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TETRAHEDRON

Novel Chiral Dirhodium Catalysts derived from Aziridine and Azetidine Carboxylic Acid for Intermolecular Cyclopropanation Reactions with Methyl Phenyldiazoacetate.

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Abstract: Three new chiral dirhodium(II) tetracarboxylate catalysts, based on azetidine- and aziridine-2-carboxylic acid, were prepared. Their selectivities in the cyclopropanation reaction of methyl phenyldiazoacetate and olefins were determined in solvents of decreasing polarity and compared with those obtained with proline derived catalysts.

INTRODUCTION

Rhodium(II) carboxylates are very efficient catalysts for the generation of carbenoid species from α-diazocarbonyl compounds. In several typical carbene reactions like C-H or Si-H insertion, cyclopropanation and aromatic cycloaddition, Rh(II) catalysts were more frequently employed than any other metal catalyst. Since its introduction in 1973[1], rhodium(II) acetate became most popular amongst the rhodium(II) carboxylates, possibly because of its ease of preparation.[2] In the early 1990's Kennedy and McKervy reported the homochiral dirhodium(II) prolinate (Rh_2(*S*-TBSP)$_4$) catalyzed carbenoid formation[3-5] which showed a remarkably improved selectivity in the cyclopropanation reactions.[6-9] Furthermore, this rhodium(II) prolinate catalyst was used in the key step of the total synthesis of the antidepressant Sertraline by Corey and coworkers.[10] Although the stereogenic center in these D_{2h} symmetric rhodium(II) carboxylate catalysts is quite far removed from the carbene center, effective control of selectivity can be achieved as long as the carboxylate substituents extend into the space occupied by the carbene.[11, 12] It is of interest to investigate the influence of the ringsize of the ligand in Rh_2(*S*-TBSP)$_4$ on the selectivity in cyclopropanation reactions. In the case of the more rigid chiral dirhodium(II) carboxamidate catalysts, the influence of the ringsize has also been investigated[13] and results showed that the ringsize may lead to improved selectivities. We therefore synthesized the corresponding dirhodium(II) azetidine- and aziridine-2-carboxylate catalysts and compared the selectivities in different solvent systems with those obtained with Rh_2(*S*-TBSP)$_4$.

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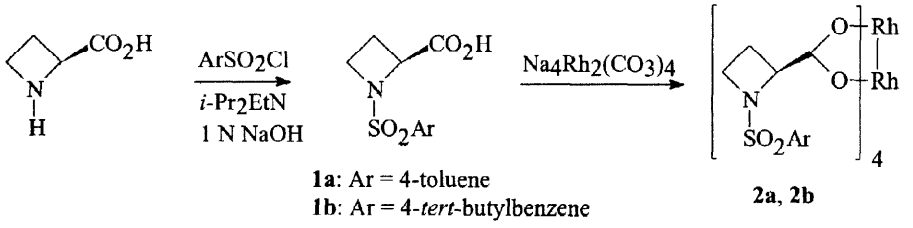
RESULTS

The azetidine-(*2S*)-carboxylate catalysts (**2a** and **2b**) were prepared in the same way as the corresponding rhodium prolinate complexes by carbonate displacement using $Na_4Rh_2(CO_3)_4$. In order to circumvent solubility problems in the catalytic cyclopropanation reactions, either the tosyl group or the 4-*tert*-butylbenzenesulfonyl group were attached to the nitrogen atom (Scheme 1).



