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Steric balance within chiral dirhodium(II) carboxamidate catalysts enhances stereoselectivity☆

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Abstract

The substitution of larger groups onto the ester moiety of various dirhodium(II) carboxamidates have led to the development of three catalysts for use in various transformations. These new chiral imidazolidinone-ligated catalysts, Rh_2(4*S*-EPPIM)$_4$, Rh_2(4*S*-BACIM)$_4$, and Rh_2(4*S*-BPPIM)$_4$, have been tested in a variety of systems, including carbon–hydrogen insertion, intramolecular cyclopropanation, and Hetero-Diels–Alder reactions. While all display high levels of selectivity, only Rh_2(4*S*-BACIM)$_4$ demonstrates higher levels of selectivity than its base catalyst, Rh_2(4*S*-MACIM)$_4$. These results show that increased levels of selectivity cannot be achieved through simply increasing the steric bulk around the active site. Instead, a delicate balance in steric distribution around the active site of the catalyst must be achieved to maximize selectivity with reactivity.

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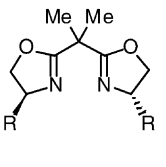
Keywords: Asymmetric catalysis; Dirhodium(II) carboxamidates; Metal carbene reactions; Hetero-Diels–Alder cycloaddition; Imidazolidinone ligands

1. Introduction

The design of effective catalysts for high stereocontrol in chemical reactions is a formidable challenge [1]. When advantageous structures are identified, modifications to improve selectivity commonly involve increasing the steric crowding near the reaction center. Thus, for example, the increase in enantiocontrol with increasingly bulky bis-oxazoline R-substituents (**1**) for copper(I) [2] and salen–ruthenium complexes (**2**) [3] in cyclopropanation reactions, as well as elaborate efforts in catalyst design for asymmetric carbonylations [1,4], exemplify this consideration. However, there are also examples where decreased steric crowding from smaller catalyst substituents leads to increased selectivity [1,5]. We are now able to demonstrate for chiral dirhodium carboxamidates that a balance in size of substituents is necessary to maximize selectivity.



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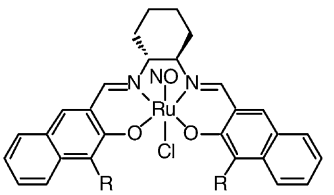

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We have previously demonstrated the effectiveness of dirhodium(II) tetrakis[methyl *N*-1-alkanoyl-2-oxai-

☆ For reviews, see [1,6].

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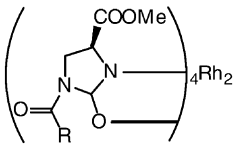
midazolidine-4(*R* or *S*)-carboxylates] (**3**) for highly selective chemical transformations [6,7], and we have shown that increasing the volume of the *N*-acyl group increased selectivity [8].



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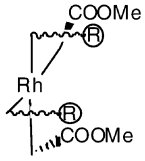

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With the design of dirhodium(II) carboxamidates so that two nitrogen and two oxygen are bound to each rhodium, each rhodium face in **3** has two COOMe and two R-groups protruding, as depicted by **4**. We anticipated further enhancements in selectivity with increasing size of the ester functionality.

2. Experimental

2.1. General methods

Products and analyses for Eqs. (1)-(3) have been described [7–11]. The synthesis of the ligands and the analyses of their dirhodium(II) complexes, Rh_2(4S-MPPIM)$_4$ and Rh_2(4S-MACIM)$_4$, have been reported [8,12]. Reactions were performed as previously described.

2.2. Synthesis of dirhodium(II) tetrakis [2-methyl-l-propyl N-3-phenylpropanoyl-2-oxaimidazolidine-4(S)-carboxylate], [Rh_2(4S-BPPIM)$_4$]

