Rh_2(*S*-1,2-NTTL)$_4$: A Novel Rh_2(*S*-PTTL)$_4$ Analog With Lower Ligand Symmetry for Asymmetric Synthesis of Chiral Cyclopropylphosphonates

FRADY G. ADLY, JOHNCARLO MADDALENA, AND ASHRAF GHANEM*
Chirality Program, University of Canberra, ACT, Australia

ABSTRACT A new series of dirhodium(II) tetracarboxylate was derived from *N*-1,2-naphthaloyl-(*S*)-amino acid ligands. In terms of enantioselectivity, Rh_2(*S*-1,2-NTTL)$_4$ (**3a**) derived from *N*-1,2-naphthaloyl-(*S*)-*tert*-leucine, was the best-performing catalyst among the new series in the enantioselective synthesis of cyclopropylphosphonate derivatives (up to >99% enantiomeric excess). A predictive model was proposed to justify the observed high enantiomeric induction exhibited by Rh_2(*S*-1,2-NTTL)$_4$ with donor-acceptor phosphonate carbenoids. *Chirality 00:000–000, 2014.*

KEY WORDS: dirhodium; cyclopropanation; cyclopropylphosphonate; Rh_2(*S*-PTAD)$_4$; Rh_2(*S*-NTTL)$_4$; Rh_2(*S*-PTTL)$_4$; metal carbenoids; paddlewheel complexes

INTRODUCTION

The chiral cyclopropyl moiety has played an important role in organic chemistry for decades.[1–6] Of particular interest, cyclopropylphosphonate derivatives have been extensively studied during the last decade as they display several interesting biological activities.[7] For instance, they have been used as moieties of nucleotides,[8] as herbicides or plant growth regulators,[9] and as insecticides.[10] They were also used as analogs of the antidepressant Milnacipran,[11] as mimics of 1-aminocyclopropane carboxylic acid (ACC) with a high inhibitory activity for ACC-deaminase and alanine racemase,[12,13] as analogs of the unusual amino acids (–)-allonorcoronamic acid[14] and (*Z*)-2,3-methanohomoserine[15] and as an analog of the $GABA_B$ receptor antagonist phaclophen.[16] Furthermore, cyclopropylphoshonates can act as *N*-methyl-D-aspartate (NMDA) receptor antagonists.[17] They also possess antiproliferation properties,[18] and are virostatics,[19] antidiabetics,[20] antitumor agents,[21] selective anti-HBV agents,[22] cytostatic agents,[23] and display antiviral activity.[24]

Typically, enantiomerically enriched compounds are produced either by chemical transformation of an enantiomerically enriched precursor—derived from natural chiral pools or by the separation of racemic mixtures. However, these approaches have drawbacks: while the former requires stoichiometric quantities of a suitable precursor, the latter yields only up to 50% of the desired enantiomer. On the other hand, asymmetric catalysis, which consists of metal complexes with chiral ligands, have demonstrated vital possible merits over these conventional procedures whereby a single molecule of the chiral catalyst can return many equivalents of molecules of the chiral product for ending catalyst molecule.[25,26]

During the last decade, new methods for the stereoselective synthesis of highly functionalized cyclopropanes have been extensively developed.[27,28] Among these methods, transition-metal-catalyzed cyclopropanation of olefins with diazoesters occupies a prominent position in the field of asymmetric catalysis (Scheme 1). Once this principle was demonstrated, highly selective catalysts were developed, mainly based on Cu^{I} and Rh^{II} associated with appropriate chiral nonracemic ligands.[29] However, to enhance the synthetic potential of cyclopropanes further, the understanding and development of new methods utilizing stereoselective cyclopropanation reactions is highly desirable. Accordingly, a great deal of effort has been devoted to render the stereoselective synthesis of substituted cyclopropanes more appealing to organic chemists.[27,28]

Remarkable progress in dirhodium(II) complex catalyzed asymmetric transformations has been achieved in a number of processes including cyclopropanation and C-H insertion[30] and was recently supported by the generation and exploration of physical and chemical properties of a metastable Rh_2-carbenoid intermediate supported by a donor-acceptor carbene fragment.[31] Efforts in this area have led to the development of a family of dirhodium(II) carboxylate complexes that are derived from *N*-protected amino acids (Fig. 1). The development in this family of dirhodium paddlewheel catalysts mainly focused on modifications of the electronic and/or the steric properties of the ligands, as different bridging ligands coordinated to the dirhodium axes can offer distinct degrees of charges to the metal.[25] Consequently, it is possible to control the electronic profile of the whole catalyst by changing these ligands. For instance, the Hashimoto and Ikegami group developed a series of *N*-phthaloyl protected amino acids as ligands for dirhodium complexes (Fig. 1),[25,32,33] with the *tert*-leucine derived catalyst Rh_2(*S*-PTTL)$_4$ giving the highest asymmetric induction.[34–40] This has been further developed by the same group and others to include many other analogs.[25,41–44] Müller et al. used the same scaffold and emerged with Rh_2(*S*-NTTL)$_4$ as a catalyst derived from *N*-1,8-naphthaloyl-(*S*)-*tert*-leucine.[29,45,46] Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-NTTL)$_4$ proved to be superior catalysts for the preparation of chiral cyclopropanes; however, none can be considered as a universal catalyst affording high enantiomeric induction with different classes of substrates and under different reaction conditions. This limitation has