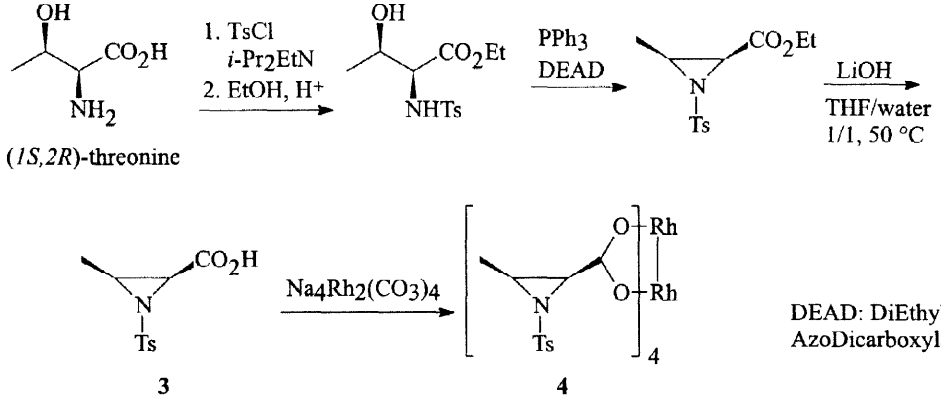
1a: Ar = 4-toluene
1b: Ar = 4-*tert*-butylbenzene

2a, 2b

Scheme 1 Homochiral rhodium(II) azetidine-(2S)-carboxylates

It should be noted that our compound **1a** has $[\alpha]_D^{20}$: -154.7° (c=1, $CHCl_3$) and a melting point of 148.5-149 °C, whereas Miyoshi and coworkers[14] reported $[\alpha]_D^{20}$: -144° (c=0.6, $CHCl_3$) and 145.5-147 °C. This indicates that Miyoshi's route towards **1a** suffered from partial racemization, which probably occurred in the ring closing reaction.

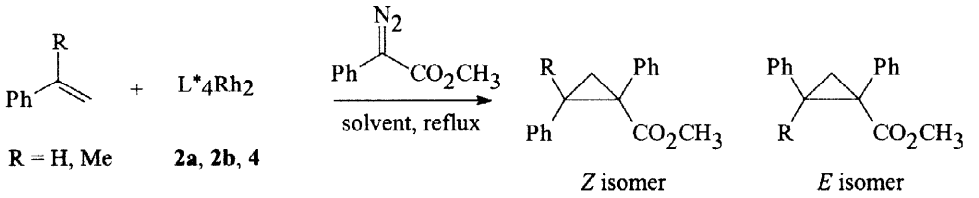
The enantiopure aziridine catalyst (**4**) was synthesized starting from commercially available (*1S,2R*)-threonine by sulfonylation and esterification, followed by a Mitsunobu ring closure. The stereochemical integrity at C-1 and C-2 was retained (Scheme 2).



3 **4**

Scheme 2 Homochiral rhodium(II) aziridine-(2S)-carboxylate

The cyclopropanation was carried out using methyl phenyldiazoacetate as the diazocarbonyl compound (Scheme 3). The results are collected in Table 1.



Scheme 3 Asymmetric cyclopropanation using chiral rhodium(II) azetidine-2-carboxylates

Table 1 Stereoselectivity of Catalysts **2a, 2b, 4** and Rh_2(*S*-TBSP)$_4$ in the Cyclopropanation of Styrene and α-Methylstyrene with Methyl Phenyldiazoacetate[a]

	Styrene (R = H)			α-methylstyrene (R = Methyl)			
Catalyst/solvent	yield[b] [%]	*E*:*Z*[c]	e.e. *E*[d] [%]	yield[b] [%]	*E*:*Z*[c]	e.e. *E*[d] [%]	e.e. *Z*[d] [%]
$Rh_2(OAc)_4/CH_2Cl_2$	96	88.4:11.6	-	93	3.85:1	-	-
2a/CH_2Cl_2	70	98.6:1.4	36 (+)	98	2.82:1	42 (+)	51 (+)
2b/CH_2Cl_2	71	98.2:1.8	35 (+)	96	2.74:1	43 (+)	50 (+)
2b/benzene	98	> 99:1	40 (+)	61	2.57:1	49 (+)	55 (+)
2b/pentane	96	> 99:1	49 (+)	94	2.56:1	64 (+)	62 (+)
2b/cyclohexane	88	97.6:2.4	51 (+)	78	2.62:1	65 (-)	63 (-)
2b[e]/cyclohexane	54	> 99:1	54 (+)				
2b[f]/cyclohexane	53	> 99:1	57 (+)				
4/CH_2Cl_2	86	> 99:1	31 (-)	94	2.86:1	26 (+)	45 (+)
Rh_2(*S*-TBSP)$_4/CH_2Cl_2$[g]	77	97:32	61 (*1R,2S*)				
Rh_2(*S*-TBSP)$_4$/pentane[g]	73	96:4	85 (*1R,2S*)	88	1.5:1	85	81