2.2.1. Synthesis of 2-methyl-l-propyl 3-benzyloxycarbonyl-2-oxaimidazolidine-4(S)-carboxylate

A 100 ml round bottom flask was charged with 3-benzyloxycarbonyl-2-oxaimidazolidinone-4(*S*)-carboxylic acid (5.0 g, 18.9 mmol), DMAP (0.57 g, 4.7 mmol), 2-methyl-l-propanol (1.5 ml, 18.9 mmol), and 40 ml of distilled dichloromethane, and the resulting solution was cooled to 0 °C. A solution of DCC (4.9 g, 23.6 mmol) in 10 ml of distilled dichloromethane was added to the reaction flask dropwise over 30 min using a syringe pump. The mixture was allowed to stir overnight, slowly warming to room temperature. A white solid was filtered, and the resulting yellow filtrate was concentrated under reduced pressure to reveal a yellow oil. The oil was taken up into ethyl acetate and washed with 1 M HCl (20 ml), saturated $NaHCO_3$ (20 ml), and water (20 ml), and then dried over anhydrous $MgSO_4$. This solution was then filtered, concentrated under reduced pressure, and purified by column chromatography on silica gel (ethyl acetate:hexanes = 1:1) to yield a colorless oil that slowly solidified to 4.5 g of a white solid (14.2 mmol, 75% yield): mp: 76–77 °C. $[\alpha]_D^{24} = -27.0$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.40–7.29 (comp, 5H), 5.77 (br s, 1H), 5.30 (d, $J = 12.2$ Hz, 1H), 5.24 (d, $J = 12.2$ Hz, 1H), 4.77 (dd, $J = 9.9$, 3.7 Hz, 1H), 3.91 (dd, $J = 10.5$, 6.6 Hz, 1H), 3.86 (dd, $J = 10.5$, 6.6 Hz, 1H), 3.79 (t, $J = 9.9$ Hz, 1H), 3.43 (dd, $J = 9.6$, 3.7 Hz, 1H), 1.85 (non, $J = 6.6$ Hz, 1H), 0.86 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 169.7, 155.4, 151.0, 135.2, 128.5, 128.4, 128.2, 71.9, 68.1, 55.9, 40.7, 27.5, 18.8. HRMS for $C_{16}H_{21}N_2O_5^+$, theoretical: 321.145; found: 321.154.

2.2.2. Synthesis of 2-methyl-l-propyl 1-(3-phenylpropanoyl)-3-benzyloxycarbonyl-2-oxaimidazolidine-4(S)-carboxylate

A 100 ml round bottom flask was charged with 2-methyl-l-propyl 3-benzyloxycarbonyl-2-oxaimidazolidine-4(*S*)-carboxylate (4.02 g, 12.5 mmol), DMAP (0.15 g, 1.3 mmol), freshly distilled pyridine (2.0 ml, 25 mmol), and 40 ml of anhydrous dichloromethane. A reflux condenser was added, and the system was flushed with argon and cooled to 0 °C. Hydrocinnamoyl chloride (2.19 ml, 15.6 mmol) was added dropwise over 30 min via syringe pump, and the system was allowed to stir at 0 °C for an additional 30 min. The reaction mixture was then heated at reflux overnight to afford an orange solution. An additional 80 ml of dichloromethane was added, and the solution was then washed with cold 1 M HCl (2 × 25 ml), saturated $NaHCO_3$ (1 × 25 ml), and brine (1 × 25 ml). The resulting solution was then dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a yellow oil. This was subsequently purified via column chromatography on silica gel (ethyl acetate:hexanes, 2:1) to yield a pale yellow oil that slowly solidified to give 5.45 g of a yellow solid (3.90 mmol, 97% yield). mp:

65–66 °C. $[\alpha]_D^{24} = -14.6$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.05 (comp, 10H), 5.27 (d, $J = 12.2$ Hz, 1H), 5.21 (d, $J = 12.2$ Hz, 1H), 4.74 (dd, $J = 10.0$, 2.4 Hz, 1H), 3.90 (dd, $J = 10.5$, 5.7 Hz, 1H), 3.86 (dd, $J = 10.5$, 5.7 Hz, 1H), 3.72 (t, $J = 9.8$ Hz, 1H), 3.40 (dd, $J = 10.0$, 2.4 Hz, 1H), 2.96 (t, $J = 7.7$ Hz, 2H), 2.65 (t, $J = 7.7$ Hz, 2H), 1.84 (non, $J = 6.6$ Hz, 1H), 0.86 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 176.6, 169.7, 155.7, 151.0, 140.5, 135.1, 128.5, 128.4, 128.3, 128.2, 126.2, 126.1, 71.9, 68.0, 55.8, 40.7, 37.0, 30.8, 27.5, 18.8. HRMS for $C_{25}H_{29}N_2O_6^+$, theoretical: 453.203; found: 453.217.

