Chiral Induction by Cinchona Alkaloids in the Rhodium(II) Catalyzed O–H Insertion Reaction

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Cinchona alkaloids are effective additives for enantioselective O–H insertion of α-phenyldiazoacetate and water by rhodium(II) complexes. Addition of silica gel promotes O–H insertion in the reaction rate and the reaction proceeds smoothly at less than the freezing point of water, *e.g.*, −10 °C, and provided mandelate in up to 50% ee. The results reported here are the highest asymmetric inductions obtained to date for O–H insertions *via* a Rh-carbenoid.

Key words O–H insertion; enantioselective; rhodium(II); cinchona alkaloid; water

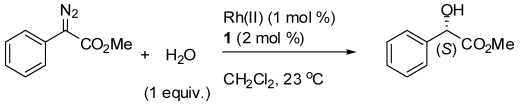
The catalytic insertion reaction into O–H bond with α-diazocarbonyl compounds *via* a metal-carbenoid intermediate is a very useful organic transformation for the synthesis of oxygen-containing compounds.[1—3] Remarkable advances, including enantioselective insertion, have been made in catalytic C–H insertions with α-diazocarbonyl compounds using Rh(II) complexes.[4—9] However, only limited success has been achieved for asymmetric insertions into O–H bond.[2,10—12] Recently, Fu and Zhou independently reported asymmetric insertion reactions into alcoholic,[13] phenolic[14] and aquatic[15] O–H bonds with α-diazoacetate using chiral Cu(I) complexes. In contrast, chiral Rh(II) complexes gave poor enantioselectivity (8% ee) in the O–H insertion reaction,[11] while they have given remarkable results in the C–H insertion reaction. Since Rh(II) complexes are unique and powerful catalysts in the insertion reaction, we attempted to apply them to the enantioselective O–H insertion reaction.

Recently, Liang *et al.* conducted a physicochemical approach to O–H insertion reactions using density functional theory (DFT).[10] They concluded that Rh(II) complex does not have enough affinity to the oxonium ylide intermediate to form firmly fixed stereocenter around the metal. Hence, we sought to design a novel approach to the enantioselective O–H insertion reaction catalyzed by Rh(II) complexes, independent of its own chirality. It is of interest that chiral amine additives expressed its own chirality on metal mediated epoxidation reaction using achiral Mn-salen complex.[16]

Accordingly, we envisaged that an intermolecular O–H insertion of α-aryldiazoacetate and water should produce a mandelate in an enantioselective manner using cinchona alkaloids and Rh(II) complexes. Using this method, we now report that a combination of quinine (**1**) or quinidine (**2**) and dirhodium(II) tetra(triphenylacetate), $Rh_2(TPA)_4$, in the O–H insertion provides mandelate as the sole product in up to 50% ee.

In our initial studies, we explored the intermolecular O–H insertion of methyl phenydiazoacetate in dichloromethane using 1 mol% of $Rh_2(TPA)_4$[17,18] and 2 mol% of quinine (**1**) (Table 1, entry 1).[19—22] As expected, the reaction proceeded smoothly at 23 °C to completion within 4 h, giving methyl mandelate in 82% yield. The enantioselectivity in this reaction was 38% ee, as determined by HPLC (Daicel Chiralcel OD-H). The preferred absolute stereochemistry was (*S*), which was established by comparing the sign of the optical rotation with the literature value.[23] It is worth noting that enantioselectivity for a particular product was provided by the cinchona alkaloids, not by the rhodium catalyst. The enantiomeric induction in this system may be due to the formation of a chiral complex between rhodium-carbenenoid and cinchona alkaoid. To rule out the possibility that the reaction was catalyzed by quinine (**1**), we performed the reaction under identical conditions in the absence of $Rh_2(TPA)_4$ and observed no background reaction. To further enhance the enantioselectivity, we evaluated the abilities of other dirhodium(II) carboxylate catalysts (Table 1, entries 2—5). While a uniform sense of asymmetric induction was observed in all cases, the enantioselectivities were lower than that of $Rh_2(TPA)_4$. The less reactive dirhodium(II) amidate catalyst, $Rh_2(cap)_4$, was not suitable for this transformation in terms of both chemical yield and enantiocontrol (Table 1, entry 6). Therefore, $Rh_2(TPA)_4$ was chosen as the optimum

Table 1. Intermolecular O–H Insertion Reaction of Methyl α-Diazophenylacetate with Water Using Rh(II) Complexes and Quinine (**1**)



Entry	Rh(II) complex	Time (h)	Yield (%)[a]	ee (%)[b]
1	$Rh_2(TPA)_4$	4	82	38
2	$Rh_2(OAc)_4$	28	59	34
3	$Rh_2(piv)_4$	2	80	31
4	$Rh_2(oct)_4$	22	73	32
5	$Rh_2(pfb)_4$	0.3	54	29
6	$Rh_2(cap)_4$	230	59	15

a) Isolated yield. *b*) Determined by HPLC (Daicel Chiralcel OD-H).