*Correspondence to: A. Ghanem, Building 3, Room D41, University of Canberra, ACT, 2601, Australia. E-mail: ashraf.ghanem@canberra.edu.au
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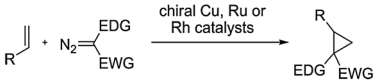


Scheme 1. Metal catalyzed decompositions of donor-acceptor diazo compounds.

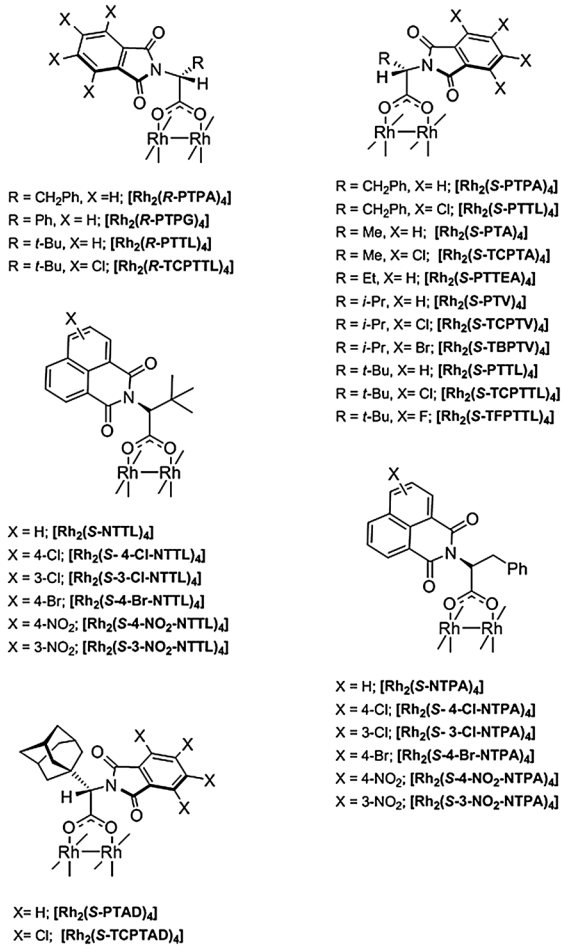


Fig. 1. Chiral dirhodium tetracarboxylates derived from *N*-protected amino acids.[25]

led to the development of other promising catalysts belonging to the same family, Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-TCPTAD)$_4$, derived from *N*-protected adamantylglycine[47–49] to access enantiomerically pure/enriched cyclopropane derivatives. But, unfortunately, the relatively long synthetic routes of these catalysts may ruin their overall appeal.[50] Therefore, the development of both synthetically accessible and highly stereoselective chiral dirhodium catalysis is still highly desirable.

As a part of our group's ongoing research and guided by our previous findings on the nature of the chiral crown cavity complexes,[29,51] we are continuing to pursue variations to the heterocyclic tether protecting the amine functionality. All previous reports used to use symmetrical *N*-protecting groups in the preparation of the chiral ligands. Herein, the effect of lowering the symmetry of the *N*-protecting group on the enantiomeric induction of the catalyst is the foundation of this article. A new catalytic series was built derived from chiral *N*-protected 1,2-naphthaloyl amino acid ligands at which the ligands can retain the *N*-phthaloyl rings of the

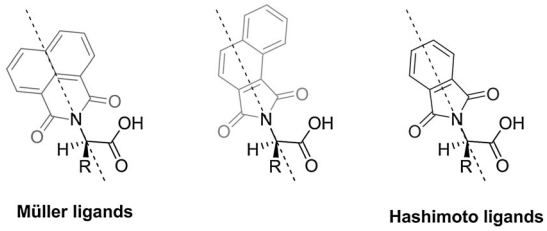


Fig. 2. Ligands backbone structure comparison.

Hashimoto catalytic series along with the horizontal naphthalene rings of Müller catalytic series (Fig. 2).

MATERIALS AND METHODS

Chemicals

All starting materials and reagents were purchased from Sigma-Aldrich (St. Louis,, MO) and Acros Organics (Morris Plains, NJ) and used without any further purification. 1,2-Napthalic anhydride was purchased from Tokyo Chemical Industry (TCI). All solvents were of high-performance liquid chromatography (HPLC) grade and dried and distilled immediately prior to use: dichloromethane over calcium hydride, 2,2-DMB, *n*-pentane and toluene over activated 4Å-MS, and chlorobenzene from potassium hydroxide. All moisture-sensitive reactions were performed using oven-dried glassware and flame dried under vacuum prior to use. Thin-layer chromatography (TLC) was performed using Sigma-Aldrich precoated silica gel 60 F254 aluminum support (20 x 20 cm, layer thickness 0.2 mm) and spots were visualized using UV light (254 nm). Preparative TLC separations were performed using Sigma-Aldrich precoated silica gel 60 F254 glass support (20 x 20 cm, layer thickness 0.25 mm). Column chromatography was carried out on silica gel 60 (130-270 mesh ASTM, Sigma-Aldrich) using the specified eluents. Rh_2(*S*-PTTL)$_4$[52] and Rh_2(*S*-NTTL)$_4$[53] were prepared according the previously published procedures.