2.2.3. Synthesis of 2-methyl-l-propyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(S)-carboxylate

A 200 ml round bottom flask was charged with 2-methyl-l-propyl 1-(3-phenylpropanoyl)-3-benzyloxycarbonyl-2-oxaimidazolidine-4(*S*)-carboxylate (5.34 g, 12.05 mmol) and 100 ml of dry methanol and placed under argon. A spatula tip of palladium black was then added carefully, and a septum was placed on the reaction vessel. The system was then flushed with hydrogen from a balloon, and the mixture was allowed to stir overnight. The following day, the mixture was filtered through celite and concentrated under reduced pressure. The resulting off-white solid was then purified by column chromatography on silica gel (ethyl acetate:hexanes = 4:1) to afford 3.15 g of a white solid (9.88 mmol, 82% yield): mp: 64–65 °C. $[\alpha]_D^{24} = 18.6$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.38–7.15 (comp, 5H), 6.02 (br s, 1H), 4.27 (dd, $J = 9.2$, 5.3 Hz, 1H), 4.13 (dd, $J = 12.0$, 11.7 Hz, 1H), 4.06 (dd, $J = 11.7$, 5.3 Hz, 1H), 3.97 (dd, $J = 6.7$, 1.6 Hz, 2H), 3.33–3.15 (comp, 2H), 2.97 (t, $J = 7.7$ Hz, 2H), 1.96 (non, $J = 6.6$ Hz, 1H), 0.93 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 172.6, 170.3, 155.5, 140.8, 128.5, 128.4, 128.2, 126.3, 126.0, 72.2, 49.7, 45.0, 37.0, 30.4, 27.6, 18.9. HRMS for $C_{17}H_{23}N_2O_4^+$, theoretical: 319.166; found: 319.070.

2.2.4. Synthesis of dirhodium(II) tetrakis[2-methyl-l-propyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(S)-carboxylate] (7)

A 50 ml two-neck round bottom flask equipped with a stirbar, Soxhlet extractor, and reflux condenser were flame-dried and assembled while still warm under a flow of argon, utilizing Teflon tape to seal all joints except the extra neck of the flask. A drying thimble, filled with an oven-dried mixture of sodium carbonate and sand (2:1) and capped with glass wool, was placed in the Soxhlet extractor during assembly. Dirhodium(II) acetate (300 mg, 0.979 mmol) was added through the open neck, along with 2-methyl-l-propyl *N*-3-phenylpropanoyl-2-oxaimidazolidine-4 (*S*)-carboxylate (1.73 g, 5.43 mmol) and 15 ml of dried chlorobenzene. The open neck was then sealed with a septum, and the system was heated at reflux for 30 h. The progress of the reaction was monitored by HPLC using a reverse-phase Licrosorb-CN column. When the reaction was complete, the mixture was concentrated under reduced pressure and purified by column chromatography on reverse phase Bakerbond®-CN resin (98:2 methanol:acetonitrile). The desired *cis*–2,2 isomer was isolated as 450 mg of a purple solid (0.44 mmol, 45% yield). $[\alpha]_D^{23} = -113.6$ (*c* 0.1, CH_3CN). ^{1}H NMR (300 MHz, CD_3CN), δ 7.33–7.07 (comp, 20H), 4.15 (dd, $J = 9.8$, 4.2 Hz, 2H), 4.07 (dd, $J = 9.8$, 4.2 Hz, 2H), 3.95–3.53 (comp, 16H), 3.03–2.69 (comp, 16H), 2.17 (s, 6H), 1.95–1.85 (comp, 2H), 1.80–1.63(comp, 2H), 0.96–0.88 (comp, 12H), 0.83–0.74 (comp, 12H); ^{13}C NMR (75 MHz, CD_3CN), δ 170.4, 141.4, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 126.2, 126.0, 71.6, 71.5, 58.2, 58.1, 46.7, 37.3, 37.2, 31.0, 30.7, 27.7, 27.6, 19.1, 19.1, 19.0, 18.9. HRMS for $C_{68}H_{85}N_8O_{16}Rh_2^+$, theoretical: 1475.4194; found: 1475.0636.

