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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

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-diazoacarbonyl 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-diazoacarbonyl compounds. The salient ability of Doyle’s dirhodium(II) carboxamidate catalysts such as Rh₃(5S-MEPeY)₄ (1a), Rh₃(4S-MEOX)₄ (1b), and Rh₃(4S-MPPIM)₄ (1c) is characteristic of intramolecular C–H insertion reactions of diazoacettes and diazoacetamides,\[4\] while Davies’ dirhodium(II) carboxylate catalysts such as Rh₃(5-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 Rh₃(5-PTPA)₄ (3a), Rh₃(5-PTA)₄ (3b), Rh₃(5-PPTA)₄ (3c) are especially well suited for intramolecular C–H insertion reactions of α-diazo-β-ketoesters,\[6\] α-methoxycarbonyl-α-diazo-

Scheme 1.
acetamides,\textsuperscript{17} and aryldiazoacetaates,\textsuperscript{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 phosphor-dihyridium(II) catalysts developed by Lahueru and Pèrez-Prieto,\textsuperscript{9,10} enantioselective reactions of α-diazo esters (α-alkyl-α-diazoacetaates) have been left unexplored. Herein we report the first successful example of an enantioselective intramolecular C–H insertion reaction of α-diazo esters, in which Rh₂(O₂CCH₃)₂ (3a) provides cis-2-arylcyclopentane-1-carboxylates as the sole product in up to 95% ee.

Rhodium(II)-catalyzed intramolecular C–H inserion reactions of α-diazoesters, developed and extensively advanced by the Taber group, offer a powerful route to the production of substituted cyclopentanes\textsuperscript{11} and tetrahydrofurans\textsuperscript{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,\textsuperscript{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.\textsuperscript{14} Compared with Rh₂(O₂CCH₃)₂, which generally favors C–H insertion, the use of Rh₂(O₂CCI₃)₂ with a more electron-withdrawing ligand would generate more electrophilic and thus more reactive rhodium(II)-carbene intermediate that would greatly favor β-hydride elimination via an early trans-ion state, while that of Rh₂(O₂CCPh)₂ 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 Rh₂(S-PPTA)₂ (3b), C–H insertion can compete effectively with β-hydride elimination is of particular interest, although as expected, insertion of methyl 2-diazo-6-phenylhexanoate (4a)\textsuperscript{15} in toluene using 1 mol % of Rh₂(S-PTTL)₂ (3a). The reaction proceeded smoothly to completion at −78 °C with 10.5 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 alken 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 ([α]ₚ⁰⁺⁺ = 98.8° (c 1.12, CHCl₃) for 95% ee) was established as (1S,2R) by its transformation \{(1) NaOMe, MeOH, reflux; (2) LiAlH₄, THF, 0 °C\} to the known trans-2-phenylcyclopentane-1-methanol ([α]ₚ⁰⁺⁺ = 44.3° (c 1.20, MeOH); lit.\textsuperscript{17} [α]ₚ⁰⁺⁺ = 48.9° (c 1.2, MeOH) for the (1R,2R)-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) alkenene 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) alkenene 7a. Using toluene as the solvent, we next evaluated the abilities of other chiral dirhodium(II) carboxylates, Rh₂(S-PPTA)₂ (3b), Rh₂(S-PTA)₂ (3c), and Rh₂(S-PTV)₂ (3d) (entries 6–8). Compared with catalysis by Rh₂(S-PTTL)₂, 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) alkenene 7a. While similar high levels of asymmetric induction as was found for Rh₂(S-PTTL)₂, were maintained with the cis isomer 5a, a sharp drop in enantioselectivity was observed with the trans isomer 6a.\textsuperscript{18} Somewhat disappointingly, switching the catalyst from Rh₂(S-PTTL)₂ to Rh₂(S-BPTTL)₂ (3e)\textsuperscript{19} characterized by an extension of the phthalimidooxid 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 Rh₂(S-PTTL)₂ (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.\textsuperscript{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](image-url)
Table 1. Enantioselective C–H insertion reactions of α-diazo esters 4 catalyzed by chiral dirhodium(II) carboxylates.[a]

\[
\text{CO}_2\text{Me} \quad \text{Rh(II) catalyst} (1 \text{ mol %}) \\
4 \quad \text{R} = \text{H} \quad \text{toluene} \quad -78 \quad 0.5 \quad 85 \quad >99;--;-- \quad 95 \quad --
\]