Instruments

Melting points were measured on a Stuart-SMP10 melting point apparatus and are uncorrected. IR was measured on a Perkin-Elmer (Boston, MA) TravelIR FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on Varian (Palo Alto, CA) 400-MR spectrometer at room temperature in the solvents given. Chemical shifts were expressed in parts per million (ppm) and reported either relative to an internal tetramethylsilane standard (TMS $\delta = 0.0$ or relative to solvent peaks ($CDCl_3$ $\delta = 7.2$, HOD $\delta = 4.8$, DMSO-d_6 $\delta = 2.5$) for ^{1}H and ($CDCl_3$ $\delta = 77.0$, DMSO-d_6 δ; = 39.5) for ^{13}C. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = double double doublet, m = multiplet, br = broad, apt = apparently. Coupling constants (*J*) are reported in Hz. Mass spectra were obtained on Finnigen mat LCQ MS/MS ESI spectrometer and AB MDS Sciex 4800 MALDI-TOF-TOF Mass Analyzer.

HPLC Analysis

The HPLC analysis was carried out at 25°C using a Prominence Shimadzu System that consists of LC-20AD solvent delivery unit, SPD-M20A photodiode-array detector, SIL-20AHT autosampler, and CTO-20A column oven. For data processing, LabSolutions data managing software, v. 5.54 SP2 was utilized. Chiralpak AD (0.46mm x 250mm), Chiralcel OJ (0.46mm x 250mm) and Chiralpak IB (0.46mm x 250mm) were obtained from Daicel Chemical Company (Tokyo, Japan). HPLC-grade *n*-hexane, ethyl acetate and 2-propanol were obtained from Scharlau Chemie (Barcelona, Spain). Chiral HPLC separation conditions were determined by obtaining a separation of a racemic sample and by applying previously reported parameters if any. Refer to supporting information for more details.

Synthesis of Dirhodium Complexes

General procedure for carboxylate ligands preparation. To a mixture of 1,2-naphthalic anhydride (1.1 equiv.) and the L-amino acid (1 equiv.) in anhydrous toluene, triethylamine (0.1 equiv.) was added

and the mixture was heated to reflux for 12 h under nitrogen atmosphere. The mixture was diluted with ethyl acetate, washed with 0.1M hydrochloric acid solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was then purified on silica gel column chromatography using ethyl acetate: *n*-hexane as an eluent. The amounts of 1,2-naphthalic anhydride and L-amino acids are presented in that order.

***N*-(1,2-Naphthaloyl)-(*S*)-*tert*-Leucine (*S*-1,2-NTTL, 1a).** 1,2-Naphthalic anhydride (0.650 g, 3.28 mmol), L-*tert*-Leucine (0.391 g, 2.98 mmol); Yellow oil (0.825 g, 89%); R_f= 0.38 (1:3 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (br s, 1H, COO*H*), 8.79 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 8.03 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 7.81 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 7.74 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.58-7.52 (m, 2H, Ar-*H*), 4.68 (s, 1H, NC*H*), 1.12 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8 (*C*OOH), 168.0, 167.5 (2 x *C*ON), 135.6, 134.2, 129.8, 128.5, 127.8, 127.6, 126.9, 125.9, 123.9, 117.5 (10 x Ar-*C*), 58.7 (N*C*H), 34.6 (*C*(CH$_3$)$_3$), 26.9 (C(*C*H$_3$)$_3$); IR (film) ν 3231, 2922, 1751, 1698, 1374, 1104, 1014, 796, 766, 725, 662 cm^{-1}; MS (ESI) *m/z*: 309.9 ($C_{18}H_{16}NO_4^-$; calc. 310.1), 266.0 ($C_{18}H_{16}NO_4^-$ - CO_2; calc. 266.1), 209.2 ($C_{18}H_{16}NO_4^-$ - CO_2 - C_4H_9; calc. 209.1).