a Reactions performed using 1 mol% of catalyst, unless noted otherwise, by controlled addition of **C** (0.5 mmol) in 5 ml of solvent to the olefin (5.0 mmol) in 3 ml of refluxing solvent. With pentane and cyclohexane, 15 and 10 ml were used, respectively.

b Isolated yields.

c Determined by capillary gas chromatography.

d Determined by 300 MHz NMR using 0.2 equivalents of (+)-Eu(hfc)$_3$. Optical rotation: (c=1, $CHCl_3$).

e 4.3 mol% **2b**.

f 0.1 mol% **2b**.

g Taken from Doyle *et al.*[9]

DISCUSSION

For all catalysts used the diastereoselectivity, as expressed by the E : Z ratio, is much higher for styrene than for α-methylstyrene. A second observation is that the rhodium catalysts **2** and **4** with 3- and 4-membered heterocyclic ligands show much better diasterocontrol in both reactions than the Rh_2(*S*-TBSP)$_4$ catalyst with 5-membered heterocyclic ligands.

The positive influence of pentane on the enantiocontrol as observed by Davies and coworkers[7] is not limited to proline derived ligands, but is also effective when azetidine-2-carboxylate ligands (**2b**) surround the active carbenoid species. Moreover, a series of cyclopropanation reactions with both styrene and α-methylstyrene in organic solvents with decreasing polarity result in steadily increasing enantiocontrol. The data in Table 1 also clearly reveal that catalysts **2** and **4** are effective catalysts in cyclopropanation reactions. The enantiocontrol of these catalysts is only moderate in polar solvents but can be improved by decreasing the solvent polarity. The best results were obtained in pentane and cyclohexane. However, the dirhodium(II) prolinate catalyst exhibited higher enantiocontrol than catalysts **2** and **4**.

EXPERIMENTAL

General remarks

All reactions were carried out in an inert atmosphere of nitrogen unless stated otherwise. Melting points were determined using a Reichert thermopan microscope and are uncorrected. Optical rotations were measured with a Perkin Elmer automatic polarimeter, model 241 MC, using concentrations c in g/100 ml at 20 °C in the solvents indicated. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 100 (100 MHz, FT) spectrometer. The chemical shift δ is denoted in ppm relative to the internal standard (TMS for ^{1}H NMR, $CDCl_3$ for ^{13}C NMR). IR spectra were recorded on a Perkin Elmer 298 spectrophotometer. The wavenumber σ is listed in cm^{-1}. For (high resolution) mass spectra a double focussing VG7070E mass spectrometer was used. GC-MS were measured using a Varian Saturn II GC-MS by on-column injection (DB-1 column, length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm). Elemental analyses were performed using a Carlo Erba Instruments CHNS-O EA 1108 element analyzer. (*2S,3S*) Ethyl 3-methyl-1-(4-toluenesulfonyl)-aziridine-2-carboxylate was a generous gift of F.J. Dommerholt. Methyl phenyldiazoacetate was prepared by a modification of the procedure by Doyle and coworkers[15], *i.e.* 4-toluenesulfonyl azide was used as diazo-transfer agent, instead of 4-acetamidobenzenesulfonyl azide .

Methyl phenyldiazoacetate

CAUTION! Diazoacetic esters are potentially explosive and must be handled with care.

