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Enhancement of Enantioselectivity in Intramolecular C-H Insertion Reactions of α-Diazo β-Keto Esters Catalyzed by Chiral Dirhodium(II) Carboxylates†

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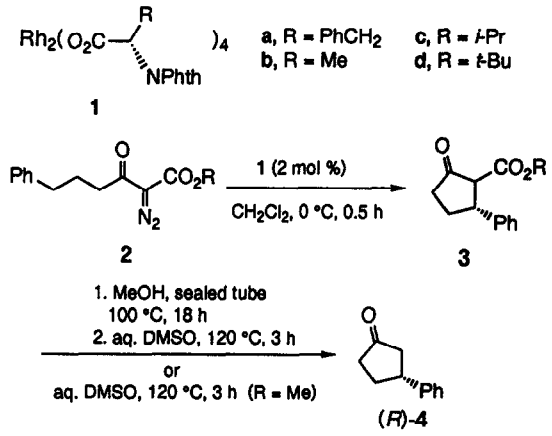
Abstract: The enantioselectivity in intramolecular C-H insertion reactions of α-diazo β-keto esters catalyzed by dirhodium(II) tetrakis[N-phthaloyl-(S)-phenylalaninate] was found to be substantially improved by evaluation of the alkoxy group of the ester moiety. Cyclization of α-diazo β-keto 2,4-dimethyl-3-pentyl esters was promoted by this catalyst to afford, after a removal of the ester group, optically active 3-substituted cyclopentanones of up to 76% ee.

The development of catalytic, asymmetric C-C bond forming reactions promoted by chiral metal complexes is one of the most important and challenging goals in organic synthesis.[3] Considering that dirhodium(II) complexes-catalyzed intramolecular C-H insertion reaction of α-diazo carbonyl compounds, featured by C-C bond formation at an unactivated carbon atom, offers a potentially powerful tool for the construction of both carbocycles and heterocycles,[4] the development of the enantioselective version of this reaction catalyzed by chiral dirhodium(II) complexes should be a significant addition to the field of asymmetric synthesis. We and other groups have recently reported that chiral dirhodium(II) carboxylates or carboxamides catalyze intramolecular C-H insertion reactions of α-diazo β-keto esters and an α-diazo β-keto sulfone to afford optically active 3-substituted cyclopentanones, albeit with modest levels of enantioselectivity (10-46% ee).[5-8] We now wish to report that the enantioselectivity of intramolecular C-H insertion reactions of α-diazo β-keto esters catalyzed by dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate] can be substantially improved by evaluation of the alkoxy group of the ester moiety as well as the substituent adjacent to the target C-H bond, wherein optically active 3-substituted cyclopentanones of up to 76% ee are attained.

Based on the previous preliminary results,[5] we explored the factors to influence the enantioselectivity through cyclization of α-diazo β-keto esters **2** bearing a phenyl group adjacent to the target C-H bond (Scheme 1). At the outset, we screened chiral dirhodium(II) carboxylates **1**[9] derived from a range of *N*-phthaloyl amino acids with the methyl ester **2a**, however, little variation in enantioselectivities was observed (40-46% ee). Thus we chose the most readily prepared dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate] (**1a**)[10] as a chiral catalyst, the superiority of which was later disclosed (*vide infra*). Knowing that the ester moiety such as Me, Et, *i*-Pr, or *t*-Bu esters showed little influences on the enantioselectivity (41-46% ee), our interest was focused on a double asymmetric induction.[11,12] Intramolecular C-H insertion reaction of chiral α-diazo β-keto ester **2c** of (+)-neomenthol was effected at 0 °C with 2 mol % of **1a** or *ent*-**1a** to afford the cyclic β-keto ester **3c** as a diastereomeric mixture. The sense and extent of the diastereotopic selection at the insertion site were determined by its transformation [(1) MeOH, sealed tube, 100 °C, 18 h; (2) aq. DMSO, 120 °C, 3h] to the known 3-phenylcyclopentanone (**4**).[13] While the matched pair of **2c** and *ent*-**1a** produced (*S*)-**4** in 80% ee, we were very

†This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 77th birthday.

Scheme 1



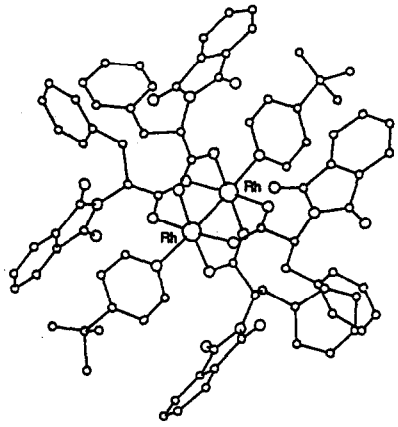


Figure 1. Ball-and-stick representation of $1a{\cdot}2C_9H_{13}N$

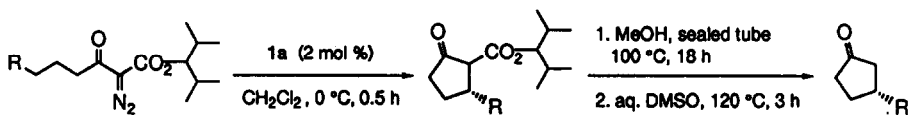
Table 1. Effects of the Ester Group and Ligand on the Enantioselectivity in Dirhodium(II) Carboxylate-Catalyzed Intramolecular C-H Insertion of α-Diazo β-Keto Esters 2[a]