***N*-(1,2-Naphthaloyl)-(*S*)-Phenylalanine (*S*-1,2-NTPA, 1b).** 1,2-Naphthalic anhydride (0.5 g, 2.52 mmol), L-Phenylalanine (0.35 g, 2.10 mmol); Pale yellow solid (0.65 g, 89%); mp 182°C; R_f = 0.20 (1:2 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 8.12 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.92 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 7.78 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 7.66 (dt, 2H, *J* = 14.9, 6.9 Hz, Ar-*H*), 7.38-7.00 (m, 5H, Ar-*H*), 5.27 (dd, 1H, *J* = 9.3, 6.9 Hz, NC*H*), 3.74-3.52 (m, 2H, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3 (*C*OOH), 168.6, 167.9 (2 x *C*ON), 136.6, 136.5, 135.1, 130.8, 129.5, 128.8, 128.7, 128.6, 127.9, 126.9, 124.9, 118.5 (16 x Ar-*C*), 52.9 (N*C*H), 34.5 (*C*H$_2$); IR (film) ν 3327, 2943, 1701, 1375, 1287, 769, 700 cm^{-1}; MS (ESI) *m/z*: 343.9 ($C_{21}H_{14}NO_4^-$; calc. 344.0), 299.9 ($C_{21}H_{14}NO_4^-$ - CO_2; calc. 300.1), 209.1 ($C_{21}H_{14}NO_4^-$ - CO_2 - C_7H_7; calc. 209.0). Re-crystallized from hot MeOH.

***N*-(1,2-Naphthaloyl)-(*S*)-Leucine (*S*-1,2-NTLU, 1c).** 1,2-Naphthalic anhydride (0.5 g, 2.52 mmol), L-Leucine (0.3 g, 2.29 mmol); Pale yellow solid (0.64 g, 90%); mp 138-139°C; R_f = 0.22 (1:3 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 (br s, 1H, COO*H*), 8.78 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 8.03 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.81 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 7.73 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.56 (dt, 2H, *J* = 24.8, 7.0 Hz, Ar-*H*), 4.94 (dd, 1H, *J* = 11.5, 4.3 Hz, NC*H*), 2.32 (ddd, 1H, *J* = 14.8, 11.0, 4.1 Hz, C*H*$_2$), 1.89 (ddd, 1H, *J* = 14.4, 10.2, 4.4 Hz, C*H*$_2$), 1.52-1.41 (m, 1H, C*H*(CH$_3$)$_2$), 0.86 (dd, 6H, *J* = 13.3, 6.6 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2 (*C*OOH), 167.8, 167.3 (2 x *C*ON), 135.6, 134.1, 129.9, 128.5, 127.8, 127.6, 126.9, 126.0, 123.9, 117.5 (10 x Ar-*C*), 49.3 (N*C*H), 36.1 (*C*H$_2$), 24.0 (*C*H(CH$_3$)$_2$), 22.0, 19.9 (2 x CH(*C*H$_3$)$_2$); IR (film) ν 2968, 1705, 1373, 1276, 764, 655 cm^{-1}; MS (ESI) *m/z*: 309.9 ($C_{18}H_{16}NO_4^-$; calc. 310.1), 266.0 ($C_{18}H_{16}NO_4^-$ - CO_2; calc. 266.1), 209.2 ($C_{18}H_{16}NO_4^-$ - CO_2 - C_4H_9; calc. 209.1). Re-crystallized from hot MeOH.

***N*-(1,2-Naphthaloyl)-(*S*)-Tryptophan (*S*-1,2-NTTR, 1d).** 1,2-Naphthalic anhydride (0.5 g, 2.52 mmol), L-Tryptophan (0.47 g, 2.29 mmol); Yellow solid (0.83 g, 85%); mp 238-239°C; R_f = 0.51 (1:1 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.3 (br s, 1H, COO*H*), 10.71 (s, 1H, N*H*), 8.68 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 8.34 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 8.11 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.81-7.69 (m, 3H, Ar-*H*), 7.51 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.22 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 7.06 (d, 1H, *J* = 2.3 Hz, Ar-*H*), 6.96 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 6.87 (t, 1H, *J* = 7.4 Hz, Ar-*H*), 5.14 (dd, 1H, *J* = 10.3, 5.6 Hz, NC*H*), 3.71-3.51 (m, 2H, C*H*$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9 (*C*OOH), 168.9, 168.1 (2 x *C*ON), 136.6, 136.4, 136.2, 130.9, 130.5, 129.6, 129.4, 127.4, 127.4, 126.4, 124.1, 123.8, 121.3, 118.8, 118.3, 111.8, 110.3 (18 x Ar-*C*), 53.1 (N*C*H), 24.6 (*C*H$_2$); IR (film) ν 3458, 3317, 2917, 1700, 1380, 1282, 769, 740 cm^{-1}; MS (ESI) *m/z*: 382.9 ($C_{23}H_{15}N_2O_4^-$; calc. 383.1), 339.2 ($C_{23}H_{15}N_2O_4^-$ - CO_2; calc. 339.1), 210.2 ($C_{23}H_{15}N_2O_4^-$ - CO_2 - C_9H_7N; calc. 210.1). Re-crystallized from hot MeOH.