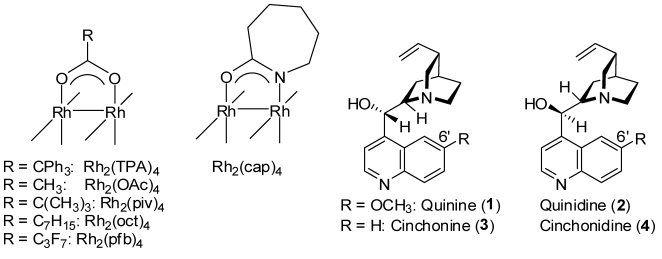


Fig. 1. Structures of Rh(II) Complexes and Cinchona Alkaloids

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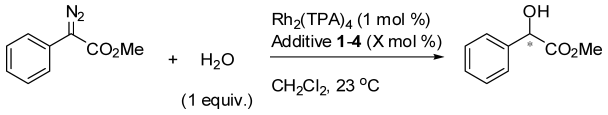
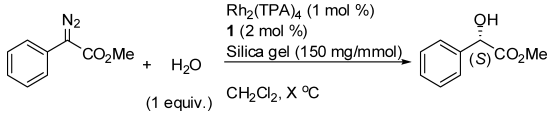
Table 2. Effects of Cinchona Alkaloids (**1**—**4**) and Their Quantities on Enantioselectivities



Entry	Additive	X (mol%)	Time (h)	Yield (%)[a]	ee (%)[b]	Confign.
1	**1**	2	4	82	38	*S*
2	**2**	2	23	80	38	*R*
3	**3**	2	15	84	30	*R*
4	**4**	2	45	77	27	*S*
5	**1**	No	0.3	30	rac	—
6	**1**	5	31	69	37	*S*
7	**1**	10	76	61	36	*S*

a) Isolated yield. *b*) Determined by HPLC (Daicel Chiralcel OD-H).

Table 3. Enantioselective O–H Insertion of α-Diazophenylacetate and Water with Silica Gel as a Solid Support



Entry	X (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	23	0.5	79	36
2	0	2	97	45
3[c]	0	56	86	45
4	−10	2	90	50
5	−20	4	89	46

a) Isolated yield. *b*) Determined by HPLC (Daicel Chiralcel OD-H). *c*) Silica gel was not used.

catalyst in terms of enantioselectivity, and was used for further study.[24]

We then investigated other cinchona alkaloids as additives and their optimal quantities. A clear *pseudo*-enantiomeric effect was observed for quinine (**1**) and quinidine (**2**) (Table 2, entries 1, 2). Structurally similar cinchona alkaloids, cinchonine (**3**) and cinchonidine (**4**), were not the additives of choice with respect to reaction rate and enantioselectivity (Table 2, entries 3, 4).[25] Interestingly, quinine (**1**) and cinchonine (**3**) afforded the opposite absolute configurations of the products. The only structural difference was the substituent on the 6′-methoxy group on quinoline ring, which suggests that the methoxy group affects the conformation of these cinchona alkaloids, which is important in terms of enantiomeric induction. Without quinine (**1**), no asymmetric induction was observed and the product yield was reduced as the formation of dimer and methyl benzoylformate (Table 2, entry 5).[26] With the amount of quinine (**1**) increased to 5 mol% and 10 mol%, similar enantiocontrol was observed, but chemical yields decreased to 69% and 61%, respectively (Table 2, entries 1 *vs.* 6, 7). The reactivity of the Rh(II) complex should be decreased by the coordination of the tertiary nitrogen in quinine (**1**) to the Rh(II) catalyst.