2.3. Synthesis of dirhodium(II) tetrakis[ethyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(S)-carboxylate], [Rh_2(4S-EPPIM)$_4$]

2.3.1. Synthesis of ethyl 3-benzyloxycarbonyl-2-oxaimidazolidine-4(S)-carboxylate

A 200 ml round bottom flask was charged with 3-benzyloxycarbonyl-2-oxaimidazolidinone–4(*S*)-carboxylic acid (4.0 g, 15.1 mmol) and 100 ml of dry absolute ethanol. Thionyl chloride (0.9 g, 7.6 mmol) was added dropwise, after which the reaction flask was capped and allowed to stir for 3 days. After this time, the solution was concentrated and then taken up in ethyl acetate and subsequently washed with saturated $NaHCO_3$ (1 × 20 ml) and brine (1 × 20 ml).

The solution was then dried over anhydrous $MgSO_4$, filtered, and concentrated to yield 4.15 g of a pale yellow solid (94% yield): mp: 79–80 °C. $[\alpha]_D^{24} = -36.2$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.45–7.26 (comp, 5H), 6.74 (br s, 1H), 5.28 (d, $J = 12.2$ Hz, 1H), 5.18 (d, $J = 12.2$ Hz, 1H), 4.72 (dd, $J = 9.9$, 3.5 Hz, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.74 (t, $J = 9.9$ Hz, 1H), 3.40 (dd, $J = 9.8$, 3.5 Hz, 1H), 1.16 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 155.5, 151.1, 135.1, 128.5, 128.4, 128.2, 68.1, 62.1, 55.8, 40.6, 13.9. HRMS for $C_{14}H_{17}N_2O_5^+$, theoretical: 293.113; found: 293.300.

2.3.2. Synthesis ethyl 1-(3-phenylpropanoyl)-3-benzyloxycarbonyl-2-oxaimidazolidine-4(S)-carboxylate

A 100 ml round bottom flask was charged with ethyl 3-benzyloxycarbonyl-2-oxaimidazolidinone-4(*S*)-carboxylate (3.24 g, 11.1 mmol), DMAP (0.13 g, 1.1 mmol), fresh pyridine (1.8 ml, 22.2 mmol), and 30 ml of distilled dichloromethane. A reflux condenser was added, and the system was flushed with argon and cooled to 0 °C. Hydrocinnamaoyl chloride (1.72 ml, 12.2 mmol) was added dropwise over 30 min via syringe pump, and the system was allowed to stir at 0 °C for an additional 30 min. The reaction mixture was then heated at reflux overnight to afford an orange solution. An additional 60 ml of dichloromethane was added, and the solution was then washed with cold 1 M HCl (2 × 20 ml), saturated $NaHCO_3$ (1 × 20 ml), and brine (1 × 20 ml). The resulting solution was then dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a yellow oil. This was subsequently purified via column chromatography on silica gel (ethyl acetate:hexanes = 2:1) to yield a pale yellow oil that slowly solidified to give 4.61 g of a yellow solid (10.9 mmol, 98% yield): mp: 70–71 °C. $[\alpha]_D^{24} = -14.4$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.16 (comp, 10H), 5.35 (d, $J = 12.2$ Hz, 1H), 5.23 (d, $J = 12.2$ Hz, 1H), 4.67 (dd, $J = 10.0$, 3.7 Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.96 (dd, $J = 12.0$, 10.0 Hz, 1H), 3.85 (dd, $J = 12.0$, 3.7 Hz, 1H), 3.27 (t, $J = 7.6$ Hz, 2H), 2.98 (t, $J = 7.6$ Hz, 2H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 169.0, 164.2, 154.6, 140.4, 134.6, 128.6, 128.5, 128.4, 128.3, 126.2, 68.9, 62.5, 52.4, 42.2, 37.6, 30.1, 13.9. HRMS for $C_{23}H_{25}N_2O_6^+$, theoretical: 425.171; found: 425.463.