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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Rh(II) catalyst</th>
<th>Solvent</th>
<th>(T) [°C]</th>
<th>Time [h]</th>
<th>Yield [%]</th>
<th>ee [%][a]</th>
<th>5:6:7 [%]</th>
<th>ee [%][a]</th>
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<tr>
<td>1</td>
<td>4a H</td>
<td>Rh₂(S-PPTL)₄ (3a)</td>
<td>toluene</td>
<td>-78</td>
<td>0.5</td>
<td>85</td>
<td>&gt;99;--;--;--</td>
<td>95</td>
<td>--</td>
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<tr>
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<td>4a H</td>
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<td>0.2</td>
<td>85</td>
<td>91;--;--;9</td>
<td>90[a]</td>
<td>--</td>
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<tr>
<td>3</td>
<td>4a H</td>
<td>Rh₂(S-PPTL)₄ (3a)</td>
<td>toluene</td>
<td>0</td>
<td>0.1</td>
<td>80</td>
<td>82;--;--;18</td>
<td>81[a]</td>
<td>--</td>
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<tr>
<td>4</td>
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<td>CH₃Cl</td>
<td>-78</td>
<td>0.5</td>
<td>76</td>
<td>93;--;--;7</td>
<td>95[a]</td>
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<tr>
<td>5</td>
<td>4a H</td>
<td>Rh₂(S-PPTL)₄ (3a)</td>
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<td>0.5</td>
<td>73</td>
<td>97;--;--;3</td>
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<td>7</td>
<td>66</td>
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<td>27[b][c]</td>
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<td>-78</td>
<td>30</td>
<td>69</td>
<td>73:19;--;8</td>
<td>90[a]</td>
<td>56[b][c]</td>
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<tr>
<td>8</td>
<td>4a H</td>
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<td>toluene</td>
<td>-78</td>
<td>6</td>
<td>67</td>
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<td>95[a]</td>
<td>22[b][c]</td>
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<td>9</td>
<td>4a H</td>
<td>Rh₂(S-PPTL)₄ (3a)</td>
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<td>-78</td>
<td>0.5</td>
<td>76</td>
<td>&gt;99;--;--;--</td>
<td>67</td>
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<td>10[a]</td>
<td>4a H</td>
<td>Rh₂(S-PPTL)₄ (3a)</td>
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<td>-78</td>
<td>9</td>
<td>82</td>
<td>&gt;99;--;--;--</td>
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<td>11</td>
<td>4b MeO</td>
<td>Rh₂(S-PPTL)₄ (3a)</td>
<td>toluene</td>
<td>-78</td>
<td>0.5</td>
<td>85</td>
<td>&gt;99;--;--;--</td>
<td>92</td>
<td>--</td>
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<tr>
<td>12</td>
<td>4c Cl</td>
<td>Rh₂(S-PPTL)₄ (3a)</td>
<td>toluene</td>
<td>-78</td>
<td>0.5</td>
<td>81</td>
<td>&gt;99;--;--;--</td>
<td>93</td>
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[a] Typical procedure for C–H insertion reaction (entry 1): 3a [2EtOAc (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 HPLC [column: Chiralcel OD-H followed by Chiralpak AS-H, eluent: 100:1 hexane/iPrOH, flow rate: 1.0 mL/min, detection: UV (254 nm)].

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

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

[f] 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-diazoester 4d containing a benzeno ring on the tether giving methyl cis-2,3-dihydro-1-phenyl-1H-indene-2-carboxylate 5d) ([α]D)° = 69.3° (c 1.24, CHCl₃) as the sole product in 85% yield with 92% ee (Scheme 2).[2b] 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 cyclo pentane 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 (15,2S) and 94% ee by HPLC, using a connected series of Daicel Chiralpak IA, Chiralcel OD-H (x 2) and Chiralpak AD-H columns after conversion to the corresponding p-bromobenzoate [(1) LiAIH₄, THF, 0 °C; (2) p-bromobenzoyl chloride, cat. DMAP, pyridine, CH₂Cl₂, 0°C]. While the reasons for the reversal of diastereo- and enantioselectivity 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 Rh₃(S-PTTL₂)₂EtOAc 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 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).

