

Highly Enantio- and Diastereoselective Construction of 1,2-Disubstituted Cyclopentane Compounds by Dirhodium(II) Tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate]-Catalyzed C–H Insertion Reactions of α -Diazo Esters

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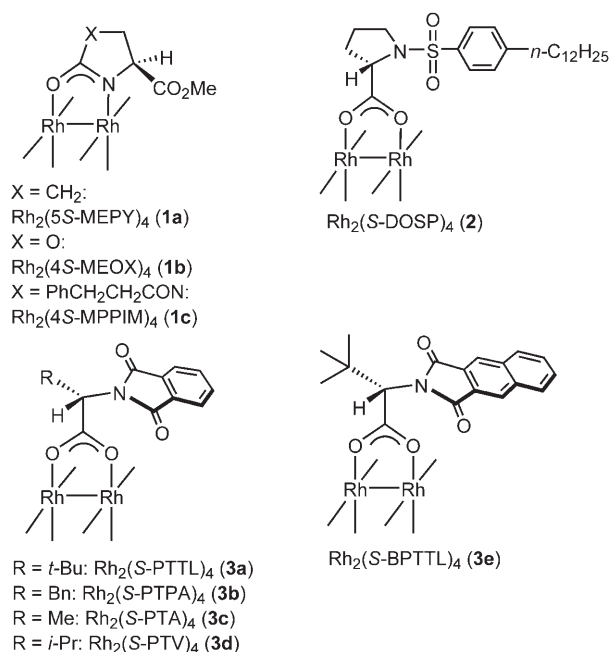
Dedicated to the memory of the late Professor Kenji Koga.

Abstract: A highly enantio- and diastereoselective intramolecular C–H insertion reaction of α -diazo esters has been achieved with the use of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] as a catalyst, providing exclusively *cis*-2-arylcyclopentane-1-carboxylates in up to 95% ee with no evidence of alkene formation.

Keywords: asymmetric catalysis; C–C bond formation; C–H insertion; chiral dirhodium(II) carboxylates; cyclization; α -diazo esters

$\text{Rh}_2(5S\text{-MEPY})_4$ (**1a**), $\text{Rh}_2(4S\text{-MEOX})_4$ (**1b**), and $\text{Rh}_2(4S\text{-MPPIM})_4$ (**1c**) is characteristic of intramolecular C–H insertion reactions of diazoacetates and diazoacetamides,^[4] while Davies' dirhodium(II) carboxylate catalysts such as $\text{Rh}_2(S\text{-DOSP})_4$ (**2**) are exceptionally effective for intermolecular C–H insertion reactions with aryl and arylvinyl diazoacetates when hydrocarbons are used as a solvent.^[5] Dirhodium(II) carboxylate catalysts developed in this laboratory, such as $\text{Rh}_2(S\text{-PTTL})_4$ (**3a**), $\text{Rh}_2(S\text{-PTPA})_4$ (**3b**), $\text{Rh}_2(S\text{-PTA})_4$ (**3c**) are especially well suited for intramolecular C–H insertion reactions of α -diazo- β -keto esters,^[6] α -methoxycarbonyl- α -diazo-

The development of catalytic enantioselective C–C bond forming reactions has been a subject of intensive investigation in the field of synthetic organic chemistry.^[1] Among the wide variety of transition metal complexes used to catalyze a broad spectrum of transformations of α -diazocarbonyl compounds, dirhodium(II) complexes have distinguished themselves as superior catalysts in C–H insertion reactions that form C–C bonds in which a new stereogenic center is created at an unactivated carbon atom.^[2] Over the past fifteen years, substantial progress has been made in the development of chiral dirhodium(II) carboxylate and carboxamidate complexes as catalysts for enantioselective intramolecular and even intermolecular C–H insertion reactions *via* a rhodium(II)-carbene intermediate (Scheme 1).^[3] A number of systems have been reported to provide enantioselectivities in greater than 90% ee; however, there still remains a need for additional development in terms of the scope with respect to the type of α -diazocarbonyl compounds. The salient ability of Doyle's dirhodium(II) carboxamidate catalysts such as



Scheme 1.