***N*-(1,2-Naphthaloyl)-(*S*)-Tyrosine (*S*-1,2-NTTY, 1e).** 1,2-Naphthalic anhydride (0.5 g, 2.52 mmol), L-Tyrosine (0.42 g, 2.29 mmol); Yellow solid (0.74 g, 90%); mp 248-249°C; R_f = 0.25 (1:1 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.11 (br s, 1H, COO*H*), 8.70 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 8.38 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 8.14 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.88-7.69 (m, 3H, Ar-*H*), 6.94 (apt d, 2H, *J* = 8.5 Hz, Ar-*H*), 6.51 (apt d, 2H, *J* = 8.5 Hz, Ar-*H*), 5.01 (dd, 1H, *J* = 11.6, 4.8 Hz, NC*H*), 3.40-3.25 (m, 3H, C*H*$_2$, O*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3 (*C*OOH), 168.4, 167.5 (2 x *C*ON), 155.8, 136.4, 135.9, 130.3, 130.1, 129.6, 129.2, 129.1, 127.3, 127.0, 125.9, 123.7, 118.4, 115.1 (16 x Ar-*C*), 53.3 (N*C*H), 33.2 (*C*H$_2$); IR (film) ν 3437, 3243, 2943, 1734, 1686, 1387, 1225, 772, 675 cm^{-1}; MS (ESI) *m/z*: 359.9 ($C_{21}H_{14}NO_5^-$; calc. 360.1), 210.2 ($C_{21}H_{14}NO_5^-$ - CO_2 - C_7H_6O; calc. 210.1). Re-crystallized from hot MeOH.

General Procedure for Ligand Exchange

A mixture of the carboxylate ligand (6 equiv.) and dirhodium acetate (1 equiv.) in dry chlorobenzene was refluxed for 24 h under nitrogen atmosphere using a soxhelt extractor fitted with a thimble containing a dry mixture of Na_2CO_3 and sand (1:1) for the removal of acetic acid. After this, the solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The green residue was then purified on silica gel column chromatography using ethyl acetate: *n*-hexane as an eluent. Products were dried overnight under vacuum at 50°C. The amounts of carboxylate ligand and dirhodium acetate are presented in that order.

Dirhodium(II,II) tetrakis[*N*-(1,2-naphthaloyl)-(*S*)-*tert*-Leucinate] (Rh_2(*S*-1,2-NTTL)$_4$, 3a). Ligand (0.69 g, 2.23 mmol), $Rh_2(OAc)_4$ (0.17 g, 0.38 mmol); green solid (0.36 g, 65%); R_f = 0.54 (1:2 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (br s, 4H, Ar-*H*), 7.92 (br s, 4H, Ar-*H*), 7.74 (br s, 8H, Ar-*H*), 7.52 (br s, 8H, Ar-*H*), 4.92 (s, 4H, 4 x NC*H*), 1.1 (s, 36H, 4 x C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.2 (*C*OO), 167.3 (*C*ON), 135.3, 133.5, 130.1, 128.2, 127.3, 126.9, 126.1, 124.3, 117.6 (Ar-*C*), 60.3 (N*C*H), 34.8 (*C*(CH$_3$)$_3$), 27.0 (C(*C*H$_3$)$_3$); IR (film) ν 2958, 1707, 1610, 1396, 1366, 1341, 1105, 783, 765 cm^{-1}; HRMS (MALDI-TOF) *m/z*: 1661.2025 ($C_{72}H_{61}N_4O_{16}Rh_2 + K^+$ + 2EtOAc, calc. 1661.4481), 1645.2306 ($C_{72}H_{61}N_4O_{16}Rh_2 + Na^+$ + 2EtOAc, calc. 1645.3395), 1485.1979 ($C_{72}H_{61}N_4O_{16}Rh_2 + K^+$, calc. 1485.3433), 1469.2275 ($C_{72}H_{61}N_4O_{16}Rh_2 + Na^+$, calc. 1469.2347).

Dirhodium(II,II) tetrakis[*N*-(1,2-naphthaloyl)-(*S*)-Phenylalaninate] (Rh_2(*S*-1,2-NTPA)$_4$, 3b). Ligand (0.5 g, 1.45 mmol), $Rh_2(OAc)_4$ (0.11 g, 0.24 mmol); green solid (0.25 g, 63%); R_f = 0.28 (1:1 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 4H, *J* = 8.1 Hz, Ar-*H*), 7.82 (d, 4H, *J* = 7.4 Hz, Ar-*H*), 7.71 (d, 4H, *J* = 8.3 Hz, Ar-*H*), 7.57 (m, 8H, Ar-*H*), 7.35-6.99 (m, 24H, Ar-*H*), 5.37 (dd, 4H, *J* = 11.4, 4.7 Hz, 4 x NC*H*), 3.73-3.50 (m, 8H, 4 x C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5 (*C*OO), 168.4, 167.9 (*C*ON), 137.9, 136.5, 135.0, 131.1, 129.4, 128.6, 128.5, 128.0, 127.2, 126.6, 125.3, 118.8 (Ar-*C*), 54.6 (N*C*H), 35.7 (*C*H$_2$); IR (film) ν 2944, 1734, 1716, 1373, 1229, 770, 697 cm^{-1}; HRMS (ESI-TOF) *m/z*: 1721.2692 ($C_{84}H_{60}N_4O_{16}Rh_2$ + 2Acetone + Na^+, calc. 1721.2536), 1663.2191 ($C_{84}H_{60}N_4O_{16}Rh_2$ + Acetone + Na^+, calc. 1663.2118), 1646.2117 ($C_{84}H_{60}N_4O_{16}Rh_2 + H_2O + 2Na^+$, calc. 1646.1702), 1606.1798 ($C_{84}H_{60}N_4O_{16}Rh_2 + Na^+ + H^+$, calc. 1606.1777).