Rh₃(S-PTTL₂)₂EtOAc (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 (1S,2R)-cis-2-phenylcyclopentene-1-carboxylate (5a) as a colorless oil; yield: 34.7 mg (85%); Rₛ = 0.39 (5:1 hexane/EtOAc); [α]ᵢ₉ = +498.₈⁰ (c 1.12, CHCl₃); IR (neat): ν = 1732, 1200, 1171, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 1.70 (m, 1H), 1.95–2.15 (m, 5H), 3.16 (dd, J = 6.2, 9.0, 9.0 Hz, 1H, C₂–H), 3.22 (s, 3H, CO₂CH₃), 3.41 (ddd, J = 7.1, 9.0, 9.0 Hz, 1H, C₁–H), 7.15–7.28 (m, 5H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ = 24.8 (CH₃), 28.6 (CH₂), 31.2 (CH₃), 49.2 (CH), 49.8 (CH), 50.9 (CH₂), 126.3 (CH), 127.8 (CH), 127.9 (CH), 141.5 (C), 174.9 (C); EI–HRMS: m/z = 204.1151 [calcld. for C₁₀H₁₆O₂ (M⁺) 204.1150]; anal. calcd for C₁₀H₁₆O₂: 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 Daicel Chiralcel OJ-H column followed by Daicel Chiralpak AS-H column (100:1 hexane/i-PrOH, 1.0 mL/min): tₘ (minor) = 12.9 min for (1R,2S) enantiomer; tᵣ (major) = 14.7 min for (1S,2R) enantiomer.

Acknowledgement

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References and Notes

[7] a) N. Watanabe, M. Anada, S. Hashimoto, S.


[15] In their studies of intramolecular N–H insertion reactions of α-diazoesters, McKervey and co-workers reported that dirhodium(H) tetrakis[(S)-mandelate]-catalyzed the N–H insertion of methyl 6-benzyloxy carbonylamino-2-diazo hexanolate competed with the C–H insertion and alkene formation, where the C–H insertion product cyclopentane with the cis stereochemistry of the substituents was produced in up to 28% ee: C. F. Garcia, M. A. McKervey, T. Ye, *J. Chem. Soc., Chem. Commun.* 1996, 1465.

[16] α-Diazo ester 4a was prepared from 1-iodo-4-phenylbutane according to the procedure of Taber.\[11a,13b\] (1) NaH, methyl acetocetate, DMF, 80 °C, 3 h; (2) MsN$_2$, Et,N, MeCN, 23 °C, 12 h.


[18] The preferred absolute stereochemistry of 6a in each case was established as (1R,2R) by HPLC comparison with the trans isomer derived from (15S,2R)-5a via C1-epimerization (NaOMe, MeOH, reflux). (1R,2R)-6a: a colorless oil; $R_f$ = 0.39 (5:1 hexane/EtOAc); [α]$^D_{25} = -103^{\circ}$ (c 1.17, CHCl$_3$) for 95% ee; H NMR (400 MHz, CDCl$_3$): $\delta$ = 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, AxH); $^1$C NMR (100 MHz, CDCl$_3$): $\delta = 25.2$ (CH$_3$), 30.9 (CH$_2$), 35.1 (CH$_3$), 49.8 (CH), 51.6 (CH$_2$), 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 Chiralpak AS-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 (1R,2R) enantiomer; $t_k$ (minor) = 20.5 min for (1S,2S) enantiomer.


[20] As expected from Taber's work,\[14\] the reaction with Rh$_3$(4S-MPPPIm)$_3$ (1e) (toluene, 23 °C, 3 h) provided exclusively (Z) alkene 7a in 80% yield.

[21] The results for Rh$_3$(5-DOSP)$_3$ (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; $t_k$ = 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 (1S,2S) enantiomer; $t_k$ (minor) = 42.6 min for (1R,2R) enantiomer] was carried out by comparison with [(1S,2S)-2-butylyclopienyl]methyl p-bromobenzoate prepared from the known (1S,2S)-6c.\[17\]