A solution of methyl phenylacetate (4.505 g, 30.0 mmol) and 4-toluenesulfonyl azide (6.915, 35.0 mmol) in acetonitrile (60 ml) was cooled to 0 °C. Then DBU (6.1 ml, 40.8 mmol) was added and the reaction mixture stirred overnight. The reaction was quenched by adding diethyl ether and saturated NH_4Cl solution. The organic layer was successively washed with NH_4Cl- and NaCl solution. The combined aqueous layers were extracted twice with diethyl ether and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. The 4-toluenesulfonylamide solid by-product was removed by washing the product with hexane: diethyl ether (1:1, *v/v*). Finally, the product was purified by flash chromatography (hexane: ethyl acetate, 40:1, *v/v*) and stored in the dark at 4 °C.

Yield: 50 %. ^{1}H NMR ($CDCl_3$): δ 7.55-7.11 (m, 5H, Ph), 3.87 (s, 3H, $COOCH_3$). IR (CCl_4): σ 2080 (s, CN_2), 1700 (s, $COOCH_3$), 690 (s, monosubstituted phenyl).

1-(4-Toluenesulfonyl)azetidine-(*2S*)-carboxylic acid (1a)

A solution of azetidine-(*2S*)-carboxylic acid (204 mg, 2.02 mmol) in 1N NaOH solution (2.5 ml, 2.5 mmol) was cooled to 0 °C. To this solution 4-toluenesulfonyl chloride (415 mg, 2.18 mmol), diisopropylethylamine (396 µl, 2.27 mmol) and acetone (2.5 ml) were added. After 35 min. the reaction mixture was brought to room temperature and stirred overnight. The aqueous solution was extracted three times with diethyl ether to remove excess tosyl chloride. The combined organic extracts were extracted twice with 1 N NaOH solution and the combined alkaline aqueous layers acidified with concentrated HCl solution to pH 1. The aqueous layer was extracted three times with ethyl acetate, the combined extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Yield: 462 mg, 90 %. Mp.: 148.5-149 °C, lit.[14]: 145.5-147 °C. $[\alpha]_D^{20}$: -154.7° (c=1, $CHCl_3$), lit.[14]: -144° (c=0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.45 (broad s, 1H, COOH), 7.78 (d, A part of AB quartet, 2H, aromate), 7.41 (d, B part of AB quartet, 2H, aromate), 4.53 (t, 1H, NCH), 3.74 (t, 2H, NCH_2), 2.69-2.17 (m, 2H, CH_2), 2.46 (s, 3H, CH_3). IR (KBr): σ 3000 (broad, OH), 1715 (s, COOH), 1342 (s, SO_2), 1160 (s, SO_2). Mass (EI): *m/e* 255 (M^+), 210 (M^+ - COOH), 91 (Tropilium).

Tetrakis (1-(4-toluenesulfonyl)azetidine-(*2S*)-carboxylato) dirhodium(II) dihydrate (2a)

A suspension of $Na_4Rh_2(CO_3)_4$ (58.4 mg, 0.109 mmol) and **1a** (231 mg, 0.905 mmol) in distilled water (3.5 ml) was heated to 80-90 °C for 35 min., during which time the initial blue color disappeared and a green solid precipitated. The precipitate was dried in a vacuum stove at 35 °C to give 123.5 mg **2a**.

Yield: 93 %. $[\alpha]_D^{20}$: -261.0° (c=0.08, CH_2Cl_2). Mass (FAB): *m/e* 1223 (M^+ + 1), 1067 (M^+ - $SO_2C_6H_4CH_3$). Elemental analysis: Calculated for $Rh_2C_{44}H_{48}N_4O_{16}S_4.2H_2O$ %C 41.98, %H 4.16, %N 4.45, %S 10.19. Found %C 42.02, %H 4.13, %N 4.49, %S 9.67.