Dirhodium(II,II) tetrakis[*N*-(1,2-naphthaloyl)-(*S*)-Leucinate] (Rh_2 (*S*-1,2-NTLU)$_4$, 3c). Ligand (0.5 g, 1.60 mmol), $Rh_2(OAc)_4$ (0.12 g, 0.27 mmol); green solid (0.166 g, 61 %); R_f = 0.69 (1:2 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (d, 4H, *J* = 7.8 Hz, Ar-*H*), 8.22-7.95 (m, 4H, Ar-*H*), 7.95-7.73 (m, 8H, Ar-*H*), 7.73-7.43 (m, 8H, Ar-*H*), 5.02 (br s, 1H, 4 x NC*H*), 2.23 (br s, 4H, 2 x C*H*$_2$), 2.03 (br s, 4H, 2 x C*H*$_2$), 1.50 (br s, 4H, 4 x C*H*(CH$_3$)$_2$), 1.01 (br s, 12H, 2 x CH(C*H*$_3$)$_2$), 0.93 (br s, 12H, 2 x CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9 (*C*OO), 168.5, 168.0 (*C*ON), 136.3, 134.5, 131.2, 129.1, 128.5, 128.4, 128.0, 127.9, 127.2, 125.2, 118.7, 118.6 (Ar-*C*), 51.8 (N*C*H), 38.2, 38.0 (*C*H$_2$), 25.1 (*C*H(CH$_3$)$_2$), 23.4, 21.4, 21.3 (CH(*C*H$_3$)$_2$); IR (film) ν 2954, 1734, 1716, 1374, 1229, 770, 675 cm^{-1}; HRMS (MALDI-TOF) *m/z*: 1661.2783 ($C_{72}H_{61}N_4O_{16}Rh_2 + K^+$ + 2EtOAc, calc. 1661.4481), 1645.3109 ($C_{72}H_{61}N_4O_{16}Rh_2 + Na^+$ + 2EtOAc, calc. 1645.3395), 1485.2178 ($C_{72}H_{61}N_4O_{16}Rh_2 + K^+$, calc. 1485.3433), 1469.2975 ($C_{72}H_{61}N_4O_{16}Rh_2 + Na^+$, calc. 1469.2347).

Dirhodium(II,II) tetrakis[*N*-(1,2-naphthaloyl)-(*S*)-Tryptophanate] (Rh_2(*S*-1,2-NTTR)$_4$, 3d). Ligand (0.73 g, 1.90 mmol), $Rh_2(OAc)_4$ (0.14 g, 0.32 mmol); green solid (0.30 g, 55 %); R_f = 0.20 (2:1 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.75 (s, 4H, 4 x N*H*), 8.50 (m, 4H, Ar-*H*), 8.31 (br s, 4H, Ar-*H*), 8.07 (br s, 4H, Ar-*H*), 7.80-7.41 (m, 12H, Ar-*H*), 7.25 (d, 4H, *J* = 7.8 Hz, Ar-*H*), 7.17-6.69 (m, 16H, Ar-*H*), 5.27 (br s, 4H, 4 x NC*H*), 3.57 (br s, 8H, 4 x CH_2); IR (film) ν 2970, 1734, 1699, 1374, 1228, 768, 740 cm^{-1}; MS (ESI) *m/z*: 1760.6 ($C_{92}H_{60}N_8O_{16}Rh_2$ + Na^+ - H^+, calc. 1760.2), 1376.7 ($C_{92}H_{60}N_8O_{16}Rh_2$ + Na^+ - $C_{23}H_{16}N_2O_4$, calc. 1377.1), 992.7 ($C_{92}H_{60}N_8O_{16}Rh_2$ + Na^+ - $C_{46}H_{32}N_4O_8$, calc. 992.9).

Dirhodium(II,II) tetrakis[*N*-(1,2-naphthaloyl)-(*S*)-Tyrosinate] (Rh_2 (*S*-1,2-NTTY)$_4$, 3e). Ligand (0.63g, 1.76 mmol), $Rh_2(OAc)_4$ (0.13 g, 0.30 mmol); green solid (0.27 g, 56 %); R_f = 0.23 (2:1 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43-8.25 (m, 4H, Ar-*H*), 8.21-8.04 (m, 4H, Ar-*H*), 7.92-7.25 (m, 16H, Ar-*H*), 7.04-6.82 (m, 8H, Ar-*H*), 6.65-6.34 (m, 8H, Ar-*H*), 5.18-4.90 (m, 4H, 4 x NCH), 3.50-3.05 (m, 12H, 4 x CH_2, 4 x O*H*); IR (film) ν 3294, 2970, 1734, 1699, 1375, 1217, 770, 742, 685 cm^{-1}.