	substrate 2		Rh(II)	β-keto ester 3[b]	product 4	
entry		R	catalyst	% yield[c]	% ee[d]	confign
1	a	Me	**1a**	96	46	*R*
2	b	*t*-Bu	**1a**	60	45	*R*
3	c	(+)-neomenthyl	**1a**	78	53	*R*
4	c	(+)-neomenthyl	*ent*-**1a**	79	80	*S*
5	d	*t*-$BuCH_2$	**1a**	71	57	*R*
6	e	*c*-C_6H_{11}	**1a**	91	56	*R*
7	f	Et_2CH	**1a**	86	62	*R*
8	g	*i*-Pr_2CH	**1a**	86	76	*R*
9	g	*i*-Pr_2CH	*ent*-**1a**	88	73	*S*
10	h	*i*-Pr_2CMe	**1a**	57	75	*R*
11	i	*t*-Bu_2CH	**1a**	68	76	*R*
12	j	(*i*-$PrMe_2C)_2CH$	**1a**	76	74	*R*
13	g	*i*-Pr_2CH	**1b**	80	63 (43)[e]	*R*
14	g	*i*-Pr_2CH	**1c**	85	64 (40)[e]	*R*
15	g	*i*-Pr_2CH	**1d**	67	53 (40)[e]	*R*

[a] The following procedure is representative (entry 8): the bis(ethyl acetate) adduct of **1a** (38 mg, 0.024 mmol) was added in one portion to a stirred solution of **2g** (400 mg, 1.21 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under an argon atmosphere. After 0.5 h, the mixture was concentrated in vacuo, and chromatographed on silica gel to afford **3g** (314 mg, 86%) as white solid. A solution of **3g** (300 mg, 0.99 mmol) in MeOH (8 mL) was heated at 100 °C in a sealed tube for 18 h. Concentration of the resulting mixture was followed by chromatography to give the corresponding methyl ester **3a** (196 mg, 91%), which was treated with 10% aqueous DMSO (3.2 mL) at 120 °C for 3 h. Conventional workup followed by chromatography provided (*R*)-**4** (129 mg, 94%) as a colorless oil: $[\alpha]^{23}_D$ +69.4° (*c* 1.07, $CHCl_3$). [b] A mixture of the keto and enol forms. [c] Isolated yields. [d] Determined by analysis of ^{13}C NMR spectrum of the diastereomeric ketals prepared from the ketone **4** and (2*R*,3*R*)-2,3-butanediol: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* 1977, 2183. The value is virtually consistent with the rotation value based on $[\alpha]^{23}_D$ -93.6° (*c* 1.15, $CHCl_3$) for (*S*)-**4**; see ref 13. [e] The values in parentheses were obtained with the corresponding methyl esters.

surprised to find that even the mismatched pair of **2c** and **1a** led to the formation of (*R*)-**4** in 53% ee, higher than the value obtained with the foregoing esters.[14] Furthermore, from the fact that the preferred absolute configuration at the insertion site was dependent on the chirality of the catalyst used rather than that of (+)-neomenthol, it was suggested that the steric bulk of the ester moiety might amplify the chiral recognition ability of the catalyst, though such was not the case with the foregoing esters. Thus we reinvestigated the effects of an achiral alkoxy group in the ester moiety on enantioselectivities. Some representative results highlighted in Table 1 deserve some comments. (1) To our surprise, α-diazo β-keto esters **2d-f** of 2,2-dimethyl-1-propanol, cyclohexanol, and 3-pentanol, less hindered alcohols than *tert*-butyl alcohol, exhibited higher enantioselectivities than **2b** (entry 2 vs 5-7). (2) Successive substitution of 3-pentanol with a methyl group greatly enhanced the enantioselectivity up to 76% ee (entries 8-12). (3) However, even more sterically demanding ester **2j** of 2,3,3,5,5,6-hexamethyl-4-heptanol showed no more increased selectivity than the ester **2g** of 2,4-dimethyl-3-pentanol (entry 12). Although the last point still remains open to question, these findings clearly demonstrate that the steric shielding at both positions β and β' to the hydroxy group is crucial to the high enantioselectivity.[15] Eventually, we assessed the 2,4-dimethyl-3-pentyl ester as the ester of choice from the standpoint of cyclization yield and practicality. Here again, we tried to evaluate the catalysts **1** through cyclization of **2g**. It has now been disclosed that the dirhodium(II) catalyst **1a** (or *ent*-**1a**) is among the most effective (entries 8 and 9 vs 13-15).