1-(4-*tert*-Butylbenzenesulfonyl)azetidine-(*2S*)-carboxylic acid (1b)

A solution of azetidine-(*2S*)-carboxylic acid (253 mg, 2.50 mmol) in 1N NaOH solution (3.5 ml, 3.5 mmol) was cooled to 0 °C. To this solution was added 4-*tert*-butylbenzenesulfonyl chloride (641 mg, 2.75 mmol), diisopropylethylamine (0.50 ml, 2.88 mmol) and acetone (3.5 ml). After 35 min. the reaction was brought to room temperature and stirred overnight. The aqueous solution was extracted three times with diethyl ether to remove excess tosyl chloride. The combined organic extracts were extracted twice with 1 N NaOH solution and the combined alkaline aqueous layers acidified with concentrated HCl solution to pH 1. The aqueous layer was extracted three times with ethyl acetate, the combined extracts dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Yield: 733 mg, 98 %. Mp.: 154-159 °C. $[\alpha]_D^{20}$: -141.8° (c=1, methanol). ^1H NMR ($CDCl_3$): δ 7.83 (d, A part of AB quartet, 2H, aromate), 7.62 (d, B part of AB quartet, 2H, aromate), 4.54 (t, 1H, NCH), 3.76 (t, 2H, NCH_2), 2.65-2.19 (m, 2H, CH_2), 1.37 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 172.7 (s, COOH), 157.9, 131.4 (s, aromatic C), 128.3, 126.5 (d, aromatic C), 60.6 (d, NCH), 47.7 (t, NCH_2), 35.3 (s, $C(CH_3)_3$), 31.1 (q, $C(CH_3)_3$), 19.8 (t, CH_2). IR (KBr): σ 3000 (broad, OH), 1700 (s, COOH), 1338 (s, SO_2), 1160 (s, SO_2). Mass (EI): *m/e* 252 (M^+ - COOH), 197 (M^+ - $SO_2C_6H_4C(CH_3)_3$), 133 ($C_6H_4C(CH_3)_3^+$). Elemental analysis: Calculated for $C_{14}H_{19}NO_4S$ %C 56.55, %H 6.44, %N 4.71, %S 10.78. Found %C 56.05, %H 6.40, %N 4.86, %S 10.56.

Tetrakis(1-(4-*tert*-butylbenzenesulfonyl)azetidine-(*2S*)-carboxylato) dirhodium(II) dihydrate (2b)

A suspension of $Na_4Rh_2(CO_3)_4$ (63.3 mg, 0.117 mmol) and **1b** (280 mg, 0.94 mmol) in distilled water (3.5 ml) was heated to 80-90 °C for 35 min., during which time the initial blue color disappeared and a green solid precipitated. The precipitate was washed twice with water and dried in a vacuum stove at 50 °C.

Yield: 151 mg, 90 %. Mp.: 155-160 °C. $[\alpha]_D^{20}$: -177.1° (c=0.02, CH_2Cl_2). Mass (FAB): *m/e* 1391 (M^+). Elemental analysis: Calculated for $Rh_2C_{44}H_{48}N_4O_{16}S_4.2H_2O$ %C 47.12, %H 5.37, %N 3.93, %S 8.99. Found %C 47.88, %H 5.39, %N 4.10, %S 8.55.

(*2S,3S*) 3-Methyl-1-(4-toluenesulfonyl)aziridine-2-carboxylic acid (3)

A solution of (*2S,3S*) methyl 3-methyl-1-(4-toluenesulfonyl)aziridine-2-carboxylate (502 mg, 1.76 mmol) and lithium hydroxide monohydrate (74 mg, 1.76 mmol) in THF:water (50 ml, 1:1, *v/v*) was stirred for 24 h. at 50

°C. The solution was neutralized by adding 10 wt% aqueous tartaric acid and extracted with ethyl acetate. The organic extracts were washed with NaCl solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Yield: quantitative. $[\alpha]_D^{20}$: -29.7° (c=1, methanol). ^1H NMR ($CDCl_3$): δ 10.34 (broad s, 1H, COOH), 7.76 (d, A part of AB quartet, 2H, aromate), 7.27 (d, B part of AB quartet, 2H, aromate), 3.31 (d, 1H, NCH), 3.06 (dq, 1H, NC*H*(CH_3)), 2.37 (s, 3H, CH_3), 1.25 (d, 3H, NCH(CH_3)). IR (KBr): σ 3000 (broad, OH), 1710 (s, COOH), 1327 (s, SO_2), 1160 (s, SO_2).