2.3.3. Synthesis of ethyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(S)-carboxylate

A 200 ml round bottom flask was charged with ethyl 1-(3-phenylpropanoyl)-3-benzyloxycarbonyl-2 - oxaimidazolidinone-4(*S*)-carboxylate (4.60 g, 10.8 mmol) and 100 ml of dry methanol and placed under argon. Hydrogenation was performed as described for the isobutyl analog. The resulting off-white solid was purified by column chromatography on silica gel (ethyl acetate:hexanes = 1:1) to afford 2.66 g of a white solid (9.17 mmol, 85% yield): mp: 63–64 °C. $[\alpha]_D^{24} = 40.2$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.16 (comp, 5H), 5.83 (br s, 1H), 4.29–4.22 (comp, 3H), 4.16–4.06 (comp, 2H), 3.23 (t, $J = 7.7$ Hz, 2H), 2.97 (t, $J = 7.7$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 170.2, 155.3, 140.8, 128.5, 128.4, 126.0, 62.4, 49.6, 45.0, 37.0, 30.4, 14.1. HRMS for $C_{15}H_{19}N_2O_4^+$, theoretical: 291.134; found: 291.228.

*2.3.4. Synthesis of dirhodium(II) tetrakis[ethyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(S)-carboxylate] (**6**)*

Reaction was performed as described for the isobutyl analog. Dirhodium(II) acetate (267 mg, 0.603 mmol) was added, along with ethyl 1-(3-phenylpropanoyl)-2-oxaimidazolidinone-4(*S*)-carboxylate (1.40 g, 4.82 mmol) and 15 ml of dried chlorobenzene. The system was heated at 160 °C for 20 h, and reaction progress was monitored by HPLC. The reaction mixture was concentrated and purified via column chromatography on reverse phase Bakerbond® CN resin (methanol to 98:2 methanol:acetonitrile). The *cis*-2,2 isomer was isolated as 164 mg of a purple solid in low yield (0.121 mmol, 20% yield). $[\alpha]_D^{23} = -113.6$ (*c* 0.1, CH_3CN). ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.28–7.11 (comp, 20H), 4.18 (dd, $J = 10.6$, 3.5 Hz, 2H), 3.96 (dd, $J = 10.6$, 4.5 Hz, 2H), 4.30–3.65 (comp, 16H), 3.20–2.65 (comp, 16H), 1.29 (t, $J = 7.1$ Hz, 6H), 1.10 (t, $J = 7.1$ Hz, 6H), ^{13}C NMR (75 MHz, $CDCl_3$), δ 173.1, 172.6, 171.8, 170.4, 164.3, 163.9, 141.3, 140.3, 128.5, 128.3, 128.1, 127.9, 127.6, 126.0, 61.6, 58.1, 46.5, 45.9, 38.0, 37.2, 31.3, 31.0, 30.9, 30.7, 14.2, 14.0. HRMS for $C_{60}H_{69}N_8O_{16}Rh_2^+$, theoretical: 1363.294; found: 1363.425.

2.4. Synthesis of dirhodium(II) tetrakis[2-methyl-l-propyl 1-acetyl-2-oxaimidazolidine-4(S)-carboxylate], (Rh_2(4S-BACIM)$_4$)

2.4.1. Synthesis of 2-methyl-l-propyl 1-acetyl-3-benzyloxycarbonyl-2-oxaimidazolidine-4(S)-carboxylate

A 100 ml round bottom flask was charged with 2-methyl propyl 3-benzyloxycarbonyl-2-oxaimidazolidinone-4(*S*)-carboxylate (2.5 g, 7.8 mmol), DMAP (0.095 g, 0.78 mmol), fresh pyridine (1.26 ml, 15.6 mmol), and 20 ml of distilled dichloromethane. The system was flushed with argon and cooled to 0 °C. Acetyl chloride (0.69 ml, 9.4 mmol) was added dropwise over 30 min via syringe pump, and the solution was allowed to stir at 0 °C for an additional 30 min. The reaction mixture was then heated at reflux overnight to afford an orange solution. An additional 50 ml of dichloromethane was added, and the solution was then washed with cold 1 M HCl (2 × 15 ml), saturated $NaHCO_3$ (1 × 15 ml), and brine (1 × 15 ml). The resulting solution was then dried over anhydrous $MgSO_4$, filtered, and concentrated to afford an orange oil. This was subsequently purified via column chromatography on silica gel (ethyl acetate:hexanes = 2:1) to yield a colorless oil that slowly solidified to afford 2.57 g of a white solid (7.10 mmol, 91% yield): mp: 78–79 °C. $[\alpha]_D^{24}$ = 107.6 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.22 (comp, 5H), 5.30 (d, J = 12.2 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 4.69 (dd, J = 10.0, 3.4 Hz, 1H), 3.94 (dd, J = 12.0, 10.0 Hz, 1H), 3.89 (d, J = 6.7 Hz, 2H), 3.82 (dd, J = 12.0, 3.4 Hz, 1H), 1.85 (non, J = 6.7 Hz, 1H), 0.86 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 168.8, 150.4, 149.0, 134.4, 128.2, 128.1, 127.8, 71.8, 68.4, 52.0, 41.9, 27.2, 23.5, 18.4. HRMS for $C_{18}H_{23}N_2O_6^+$, theoretical: 363.156; found: 363.100.