Next, we attempted to use silica gel in the O–H insertion reaction of α-phenyldioazoacetate and water. Silica gel is a good solid support for organic transformations.[27—30] In this reaction system, water was employed as a substrate, which limits the temperature to no less than 0 °C. Silica gel can absorb water molecules on its surface, thus its surface may serve to enhance the reaction rate at a temperature less than the freezing point of water. As expected, the reaction rate was 8 times faster at 23 °C without affecting the yield and enantioselectivity (Table 2, entry 1 *vs.* Table 3, entry 1). Further, the reaction proceeded smoothly at 0 °C to completion within 2 h, providing the product quantitatively in 45% ee (Table 3, entry 2). Without silica gel, 56 h was needed for completion of this transformation with a slight decrease in chemical yield (Table 3, entry 3). We were gratified to find that the enantioselectivity was further enhanced up to 50% ee by lowering the temperature to −10 °C without affecting the reaction rate (Table 3, entry 4). This result suggested that the reaction seems to be controlled by rather reaction kinetics than thermodynamics. However, as the reaction temperature was further decreased to −20 °C, enantioselectivity of the product dropped to 46% (Table 3, entry 5).

In summary, we have developed a highly efficient method for the catalytic enantioselective O–H insertion reaction of α-phenyldiazoacetate. The enantioselectivity of 50% is the highest achieved in Rh(II) catalyzed O–H insertion reactions to date. While the mechanism of Rh(II) complex/cinchona alkaloid catalyzed O–H insertion reactions remains unclear, it is apparent that the enantioselectivity is substantially influenced by the stereochemistry of the cinchona alkaloids. Further studies on substituent effects as well as the design of chiral additives to further enhance enantioselectivity are currently underway in our laboratories.

Experimental

General Procedure for the Preparation of (*S*)-Methyl Mandelate[23] (Table 3, Entry 4) To a solution of $Rh_2(TPA)_4$ (2.8 mg, 0.002 mmol) and quinine (1.3 mg, 0.004 mmol) in CH_2Cl_2 (1 ml) was added silica gel (30 mg, Wako gel® C-200) and H_2O (3.6 μl, 0.20 mmol). A solution of methyl 2-diazo-2-phenylacetate (36 mg, 0.20 mmol) in CH_2Cl_2 (1 ml) was added to the reaction mixture at −10 °C. After stirring at the same temperature for 2 h, filtration and evaporation *in vacuo* furnished the crude product, which was purified by preparative TLC (3 : 1 hexane/EtOAc) to provide methyl mandelate (30 mg, 90%) as a colorless needle. The enantiomeric excess was determined by HPLC with a chiral stationary phase column.

Rf=0.15 (5 : 1 hexane/EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 3.43 (1H, d, J=5.5 Hz), 3.76 (3H, s), 5.18 (1H, d, J=5.5 Hz), 7.33—7.43 (5H, m). $[\alpha]_D^{22}$ +82.0 (c=1.2, $CHCl_3$) for 50% ee [lit.,[23] $[\alpha]_D^{20}$ +180.5 (c=1.3, $CHCl_3$) for 97.1% ee of (*S*)-form]. HPLC t_R (major enantiomer)=8.2 min (74.8%); t_R (minor enantiomer)=12.1 min (25.2%) (Daicel Chiralcel OD-H, 9 : 1 hexane/^{i}PrOH, 1.0 ml/min, detection 254 nm).

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References and Notes

1) Ye T., McKervey M. A., *Chem. Rev.*, **94**, 1091—1160 (1994).
2) Doyle M. P., McKervey M. A., Ye T., "Modern Catalytic Methods for Organic Synthesis with Diazo Compounds," Wiley-Interscience, New York, 1998, pp. 433—486.
3) Miller D. J., Moody C. J., *Tetrahedron*, **51**, 10811—10843 (1995).
4) Doyle M. P., Forbes D. C., *Chem. Rev.*, **98**, 911—936 (1998).
5) Sulikowski G. A., Cha K. L., Sulikowski M. M., *Tetrahedron: Asymmetry*, **9**, 3145—3169 (1998).
6) Doyle M. P., "Catalytic Asymmetric Synthesis," ed. by Ojima I.,