General Procedure for the Preparation of Cyclopropylphosphonate Derivatives

To a stirred solution of alkene (5 equiv.) and Rh(II) catalyst (0.01 equiv.) in 2,2-DMB (5 mL) heated under reflux (59°C) under nitrogen atmosphere, a solution of α-diazobenzylphosphonate (1 equiv.) in 2,2-DMB (10 mL) was added dropwise via syringe pump over 1 h. After the addition, the reaction was refluxed until the TLC indicates a complete consumption of the diazo starting material. The diastereomeric ratio (dr) of the product was determined by ^{1}H NMR of the crude mixture. The product was purified by means of preparative TLC (ethyl acetate/ *n*-hexane) and the enantiomeric excess (*ee* %) of the product was determined by chiral HPLC analysis.

(1*S*,2*R*)-Dimethyl 1,2-diphenylcyclopropylphosphonate (5)[54,55]. Colorless oil; R_f = 0.15 (1:1 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralcel OJ column, 25 x 0.46 cm, 2% 2-propanol in *n*-hexane (*v/v*%); 1 mL/min, 220 nm, τ_1 = 18 min, τ_2 = 21 min). The spectroscopic data are consistent with previously reported data.[54,55]

(1*S*,2*R*)-Dimethyl 1-pheny-2-(*p*-chlorophenyl)-cyclopropylphosphonate (6)[55]. Colorless oil; R_f = 0.11 (1:1 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralcel OJ column, 25 x 0.46 cm, 8% 2-propanol in *n*-hexane (*v/v*%); 1 mL/min, 220 nm, τ_1 = 10 min, τ_2 = 12 min). The spectroscopic data are consistent with previously reported data.[55]

(1*S*,2*R*)-Dimethyl 1-pheny-2-(*p*-methoxyphenyl)-cyclopropylphosphonate (7)[55]. Colorless oil; R_f = 0.11 (1:1 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralcel OJ column, 25 x 0.46 cm, 3% 2-propanol in *n*-hexane (*v/v*%); 1 mL/min, 220 nm, τ_1 = 37 min, τ_2 = 42 min). The spectroscopic data are consistent with previously reported data.[55]

(1*S*,2*R*)-Dimethyl 1-pheny-2-(*p*-methylphenyl)-cyclopropylphosphonate (8). White solid; R_f = 0.17 (1:1 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.10 (m, 3H, Ar-*H*), 7.07-7.04 (m, 2H, Ar-*H*), 6.85 (d, 2H, *J* = 7.8 Hz, Ar-*H*), 6.61 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 3.72 (d, 3H, J_{HP} = 10.6 Hz, OCH_3), 3.66 (d, 3H, J_{HP} = 10.6 Hz, OCH_3), 2.97 (ddd, 1H, J_{HP} = 16.1, *J* = 9.1, 6.6 Hz, C*H*), 2.19 (s, 3H, CH_3), 2.03 (ddd, 1H, J_{HP} = 17.5, *J* = 9.0, 5.1 Hz, CH_2), 1.67 (ddd, 1H, J_{HP} = 12.5, *J* = 6.6, 5.1 Hz, CH_2); Enantiomer separation by HPLC (Chiralcel OJ column, 25 x 0.46 cm, 3% 2-propanol in *n*-hexane (*v/v*%); 1 mL/min, 220 nm, τ_1 = 12 min, τ_2 = 15 min).

(1*S*,2*R*)-Dimethyl 1-pheny-2-(1-naphthyl)-cyclopropylphosphonate (9). Colorless oil; R_f = 0.14 (1:1 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.53 (m, 2H, Ar-*H*), 7.50 (d, 1H, *J* = 7.50 Hz, Ar-*H*), 7.35 (m, 2H, Ar-*H*), 7.29 (s, 1H, Ar-*H*), 7.07 (m, 4H, Ar-*H*), 6.76 (dd, 1H, *J* = 8.5, 1.8 Hz, Ar-*H*), 3.75 (d, 3H, J_{HP} = 10.6 Hz, OCH_3), 3.70 (d, 3H, J_{HP} = 10.6 Hz, OCH_3), 3.16 (ddd, 1H, J_{HP} = 16.1, *J* = 9.1, 6.6 Hz, C*H*), 2.14 (ddd, 1H, J_{HP} = 17.5, *J* = 9.0, 5.3 Hz, CH_2), 1.85 (ddd, 1H, J_{HP} = 12.5, *J* = 6.6, 5.1 Hz, CH_2); Enantiomer separation by HPLC (Chiralpak AD column, 25 x 0.46 cm, 1% 2-propanol in *n*-hexane (*v/v*%); 2 mL/min, 220 nm, τ_1 = 36 min, τ_2 = 42 min).