2.4.2. Synthesis of 2-methyl-l-propyl 1-acetyl-2-oxaimidazolidine-4(S)-carboxylate

A 100 ml round bottom flask was charged with 2-methyl-1-propyl 1-acetyl-3-benzyloxycarbonyl-2-oxaimidazolidinone-4(*S*)-carboxylate (2.4 g, 6.6 mmol) and 40 ml of dry methanol and placed under argon. Hydrogenation was performed as previously described. The resulting off-white oil was purified by column chromatography on silica gel (ethyl acetate:hexanes = 3:1) to afford 1.28 g of a colorless oil (5.6 mmol, 85% yield). $[\alpha]_D^{24}$ = 44.6 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.28 (dd, J = 9.3, 5.4 Hz, 1H), 4.19–4.03 (comp, 2H), 3.98 (dd, J = 6.6, 1.7 Hz, 1H), 2.50 (s, 3H), 1.97 (non, J = 6.6 Hz, 1H), 0.95 (d, J = 6.6 Hz, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 155.3, 154.6, 72.2, 49.5, 44.9, 27.6, 23.4, 18.9. HRMS for $C_{10}H_{17}N_2O_4^+$, theoretical: 229.119; found: 229.257.

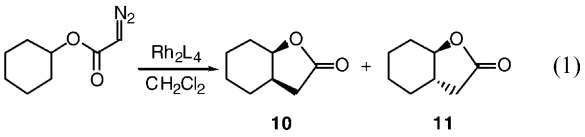
2.4.3. Synthesis of dirhodium(II) tetrakis[2-methyl-l-propyl 1-acetyl-2-oxaimidazolidine-4(S)-carboxylate] (**9**)

Reaction was performed as described for **6** and **7**. Dirhodium (II) acetate (200 mg, 0.452 mmol) was added, along with 2-methyl-1-propyl 1-acetyl-2-oxaimidazolidinone-4(*S*)-carboxylate (0.843 g, 3.70 mmol) and 15 ml of dried chlorobenzene. The system was heated at 160 °C for 15 h, and reaction progress was monitored by HPLC. The reaction mixture was concentrated and purified via column chromatography on reverse phase Bakerbond® CN resin (THF). The *cis*-2,2 isomer was isolated as a purple solid in 26% yield. $[\alpha]_D^{24}$ = −173.52 (*c* 0.1, CH_3CN). ^{1}H NMR (300 MHz, CD_3CN) δ 4.13 (dd, J = 10.3, 4.4 Hz, 2H), 4.02–3.61 (comp, 16H), 2.28 (s, 6H), 2.27 (s, 3H), 2.23 (s, 6H), 2.05–1.83 (comp, 4H), 0.95 (d, J = 6.8 Hz, 6H), 0.94 (d, J = 6.6 Hz, 6H), 0.90 (d, J = 6.8 Hz, 6H), 0.89 (d, J = 6.6 Hz, 6H), ^{13}C NMR (75 MHz, CD_3CN) δ 174.4, 173.4, 168.9, 166.2, 165.8, 71.7, 71.2, 50.3, 48.1, 47.8, 45.7, 30.5, 28.5, 23.3, 23.2, 19.2, 19.1, 19.0. HRMS for $C_{40}H_{60}N_8O_{16}Rh_2^+$, theoretical: 1115.232; found: 1115.534.