Wiley-VCH, New York, 2000, pp. 191—228.
7) Davies H. M. L., Manning J. R., *Nature* (London), **451**, 417—424 (2008).
8) Saito H., Oishi H., Kitagaki S., Nakamura S., Anada M., Hashimoto S., *Org. Lett.*, **4**, 3887—3890 (2002).
9) Minami K., Saito H., Tsutsui H., Nambu H., Anada M., Hashimoto S., *Adv. Synth. Catal.*, **347**, 1483—1487 (2005).
10) Liang Y., Zhou H., Yu Z.-X., *J. Am. Chem. Soc.*, **131**, 17783—17785 (2009).
11) Bulugahapitiya P., Landais Y., Parra-Rapado L., Planchenault D., Weber V., *J. Org. Chem.*, **62**, 1630—1641 (1997).
12) Li Z., Davies H. M. L., *J. Am. Chem. Soc.*, **132**, 396—401 (2010).
13) Maier T. C., Fu G. C., *J. Am. Chem. Soc.*, **128**, 4594—4595 (2006).
14) Chen C., Zhu S.-F., Liu B., Wang L.-X., Zhou Q.-L., *J. Am. Chem. Soc.*, **129**, 12616—12617 (2007).
15) Zhu S.-F., Chen C., Cai Y., Zhou Q.-L., *Angew. Chem. Int. Ed.*, **47**, 932—934 (2008).
16) Hashihayata T., Ito Y., Katsuki T., *Tetrahedron*, **53**, 9541—9552 (1997).
17) Hashimoto S., Watanabe N., Ikegami S., *J. Chem. Soc., Chem. Commun*, 1508—1510 (1992).
18) Hashimoto S., Watanabe N., Ikegami S., *Tetrahedron Lett.*, **33**, 2709—2712 (1992).
19) Nelson and co-workers reported that the properties of Rh(II) catalysts could be modified by the presence of additives such as tetramethyl urea or Hünig's base for intermolecular O–H insertion reactions, see: Nelson T. D., Song Z. J., Thompson A. S., Zhao M., DeMarco A., Reamer R. A., Huntington M. F., Grabowski E. J. J., Reider P. J., *Tetrahedron Lett.*, **41**, 1877—1881 (2000).
20) Doyle and co-workers reported that the enantioselective [2+2]-cycloaddition reaction between ethyl glyoxylate and trimethylsilylketene in the presence of 1 mol% of chiral dirhodium(II) carboxamidates and 10 mol% of quinine gave β-lactone derivative in up to 99% ee, see: Forslund R. E., Cain J., Colyer J., Doyle M. P., *Adv. Synth. Catal.*, **347**, 87—92 (2005).
21) For examples of enantioselective transformation using achiral dirhodium(II) carboxylates and chiral co-catalysts, see: Suga H., Inoue K., Inoue S., Kakehi A., *J. Am. Chem. Soc.*, **124**, 14836—14837 (2002).
22) Hu W., Xu X., Zhou J., Liu W.-J., Huang H., Hu J. Yang L., Gong L. -Z., *J. Am. Chem. Soc.*, **130**, 7782—7783 (2008).
23) Wang C.-J., Sun X., Zhang X., *Synlett*, **2006**, 1169—1172 (2006).
24) We also investigated a combination of 1 mol% of $Rh_2(TPA)_4$ and 2 mol% of quinine for O–H insertion reaction between methyl phenyldiazoacetate and methanol, ethanol, isopropyl alcohol and phenol. Reaction times, chemical yields and enantioselectivities as follows; MeOH, 5 h, 13%, 34% ee; EtOH, 4.5 h, 18%, 36% ee; ^{i}PrOH, 5 h, 31%, 37% ee, PhOH, 3.5 h, 64%, 1% ee.
25) Reaction times, chemical yields and enantioselectivities obtained with other chiral additives are as follows: (−)-sparteine, 0.5 h, 50%, 3% ee (*R*); brucine, 22 h, 72%, 5% ee (*S*).
26) Lu C.-D., Liu H., Chen Z.-Y., Hu W.-H., Mi A.-Q., *Chem. Commun.*, 2624—2626 (2005).
27) Kumar K. H., Muralidharan D., Perumal P. T., *Synthesis*, **2004**, 63—68 (2004).
28) Basu B., Das P., Hossain I., *Synlett*, **2004**, 2630—2632 (2004).
29) Sekimura N., Saito H., Miyairi S., Takabatake T., *Heterocycles*, **65**, 1589—1600 (2005).
30) Sumiyoshi Y., Saito H., Miyairi S., Takabatake T., *Heterocycles*, **78**, 905—909 (2009).