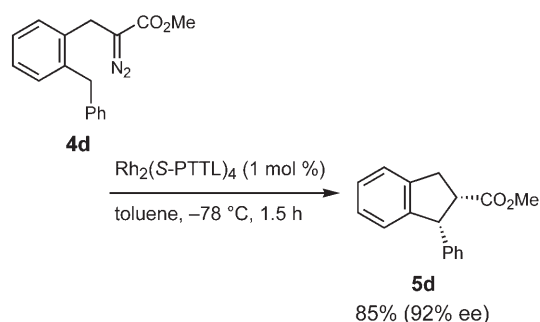
acetamides,^[7] and aryl diazoacetates.^[8] While the highest enantioselectivity in intramolecular C–H insertion reactions of α -diazo ketones remains 73% ee with the use of chiral *ortho*-metalated arylphosphine-dirhodium(II) catalysts developed by Lahuerta and Pérez-Prieto,^[9,10] enantioselective reactions of α -diazo esters (α -alkyl- α -diazoacetates) have remained unexplored. Herein we report the first successful example of an enantioselective intramolecular C–H insertion reaction of α -diazo esters, in which $\text{Rh}_2(\text{S-PTTL})_4$ (**3a**) provides *cis*-2-arylcyclopentane-1-carboxylates as the sole product in up to 95% ee.

Rhodium(II)-catalyzed intramolecular C–H insertion reactions of α -diazo esters, developed and extensively advanced by the Taber group, offer a powerful route to the production of substituted cyclopentanes^[11] and tetrahydrofurans^[12] in natural product synthesis. Since rhodium(II)-carbene intermediates, generated from α -diazo esters bearing a C–H bond adjacent to the diazo carbon, tend to form α,β -unsaturated esters *via* a 1,2-hydride shift,^[13] the efficiency of these reactions relies on the judicious choice of conditions in which β -hydride elimination can be suppressed and C–H insertion can be favored. Taber and Joshi recently reported that the ratio of C–H insertion to β -hydride elimination products is significantly influenced by the electronic nature and the steric bulk of the bridging ligands of dirhodium(II) catalysts.^[14] Compared with $\text{Rh}_2(\text{O}_2\text{CCH}_3)_4$, which generally favors C–H insertion, the use of $\text{Rh}_2(\text{O}_2\text{CCF}_3)_4$ with a more electron-withdrawing ligand would generate a more electrophilic and thus more reactive rhodium(II)-carbene intermediate that would greatly favor β -hydride elimination *via* an early transition state, while that of $\text{Rh}_2(\text{O}_2\text{CCPh}_3)_4$ with an exceptionally bulky ligand also increases the proportion of β -hydride elimination *via* an entropically less demanding pathway for steric reasons. In their studies, the finding that with $\text{Rh}_2(\text{S-PTPA})_4$ (**3b**), C–H insertion can compete effectively with β -hydride elimination is of particular interest, although asymmetric induction has not been explored.^[15]

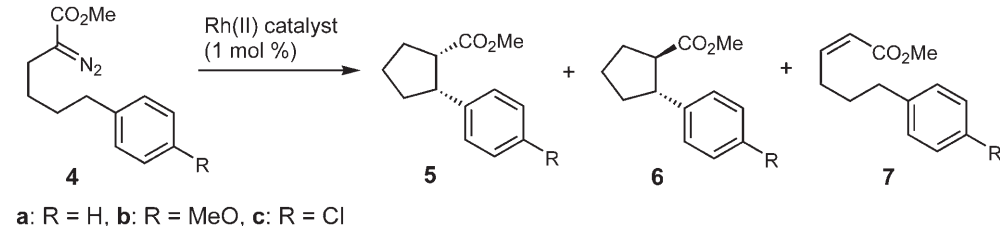
At the outset, we explored the intramolecular C–H insertion of methyl 2-diazo-6-phenylhexanoate (**4a**)^[16] in toluene using 1 mol % of $\text{Rh}_2(\text{S-PTTL})_4$ (**3a**). The reaction proceeded smoothly to completion at -78°C within 0.5 h, giving methyl *cis*-2-phenylcyclopentane-1-carboxylate (**5a**) as the sole product in 85% yield (Table 1, entry 1). Gratifyingly, no signs of *trans* isomer **6a** or alkene product **7a** could be detected in the crude reaction mixture by NMR spectroscopy. The enantioselectivity of this reaction was determined to be 95% by HPLC with a connected series of Daicel Chiralcel OJ-H and Chiralpak AS-H columns. The preferred absolute stereochemistry of **5a** $[[\alpha]_{\text{D}}^{25}: +98.8^\circ$ (*c* 1.12, CHCl_3) for 95% ee] was established as (1*S*,2*R*) by its transformation [(1) NaOMe, MeOH, reflux; (2) LiAlH_4 , THF, 0°C] to the known *trans*-2-phenylcyclopentane-1-methanol

