Asymmetric aldol reaction of 2-cyanopropionates catalysed by *trans*-chelating chiral diphosphine ligand TRAP–rhodium(I) complex

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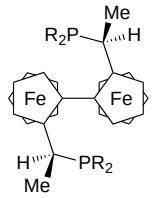
***trans*-Chelating chiral diphosphine TRAP ligands bearing *P*-aromatic groups are effective for Rh^{I}-catalysed asymmetric aldol reaction of 2-cyanopropionates with an aldehyde to give the corresponding aldol adduct with up to 93% ee.**

The asymmetric aldol reaction provides a most useful tool for stereoselective construction of α-substituted β-hydroxy carbonyl units with vicinal chiral centres, and is widely used in the synthesis of complex organic molecules.[1] Recently, it was found that some low-valent transition metal complexes catalyse aldol and Michael reactions with cyano compounds having active α-methylene groups,[2] and we developed a highly enantioselective Michael reaction of 2-cyanopropionates catalysed by a rhodium(I) complex coordinated with *trans*-chelating chiral diphosphine TRAP (**1**).[3–6] The transition metal



(*S*,*S*)-(*R*,*R*)-TRAP

1a R = Ph (PhTRAP)
b R = *p*-MeO-C_6H_4
c R = *p*-Cl-C_6H_4
d R = Pr^{i}
e R = Pr

catalysed reactions involve enolate intermediates of 2-cyanopropionates coordinating to the metal atom through the cyano nitrogen, which then react directly with electrophiles.[2] Herein, we report the catalytic asymmetric aldol reaction of 2-cyanopropionates **2** using a TRAP–Rh^{I} complex.

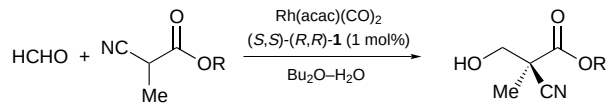
Asymmetric aldol reactions of **2** with paraformaldehyde (10 wt% in water) were carried out with a rhodium(I) catalyst generated *in situ* from Rh(acac)$(CO)_2$ and (*S*,*S*)-(*R*,*R*)-PhTRAP **1a** (Table 1).‡ The enantioselectivity of the asymmetric aldol reaction was heavily dependant upon reaction solvent. Bu_2O was the solvent of choice.§ Bulky ester groups of **2** are essential to attain high enantioselectivities for the aldol reactions (entries 1–5). 2-Cyanopropionates **2d** and **2e** bearing bulky secondary alkyl ester group gave aldol adducts (*S*)-**3d** and (*S*)-**3e** in 91 and 93% ee, respectively. Surprisingly, use of formalin hardly affected the enantiopurity of **3d** (93% ee). The enantioselectivity of the aldol reaction of **2d** was slightly increased by using **1b**, which has electron-donating aromatic groups attached to the phosphorus atoms (entry 6), while electron-withdrawing substituents on the *P*-aromatics group gave lower enantioselectivity and reactivity (entry 7). Conceivably, the *P*-aromatic substituents of TRAP play an important role in the enantioface selection of enolate of **2** coordinated to the rhodium atom, because ligands **1d** and **1e** with *P*-aliphatic substituents showed lower enantioselectivities (entries 8 and 9).

Other aldehydes **4a**–**d** were subjected to asymmetric aldol reaction with (*S*,*S*)-(*R*,*R*)-PhTRAP–Rh^{I} catalyst (Table 2). The aldol reactions of ethyl ester **2b** and isopropyl ester **2c** with acetaldehyde **4a** resulted in not only low enantioselectivities but also low diastereoselectivities (entries 1 and 2). However, the use of **2d** gave *anti*-(2*S*,3*S*)-**7a** (86% ee) with good *anti*-selectivity (*anti* : *syn* = 81 : 19) (entry 3). The aldol reaction of **2d** with **4b** proceeded, but with lower stereoselectivity (entry 4). Benzaldehyde **4c** did not react at all (entry 5). However, aldehyde **4d** smoothly reacted with **2d** giving a mixture of *anti*-(2*S*,3*R*)-**7d** (91% ee) and *syn*-(2*S*,3*S*)-**7d** (63% ee) in a ratio of 68 : 32 (entry 6).

The observed stereochemistry at the 2-position of the aldol products suggests that (*S*,*S*)-(*R*,*R*)-PhTRAP on the catalyst can differentiate between the steric bulkiness of the α-Me and ester substituents of **2**, with one of the *P*-phenyl substituents blocking the approach of the aldehyde to the *si*-face of the enolate coordinated to the rhodium atom.[4] The preferential formation of *anti*-**7** in the aldol reactions of **2d** with **4** may suggest that this reaction proceeded through antiperiplanar transition state **TS1**, which avoids the steric repulsion between the aldehyde substituent (R) and the bulky $CHPr^{i}_2$ ester (Fig. 1). The lack of diasereoselectivity in the reactions with **2b** and **2c** may be due to the lesser steric repulsion between the R and ester groups, which does not produce any enantioface selection by the aldehyde. Synclinal transition state **TS2** giving an *anti*-aldol would be sterically unfavourable due to the steric interaction between R and one of *P*-phenyl groups of **1a**.

In conclusion, we have accomplished the highly enantioselective aldol reaction of **2** with some aldehydes. Further studies are currently in progress to improve the catalyst's efficiency and to widen its applicability to a variety of aldehydes.