3. Results and discussion

Since dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxy-late, Rh_2(4*S*-MPPIM)$_4$ (**5**), has given the highest selectivities in catalytic reactions [6,7], enlarging the ester from methyl to ethyl (**6**) and isobutyl (**7**) on this ligand was considered to be advantageous. Similar changes in the ester of the base structure Rh_2(4*S*-MACIM)$_4$ (**8**) were evaluated. However, application of these catalysts to reactions for which Rh_2(MPPIM)$_4$ was superior to other dirhodium carboxamidates [9]—intramolecular carbon–hydrogen insertion (Eq. (1)), intramolecular cyclopropanation (Eq. (2)), and the

Table 1
Diastereoselectivity and enantioselectivity as a function of catalyst in the carbon–hydrogen insertion reactions of cyclohexyl diazoacetate[a]

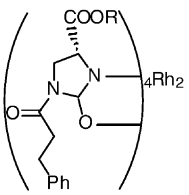


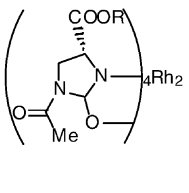
10 11 (1)

Catalysts	Yield (%)		e.e. (%)	
	10 + **11**[b]	**10**:**11**[c]	**10**[d]	**11**[d]
Rh_2(4S-MPPIM)$_4$ (**5**)	71	100:0	92	–
Rh_2(4S-EPPIM)$_4$ (**6**)	57	84:16	88	37
Rh_2(4S-BPPIM)$_4$ (**7**)	69	78:22	88	73
Rh_2(4S-MACIM)$_4$ (**8**)[e]	70	97:3	97	65
Rh_2(4S-BACIM)$_4$ (**9**)	82	99:1	99	64

[a] Reactions were performed in refluxing dichloromethane with 1.0 mol% of catalyst.
[b] Weight yield of isolated products following chromatography.
[c] Determined by GC on a SPB-5 column.
[d] Determined by GC on a Chiraldex G-TA column.
[e] [9].

Hetero-Diels–Alder reaction (Eq. (3))—showed that the bulkier catalysts gave lower selectivities in these transformations (Tables 1–3).

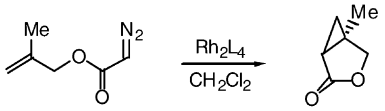




(5) R = Me, Rh_2(4*S*-MPPIM)$_4$
(6) R = Et, Rh_2(4*S*-EPPIM)$_4$
(7) R = ^{i}Bu, Rh_2(4*S*-BPPIM)$_4$
(8) R = Me, Rh_2(4*S*-MACIM)$_4$
(9) R = ^{t}Bu, Rh_2(4*S*-BACIM)$_4$

For the intramolecular C–H insertion reaction of cyclohexyl diazoacetate both high diastereocontrol and high enantioselectivity characterizes the use of Rh_2(4*S*-MPPIM)$_4$. However, changing its ester alkyl group from methyl to isobutyl (**7**) or even to ethyl (**6**) adversely affects both diastereoselectivity and enantioselectivity (Table 1). In the event that this diminishing stereocontrol is a consequence of overcrowding in the reaction space conducive to the favored selectivity, we sought to balance the size of the *N*-acyl and ester alkyl groups. Thus, with Rh_2(4*S*-MACIM)$_4$ as the base structure [9], real enhancements in stereocontrol were obtained with Rh_2(4*S*-BACIM)$_4$, and this catalyst must now be considered to be optimum for intramolecular carbon–hydrogen insertion reactions [12].

Table 2
Enantiocontrol as a function of catalyst in the intramolecular cyclopropanation reaction of methallyl diazoacetate[a]



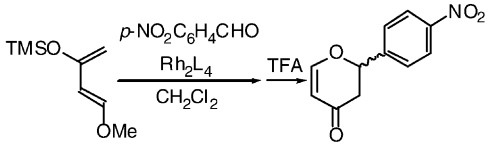
12 13 (2)

Catalysts	Yield (%) **13**[b]	e.e. (%) **13**[c]
Rh_2(4S-MPPIM)$_4$ (**5**)	64	88
Rh_2(4S-EPPIM)$_4$ (**6**)	83	70
Rh_2(4S-BPPIM)$_4$ (**7**)	62	58
Rh_2(4S-MACIM)$_4$ (**8**)	44	82
Rh_2(4S-BACIM)$_4$ (**9**)	53	87

[a] Reactions were performed in refluxing dichloromethane with 1.0 mol% of catalyst.
[b] Weight yield of isolated products following chromatography.
[c] Determined by GC on a Chiraldex G-TA column.