$[[\alpha]_{\text{D}}^{25}: -44.3^\circ$ (*c* 1.20, MeOH); lit.,^[17] $[\alpha]_{\text{D}}^{25}: -48.9^\circ$ (*c* 1.2, MeOH) for the (1*R*,2*R*)-enantiomer]. Not unexpectedly, an increase in the reaction temperature was accompanied by a significant decrease in enantioselectivity as well as the formation of a large amount of (*Z*) alkene **7a**, but somewhat surprisingly, not even a trace of *trans* isomer **6a** could be detected (entries 2 and 3). A survey of solvents at -78°C revealed that toluene was the optimal solvent for this transformation. Although dichloromethane and ether exhibited essentially the same rate, enantioselectivity and *cis* selectivity as those found with toluene (95% and 94% ee, entries 4 and 5), the reactions in these solvents produced small amounts of (*Z*) alkene **7a**. Using toluene as the solvent, we next evaluated the abilities of other chiral dirhodium(II) carboxylates, $\text{Rh}_2(\text{S-PTPA})_4$ (**3b**), $\text{Rh}_2(\text{S-PTA})_4$ (**3c**), and $\text{Rh}_2(\text{S-PTV})_4$ (**3d**) (entries 6–8). Compared with catalysis by $\text{Rh}_2(\text{S-PTTL})_4$, reactions with these catalysts at -78°C required significantly longer times to reach completion. These reactions were also found to provide a mixture of *cis* and *trans* cyclopentane products **5a** and **6a** with **5a** as the major constituent, together with small amounts of (*Z*) alkene **7a**. While similar high levels of asymmetric induction as was found for $\text{Rh}_2(\text{S-PTTL})_4$ were maintained with the *cis* isomer **5a**, a sharp drop in enantioselectivity was observed with the *trans* isomer **6a**.^[18] Somewhat disappointingly, switching the catalyst from $\text{Rh}_2(\text{S-PTTL})_4$ to $\text{Rh}_2(\text{S-BPTTL})_4$ (**3e**)^[19] characterized by an extension of the phthalimido wall with one additional benzene ring had no beneficial effect in this system, and the *cis* cyclopentane product **5a** of 67% ee was obtained as the sole product (entry 9). Although no explanation for the advantage of $\text{Rh}_2(\text{S-PTTL})_4$ (**3a**) can presently be offered, **3a** proved to be the catalyst of choice for this transformation in terms of rate and selectivity, as well as product yield.^[20,21] As expected from the robust nature and high reactivity of **3a**, 0.05 mol % of **3a** was found to catalyze the reaction in 9 h without compromising either the yield or enantioselectivity (entry 10).

We then investigated the scope of this catalytic process with respect to the substituents at the insertion site. Aside from essentially complete *cis* selectivity, a high



Scheme 2.

Table 1. Enantioselective C–H insertion reactions of α -diazo esters **4** catalyzed by chiral dirhodium(II) carboxylates.^[a]


a: R = H, b: R = MeO, c: R = Cl

Entry	Substrate	R	Rh(II) catalyst	Solvent	T [°C]	Time [h]	Yield ^[b] [%]	5:6:7 ^[c]	ee [%] ^[d]	
									5	6
1	4a	H	Rh ₂ (S-PTTL) ₄ (3a)	toluene	–78	0.5	85	> 99:–:–	95	–
2	4a	H	Rh ₂ (S-PTTL) ₄ (3a)	toluene	–45	0.2	85	91:–:9	90 ^[e]	–
3	4a	H	Rh ₂ (S-PTTL) ₄ (3a)	toluene	0	0.1	80	82:–:18	81 ^[e]	–
4	4a	H	Rh ₂ (S-PTTL) ₄ (3a)	CH ₂ Cl ₂	–78	0.5	76	93:–:7	95 ^[e]	–
5	4a	H	Rh ₂ (S-PTTL) ₄ (3a)	ether	–78	0.5	73	97:–:3	94 ^[e]	–
6	4a	H	Rh ₂ (S-PTPA) ₄ (3b)	toluene	–78	7	73	56:37:07	89 ^[e]	27 ^[e, f]
7	4a	H	Rh ₂ (S-PTA) ₄ (3c)	toluene	–78	30	69	73:19:08	90 ^[e]	56 ^[e, f]
8	4a	H	Rh ₂ (S-PTV) ₄ (3d)	toluene	–78	6	80	77:20:03	95 ^[e]	22 ^[e, f]
9	4a	H	Rh ₂ (S-BPTTL) ₄ (3e)	toluene	–78	0.5	76	> 99:–:–	67	–
10 ^[g]	4a	H	Rh ₂ (S-PTTL) ₄ (3a)	toluene	–78	9	82	> 99:–:–	95	–
11	4b	MeO	Rh ₂ (S-PTTL) ₄ (3a)	toluene	–78	0.5	85	> 99:–:–	92	–
12	4c	Cl	Rh ₂ (S-PTTL) ₄ (3a)	toluene	–78	0.5	81	> 99:–:–	93	–

^[a] Typical procedure for C–H insertion reaction (entry 1): **3a**·2 EtOAc (2.8 mg, 0.002 mmol) was added to a solution of **4a** (46.5 mg, 0.20 mmol) in toluene (1.0 mL) at –78 °C. After 0.5 h, the mixture was concentrated and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 15:1).