Table 2. Substituent Effects on the Enantioselectivity in Intramolecular C-H Insertion of α-Diazo β-Keto 2,4-Dimethyl-3-pentyl Esters Promoted by Dirhodium(II) Catalyst **1a**



	substrate	β-keto ester	3-substituted cyclopentanone			
entry	R	% yield[a]	% yield	$[\alpha]^{22}_D$ (*c*, solvent)	% ee[b]	config[c]
1	Me	71	63[d]	+49.3° (1.12, MeOH)	32 (24)[e]	*R*
2	*n*-C_5H_{11}	76	86	+41.6° (1.31, $CHCl_3$)	35 (29)[e]	*R*
3	CH_2=CH	63	61[d]	+73.4° (1.20, $CHCl_3$)	53 (38)[e]	*R*
4	Ph	86	81	+69.4° (1.42, $CHCl_3$)	76 (46)[e]	*R*
5	2-naphthyl	75	72	+41.1° (1.25, $CHCl_3$)	64 (39)[e]	—[f]

[a] Isolated yields. [b] Determined by analysis of ^{13}C NMR spectrum of the diastereomeric ketals prepared from the ketone and (2*R*,3*R*)-2,3-butanediol. [c] Determined by comparison of the sign of optical rotation. [d] Lower yields are probably due to the high volatility of the products. [e] The values in parentheses were obtained with the corresponding methyl esters; see ref 5. [f] Not determined.

To demonstrate an applicability of the steric effect of the ester moiety as an enantiocontrol element, we next examined cyclizations of α-diazo β-keto 2,4-dimethyl-3-pentyl esters possessing other substituents than a phenyl group at the insertion site. The results are summarized in Table 2. As was the case with **2g**, the catalysis of the α-diazo β-keto 2,4-dimethyl-3-pentyl esters involving enantiotopic differentiation of aliphatic or allylic methylene C-H bonds exhibited much higher selectivities than that of the corresponding methyl esters. While the consistent sense of enantioselection was observed with the catalyst **1a** regardless of the R substituents, it is of interest to note that the substituent effects on enantioselectivities were more pronounced with the aryl and vinyl groups (entries 1 and 2 vs 3-5).[16]

While the mechanism of dirhodium(II) complexes-catalyzed C-H insertion reactions remains presently unclear, it is apparent that enantioselectivity is substantially influenced by both steric and electronic factors imparted on the substrate as well as the structure of the carboxylate ligand. Further studies on substituent effects as well as the design of chiral ligands to further enhance enantioselectivity are currently in progress.[17]

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8. More recently, it has been reported that the degree of enantioselectivity can be greatly optimized with some heterocycles, wherein asymmetric synthesis of 3-alkoxy-γ-lactones and chromanones has been achieved with up to 91% ee and 82% ee, respectively: (a) Doyle, M. P.; Oeveren, A. V.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W. Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982. (b) Mckervey, M. A.; Ye, T. *J. Chem. Soc., Chem. Commun.* **1992**, 823.
9. The rhodium(II) complexes 1 slowly picked up water from the laboratory atmosphere. For this reason, the bis(ethyl acetate) adducts of 1 were used throughout the present experiments. It was confirmed that these adducts showed virtually the same reactivities and enantioselectivities as 1.
10. The structure of 1a was established as the bis(4-*tert*-butylpyridine) adduct by a single-crystal X-ray analysis, the drawing of which is presented in Figure 1. The notable feature is that two phthalimido groups in a pair of adjoining ligands are oriented to an axial position of the distorted octahedral geometry around each rhodium, the reaction site with α-diazo compounds. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center.
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13. The $[\alpha]^{25}_D$ value for the optically pure (*S*)-4 was reported to be -84.9° (*c* 0.72, $CHCl_3$): Paquette, L. A.; Gilday, J. P.; Ra, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6858 and references cited therein. We have found that the optically pure (*R*)- and (*S*)-4 exhibit $[\alpha]^{23}_D$ +93.2° (*c* 1.10, $CHCl_3$) and -93.6° (*c* 1.15, $CHCl_3$), respectively, which were derived from diastereomerically pure β-keto esters obtained by transesterification of methyl (±)-3-phenyl-2-oxo-cyclopentane-1-carboxylate with (-)-menthol and a subsequent separation.
14. $Rh_2(OAc)_4$-catalyzed cyclization of 2c furnished (*S*)-4 in 23% ee.
15. Although it has been demonstrated that diastereo- (*trans*/*cis* ratio) and enantioselectivity in catalytic, asymmetric cyclopropanation of olefins can be improved by increasing the steric bulk of the alcohol moiety of diazoacetates, such a dramatic effect on enantioselection has not previously been identified: (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1977**, 2599. (b) Nakamura, A.; Konishi, A.; Tsujitani, R.; Kudo, M.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3449. (c) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta.* **1988**, *71*, 1553. (d) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, *31*, 6613. (e) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (f) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
16. It is documented that phenyl and vinyl groups are inductively electron-withdrawing and so decrease the electron density of the adjacent C-H bond, rendering it reluctant to attack by the electrophilic rhodium-carbene species: Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. A remarkable enhancement of the enantioselectivities with the aryl and vinyl substituents might be associated with their electronic properties, though no rate reduction of cyclization was experimentally observed.

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