 15 (2004) 1569.

[9] C. Hedberg, K. Källström, P. Brandt, P.G. Andersson, J. Am. Chem. Soc. 128 (2006) 2995.

[10] K. Källström, C. Hedberg, P. Brandt, A. Bayer, P.G. Andersson, J. Am. Chem. Soc. 126 (2004) 14308.

[11] V.F. Pozdnev, Tetrahedron Lett. 36 (1995) 7115.

[12] F.C. Whitmore, A.H. Homeyer, J. Am. Chem. Soc. 54 (1932) 3435.

[13] P. Radlick, L.R. Brown, Synthesis (1974) 290.

[14] S.S. Jew, H.G. Park, Y.S. Cho, C.H. Cook, Soul Taehakkyo Yakhak Nonmunjip 13 (1988) 43.

[15] S. Takano, T. Sugihara, S. Satoh, K. Ogasawara, J. Am. Chem. Soc. 110 (1988) 6467.