^[b] Combined yield of **5**, **6** and **7**.

^[c] Determined by ¹H NMR analysis of the crude reaction mixture.

^[d] Determined by HPLC [column: Chiralcel OJ-H followed by Chiralpak AS-H, eluent: 100:1 hexane/*i*-PrOH, flow rate: 1.0 mL/min, detection: UV (254 nm)].

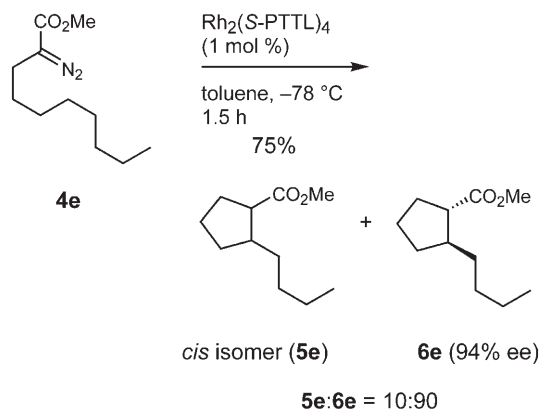
^[e] Determined after removal of (*Z*) alkene **7** by dihydroxylation [cat. OsO₄, NMO, *t*-BuOH-acetone-H₂O (1:4:2)].

^[f] Preferred absolute stereochemistry of **6a** was secured by HPLC comparison with (1*R*,2*R*)-**6a** prepared from (1*S*,2*R*)-**5a** (NaOMe, MeOH, reflux)^[18].

^[g] 0.05 mol % of **3a** was used.

enantioselectivity was consistently observed with either electron-donating or electron-withdrawing groups present at the *para* position on the benzene ring (92% and 93% ee, entries 11 and 12). Again, no evidence of alkene formation was observed. Catalyst **3a** was also found to catalyze the C–H insertion of α -diazo ester **4d** containing a benzene ring on the tether to give methyl *cis*-2,3-dihydro-1-phenyl-1*H*-indene-2-carboxylate (**5d**) {[α]_D²⁴: –69.3° (c 1.24, CHCl₃)] as the sole product in 85% yield with 92% ee (Scheme 2).^[22] On the other hand, the opposite diastereoselectivity was observed with **4e** bearing a butyl group at the insertion site, where the reaction afforded a 10:90 mixture of *cis* and *trans* cyclopentane products **5e** and **6e**, with no trace of alkene (Scheme 3). The sense and extent of asymmetric induction for *trans* isomer **6e** were determined to be (1*S*,2*S*) and 94% ee by HPLC, using a connected series of Daicel Chiralpak IA, Chiralcel OD-H (×2) and Chiralpak AD-H columns after conversion to the corresponding *p*-bromobenzoate [(1) LiAlH₄, THF, 0 °C; (2) *p*-bromobenzoyl chloride, cat. DMAP, pyridine, CH₂Cl₂, 0 °C].^[23] While

the reasons for the reversal of diastereo- and enantioselection are not clear at this time, it is noteworthy that high levels of asymmetric induction can be achieved regardless of the type of substituents at the insertion site.

**Scheme 3.**

In summary, we have developed the first highly enantio- and diastereoselective intramolecular C–H insertion reaction of α -diazo esters by using $\text{Rh}_2(\text{S-PTTL})_4$ as the catalyst, in which no evidence of α,β -unsaturated esters derived from a 1,2-hydride shift was observed. The present catalytic protocol provides an attractive and powerful access to optically active cyclopentane building blocks. Further studies on the scope of the reaction as well as mechanistic and stereochemical studies are currently in progress.