Tetrakis((*3S*)-methyl-1-(4-toluenesulfonyl)aziridine-(*2S*)-carboxylato) dirhodium(II) dihydrate (4)

A suspension of $Na_4Rh_2(CO_3)_4$ (61.7 mg, 0.114 mmol) and **3** (232 mg, 0.91 mmol) in distilled water (3.5 ml) was heated to 80-90 °C for 35 min., during which time the initial blue color disappeared and a green solid precipitated. The precipitate was washed twice with water and dried in a vacuum stove at 50 °C.

Yield: 116 mg, 81 %. Mp.: 235-245 °C (dec.). $[\alpha]_D^{20}$: +107.7° (c=0.05, CH_2Cl_2). Mass (FAB): *m/e* 1223 (M^+ + 1). Elemental analysis: Calculated for $Rh_2C_{44}H_{48}N_4O_{16}S_4.2H_2O$ %C 47.12, %H 5.37, %N 3.93, %S 8.99. Found %C 47.88, %H 5.39, %N 4.10, %S 8.55.

General procedure for cyclopropanation reactions

All glassware was oven dried and assembled under nitrogen. To a refluxing solution of olefin (5.0 mmol) and Rh(II) carboxylate (5.0 μmol) in an appropriate solvent (3 ml), a solution of methyl phenyldiazoacetate (0.50 mmol) in 5 ml solvent was added over a period of 45 to 60 min. When pentane or cyclohexane were used as solvent, the amounts were 10 and 15 ml, respectively. After refluxing for an additional 30 min. the reaction mixture was allowed to cool to room temperature, after which it was filtered through a 5-cm plug of Silica 60. The product and excess of olefin were washed from the plug with dichloromethane (25 ml) and ethyl acetate (6 ml), respectively. The catalyst was washed from the plug with additional ethyl acetate. The product was then purified by flash chromatography and obtained as a colorless oil which solidified after some time at 4 °C.

Methyl 2-methyl-1,2-diphenyl-cyclopropane-1-carboxylate

E-isomer: R_f: 0.1 (hexane:ethyl acetate, 25:1, *v/v*). ^1H NMR ($CDCl_3$): δ 7.25-6.97 (m, 10H, 2 Ph), 3.70 (s, 3H, $COOCH_3$), 2.02 (AB quartet, 2H, CH_2), 1.67 (s, 3H CH_3). IR (CCl_4): σ 1718 (s, $COOCH_3$), 692 (monosubstituted phenyl).

Z-isomer: R_f: 0.07 (hexane:ethyl acetate, 25:1, *v/v*). ^1H NMR ($CDCl_3$): δ 7.55-7.05 (m, 10H, 2 Ph), 3.19 (s, 3H, CO_2CH_3), 2.47 (d, 1H, CH_2), 1.46 (d, 1H, CH_2), 1.12 (s, 3H, CH_3). IR (CCl_4): σ 1721 (s, $COOCH_3$), 700 (monosubstituted phenyl).

Methyl 1,2-diphenyl-cyclopropane-1-carboxylate (E-isomer)

R_f: 0.21 (hexane:ethyl acetate, 15:1, *v/v*). ^1H NMR ($CDCl_3$): δ 7.30-6.71 (m, 10H, 2 Ph), 3.66 (s, 3H, $COOCH_3$), 3.12 (dd, 1H, CHPh), 2.14 and 1.88 (dd, 2H, CH_2). IR (CCl_4): σ 1718 (s, $COOCH_3$), 695 (monosubstituted phenyl).

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