Table 1 Asymmetric aldol reaction of **2** with formaldehyde catalysed by **1**–Rh^{I} complex[a]



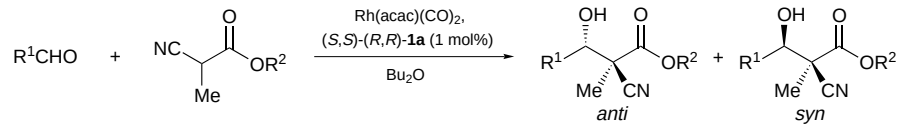
2a R = Me
b R = Et
c R = Pr^{i}
d R = $CHPr^{i}_2$
e R = $CHBu^{t}_2$

3a R = Me
b R = Et
c R = Pr^{i}
d R = $CHPr^{i}_2$
e R = $CHBu^{t}_2$

					Products **3**	
Entry	**2**	TRAP (**1**)[b]	*T*/°C	*t*/h	Yield (%)[c]	Ee (%)[d,e]
1	**2a**	**1a**	−30	100	67	35
2	**2b**	**1a**	−30	42	85	74 (−)
3	**2c**	**1a**	−30	90	86	78 (−)
4	**2d**	**1a**	−10	24	82	91 (−)
5	**2e**	**1a**	−10	24	86	93 (−)
6	**2d**	**1b**	−10	24	87	92 (−)
7	**2d**	**1c**	−10	24	44	74 (−)
8	**2d**	**1d**	−10	24	58	3 (−)
9	**2d**	**1e**	−10	24	86	22 (−)

[a] All reactions were carried out in Bu_2O. **2** (0.50 M)–formaldehyde–Rh(acac)$(CO)_2$–**1** = 1 : 1.3 : 0.010 : 0.011. [b] (*S*,*S*)-(*R*,*R*)-**1** was used. [c] Isolated yield. [d] Determined by HPLC analysis. [e] The sign of the specific rotation of **3** in $CHCl_3$ is given in parentheses.

Table 2 Asymmetric aldol reaction of **2** with **4** catalysed by (*S*,*S*)-(*R*,*R*)-**1a**–Rh[I] complex[a]



4a R^1 = Me **2b** R = Et
b R^1 = Et **c** R = Pr^i
c R^1 = Ph **d** R = $CHPr^i_2$
d R^1 = CO_2Et

5 R^1 = Me, R^2 = Et
6 R^1 = Me, R^2 = Pr^i
7a–d R^1 = Me, Et, Ph, CO_2Et, R^2 = $CHPr^i_2$

								Ee (%)[d] (config.)	
Entry	**4**	**2**	*T*/°C	*t*/h	Product	Yield (%)[b]	*anti* : *syn*[c]	*anti*	*syn*
1	**4a**	**2b**	0	24	**5**	63	45/55	31	23
2	**4a**	**2c**	0	24	**6**	61	47/53	55	50
3	**4a**	**2d**	0	24	**7a**	67	81/19	86 (2*S*,3*S*)	33
4	**4b**[e]	**2d**	0	48	**7b**	76	75/25	57 (2*S*,3*S*)	10
5	**4c**	**2d**	20	72	No reaction		—	—	—
6	**4d**[f]	**2d**	0	40	**7d**	88	68/32	91 (2*S*,3*R*)	63 (2*S*,3*S*)

[a] All reactions were carried out in Bu_2O. **2** (0.25 M)–**4**–Rh(acac)$(CO)_2$–**1a** = 1 : 7.5 : 0.010 : 0.011 unless otherwise noted. [b] Isolated yield of a mixture of *anti*- and *syn*-aldols. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] 10 equiv. of **4b** was used. [f] 2.0 equiv. of **4d** was used.

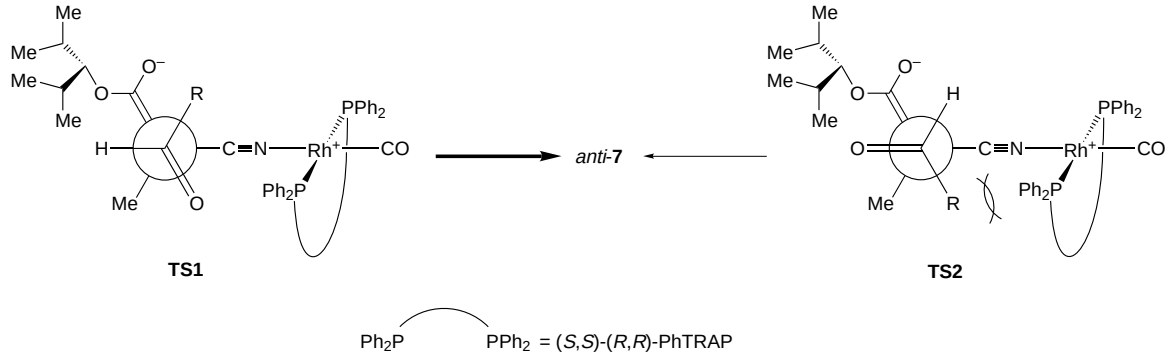


Fig. 1

Footnotes and References

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‡ *Typical procedure*: A suspension of paraformaldehyde (100 mg) in H_2O (1.0 ml) was heated under reflux for 1 h, giving a clear aqueous solution of paraformaldehyde. A solution of Rh(acac)$(CO)_2$ (5.0 μmol) and (*S*,*S*)-(*R*,*R*)-**1a** (5.4 μmol) in 2.0 ml of Bu_2O was stirred at room temperature for 10 min. To the solution was successively added **2** (0.50 mmol) and the freshly prepared solution of paraformaldehyde in water (0.67 mmol) at −10 °C. The mixture was stirred at −10 °C. After completion of the reaction, the mixture was diluted with brine, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. After passing through a short silica gel column (EtOAc), the residue was purified *via* medium-pressure liquid chromatography MPLC.
§ The enantioselectivities of the aldol reactions of **2b** at 0 °C in various solvents were as follows: MeOH: 0; CH_2Cl_2: 11; toluene: 1; THF: 47; Et_2O: 54; Bu_2O: 60% ee.

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