Experimental Section

Representative Procedure for the Intramolecular C–H Insertion (Entry 1 in Table 1)

$\text{Rh}_2(\text{S-PTTL})_4 \cdot 2 \text{ EtOAc}$ (2.8 mg, 0.002 mmol, 1 mol %) was added to a solution of **4a** (46.5 mg, 0.20 mmol) in toluene (1.0 mL) at -78°C . After 0.5 h, the mixture was concentrated and the residue purified by column chromatography (silica gel, hexane/EtOAc = 15:1) to give methyl (1*S*,2*R*)-*cis*-2-phenylcyclopentane-1-carboxylate (**5a**) as a colorless oil; yield: 34.7 mg (85%); R_f = 0.39 (5:1 hexane/EtOAc); $[\alpha]_D^{25}$: $+98.8^\circ$ (c 1.12, CHCl_3); IR (neat): ν = 1732, 1200, 1171, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.70 (m, 1H), 1.95–2.15 (m, 5H), 3.16 (ddd, J = 6.2, 9.0, 9.0 Hz, 1H, C2-*H*), 3.22 (s, 3H, CO_2CH_3), 3.41 (ddd, J = 7.1, 9.0, 9.0 Hz, 1H, C1-*H*), 7.15–7.28 (m, 5H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ = 24.8 (CH_2), 28.6 (CH_2), 31.2 (CH_2), 49.2 (CH?), 49.8 (CH), 50.9 (CH_3), 126.3 (CH), 127.8 (CH), 127.9 (CH), 141.5 (C), 174.9 (C); EI-HR-MS: m/z = 204.1151 [calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_2$ (M^+) 204.1150]; anal. calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_2$: C 76.44, H 7.90; found: C 76.33, H 7.98.

The enantiomeric excess of **5a** was determined to be 95% ee by HPLC with a Daicel Chiralcel OJ-H column followed by Daicel Chiralpak AS-H column (100:1 hexane/*i*-PrOH, 1.0 mL/min); t_R (minor) = 12.9 min for (1*R*,2*S*) enantiomer; t_R (major) = 14.7 min for (1*S*,2*R*) enantiomer.

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- [18] The preferred absolute stereochemistry of **6a** in each case was established as (1*R*,2*R*) by HPLC comparison with the *trans* isomer derived from (1*S*,2*R*)-**5a** via C1-epimerization (NaOMe, MeOH, reflux). (1*R*,2*R*)-**6a**: a colorless oil; R_f = 0.39 (5:1 hexane/EtOAc); $[\alpha]_D^{25}$: -103° (c 1.17, CHCl_3) for 95% ee; ^1H NMR (400 MHz, CDCl_3): δ = 1.73–1.89 (m, 3H), 1.96 (m, 1H), 2.10–2.22 (m, 2H), 2.84 (ddd, J = 7.9, 7.9, 7.9 Hz, 1H, C2-*H*), 3.35 (ddd, J = 7.9, 9.4, 9.4 Hz, 1H, C1-*H*), 3.60 (s, 3H, OCH_3), 7.17–7.30 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, CDCl_3): δ = 25.2 (CH_2), 30.9 (CH_2), 35.1 (CH_2), 49.8 (CH), 51.6 (CH_3), 52.0 (CH), 126.2 (CH), 127.1 (CH), 128.3 (CH), 143.8 (C), 176.2 (C). The enantiomeric excess of **6a** was determined by HPLC with a Daicel Chiralcel OJ-H column followed by Daicel Chiralpak AS-H column (100:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (major) = 17.8 min for (1*R*,2*R*) enantiomer; t_R (minor) = 20.5 min for (1*S*,2*S*) enantiomer.
- [19] S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417.
- [20] As expected from Taber's work,^[14] the reaction with $\text{Rh}_2(4\text{S-MPPIM})_4$ (**1c**) (toluene, 23 °C, 3 h) provided exclusively (*Z*) alkene **7a** in 80% yield.
- [21] The results for $\text{Rh}_2(\text{S-DOSP})_4$ (**2**) are as follows: toluene, -78°C , 8 h, 73% yield, **5a:6a:7a** = 61 (71% ee):25 (64% ee):14; hexanes, -60°C , 5 h, 73% yield, **5a:6a:7a** = 35 (67% ee):31 (92% ee):34.
- [22] The enantiomeric excess of **5d** was determined by HPLC with a Daicel Chiralcel OJ-H column (100:1 hexane/*i*-PrOH, 1.0 mL/min): t_R = 25.3 min for major enantiomer; t_R = 28.5 min for minor enantiomer. The absolute stereochemistry was not determined.
- [23] The peak assignment [750:1 hexane/*i*-PrOH, 1.0 mL/min, t_R (major) = 38.1 min for (1*S*,2*S*) enantiomer; t_R (minor) = 42.6 min for (1*R*,2*R*) enantiomer] was carried out by comparison with [(1*S*,2*S*)-2-butylcyclopentyl]methyl *p*-bromobenzoate prepared from the known (1*S*,2*S*)-**6e**.^[17]