A similar outcome was obtained for intramolecular cyclopropanation of methallyl diazoacetate (Table 2). Here, we have seen an enormous dependence of enantioselection on the catalyst and its ligands [10,11].

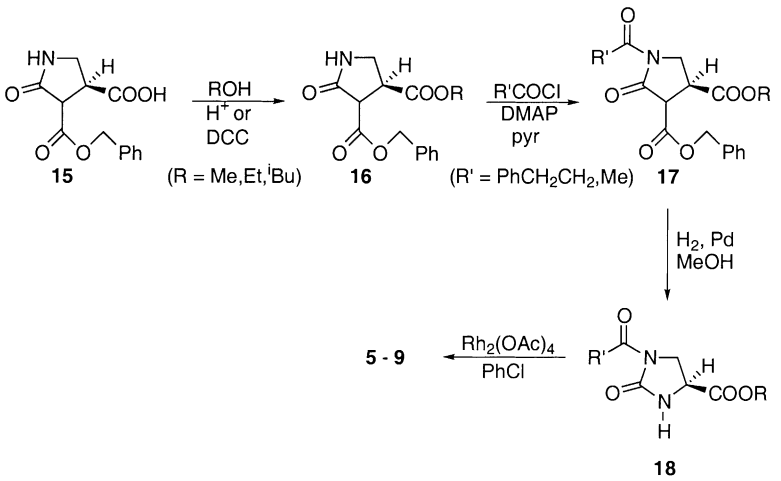
Table 3
Enantiocontrol as a function of catalyst in the Hetero-Diels–Alder reaction between the Danishevsky diene and *p*-nitrobenzaldehyde[a]



14 (3)

Catalysts	Yield (%) **14**[b]	e.e. (%) **14**[c]
Rh_2(4S-MPPIM)$_4$ (**5**)[d]	82	95
Rh_2(4S-EPPIM)$_4$ (**6**)	80	69
Rh_2(4S-BPPIM)$_4$ (**7**)	65	77
Rh_2(4S-MACIM)$_4$ (**8**)	76	81
Rh_2(4S-BACIM)$_4$ (**9**)	45	84

[a] Reactions were performed at room temperature in dichloromethane (48 h) and then quenched with trifluoracetic acid.
[b] Weight yield of isolated product after column chromatography.
[c] Determined by HPLC on a Chiralpak Daicel OD column.
[d] [7].



Scheme 1.

The Rh_2(MPPIM)$_4$ catalysts were previously reported to give the highest enantioselectivity [11]. Increasing the size of its ester alkyl group to methyl or ethyl, however, significantly diminishes enantioselection, but the balance achieved with Rh_2(4*S*-BACIM)$_4$ restores enantiocontrol to the level of that achieved with Rh_2(4*S*-MPPIM)$_4$.

Finally, for the recently reported uses of dirhodium (II) carboxamidates in Hetero-Diels–Alder reactions [7], for which Rh_2(4*S*-MPPIM)$_4$ has exhibited the highest enantiocontrol, similar steric influences are evident (Table 3). Increasing the ester size on the framework of Rh_2(4*S*-MPPIM)$_4$ lowers enantiocontrol, although not in a uniform fashion. Increasing the size of the ester alkyl group from the Rh_2(4*S*-MACIM)$_4$ frame leads to an increase in enantioselectivity, but in this case not to the level of Rh_2(4*S*-MPPIM)$_4$.

The ligands were prepared by the sequence of steps described in Scheme 1 from a common precursor **15** whose synthesis from *N*-BOC-L-asparagine has been described [10]. Esterification was followed by acylation, then deprotection to produce ligand **18**. The procedures described were not optimized for each ligand.

4. Conclusion

Increasing the packing of space that surrounds the catalytically active center in dirhodium(II) carboxamidates produces a decrease in stereoselectivity. However, by increasing the size of one substituent while decreasing the size of the other, a balance in stereoselectivity is achieved. Comparisons are made for intramolecular catalytic metal carbene carbon–hydrogen insertion and allylic cyclopropanation reactions and for the Lewis acid catalyzed Hetero-Diels–Alder reaction. The ligand employed is alkyl 1-*N*-acyl-2-oxaimidizolidine-4(*S*)-carboxylate where changes are made in both alkyl and *N*-acyl groups.

Acknowledgements

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