(1*S*,2*R*)-Diethyl 1,2-diphenylcyclopropylphosphonate (10)[55]. Colorless oil; R_f = 0.26 (1:1 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralpak AD column, 25 x 0.46 cm, 0.6% 2-propanol in *n*-hexane (*v/v*%); 0.8 mL/min, 220 nm, τ_1 = 69 min, τ_2 = 76 min). The spectroscopic data are consistent with previously reported data.[55]

(1*S*,2*R*)-Diisopropyl 1,2-diphenylcyclopropylphosphonate (11)[55]. Colorless oil; R_f = 0.40 (1:1 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralpak AD column, 25 x 0.46 cm, 0.6% 2-propanol in *n*-hexane (*v/v*%); 0.8 mL/min, 220 nm, τ_1 = 49 min, τ_2 = 54 min). The spectroscopic data are consistent with previously reported data.[55]

General Procedure for the Preparation of Cyclopropylcarboxylates

To a solution of the alkene (5.0 equiv.) and dirhodium catalyst (0.01 equiv.) in dry and degassed solvent under inert atmosphere, the diazo compound (1.0 equiv.) dissolved in the same dry and degassed solvent, was added dropwise over 1 h using a syringe pump. After that, the reaction was stirred for at least 1 h. When the diazo compound was fully consumed as indicated by TLC, the reaction solvent was removed in vacuo. The diastereomeric ratio (dr) of the product was determined by ^{1}H NMR of the crude mixture. The product was purified by means of preparative TLC (ethyl acetate/n-hexane). The enantiomeric excess (*ee* %) of the product was determined by chiral HPLC analysis.

Methyl 1,2-diphenylcyclopropanecarboxylate (13)[56,57]. White solid; mp 60-62°C; R_f = 0.30 (1:10 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralcel OJ column, 25 x 0.46 cm, 0.5% 2-propanol in *n*-hexane; 1 mL/min. 220 nm, τ_1 = 14 min, τ_2 = 20 min). The spectroscopic data are consistent with previously reported data.[56,57]

Methyl 2β-phenyl-1β-(2-(*Z*)-styryl)cyclopropane-1α-carboxylate (15)[58]. White solid; mp 58-61°C; R_f = 0.63 (1:3 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralcel OJ column, 25 x 0.46 cm, 1.5% 2-propanol in *n*-hexane; 1 mL/min. 254 nm, τ_1 = 15 min, τ_2 = 21 min). The spectroscopic data are consistent with previously reported data.[58]

General Procedure for One-Pot Intermolecular Cyclopropanation of Olefins Using Meldrum's Acid

To a stirred mixture of Meldrum's acid (1 equiv.), $PhI(OAc)_2$ (1.4 equiv.), dirhodium catalyst (0.01 equiv.), Al_2O_3 (2.3 equiv.) and 4Å molecular sieves in dry dichloromethane under N_2 atmosphere, olefin (10 equiv.) was added. After allowing the reaction mixture to stir at room temperature for 4 h, the reaction was terminated by filtration through celite and concentrated under reduced pressure. The residue was purified by means of preparative TLC chromatography using ethyl acetate: *n*-hexane (1:4) as an eluent to get the desired products. The enantiomeric ratio of the product was determined by HPLC analysis.

6,6-dimethyl-1-phenyl-5,7-dioxaspiro[2.5]octane-4,8-dione[59]. White solid; mp 132°C; R_f = 0.55 (1:3 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralpak IB column, 25 x 0.46 cm, 10% ethyl acetate in *n*-hexane; 1 mL/min. 254 nm, τ_1 = 10 min, τ_2 = 12.9 min). The spectroscopic data are consistent with previously reported data.[59]

6,6-dimethyl-1-(4-chlorophenyl)-5,7-dioxaspiro[2.5]octane-4,8-dione[59]. White solid; mp 157°C; R_f = 0.71 (1:3 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralpak IB column, 25 x 0.46 cm, 10% ethyl acetate in *n*-hexane; 0.5 mL/min. 254 nm, τ_1 = 26 min, τ_2 = 32 min). The spectroscopic data are consistent with previously reported data.[59]

6,6-dimethyl-1-(4-bromophenyl)-5,7-dioxaspiro[2.5]octane-4,8-dione. White solid; mp 144°C; R_f = 0.40 (1:3 ethyl acetate: *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, 4H, *J* = 8.5 Hz, Ar-*H*), 3.39 (apt t, 1H, *J* = 9.4 Hz, C*H*), 2.63 (dd, 1H, *J* = 9.3, 4.8 Hz, CH_2), 2.54 (dd, 1H, *J* = 9.5, 4.8 Hz, CH_2), 1.74 (s, 3H, CH_3), 1.71 (s, 3H, CH_3); Enantiomer

separation by HPLC (Chiralpak IB column, 25 x 0.46 cm, 10% ethyl acetate in *n*-hexane; 0.5 mL/min. 254 nm, $\tau_1 = 31$ min, $\tau_2 = 39$ min).

6,6-dimethyl-1-(4-methylphenyl)-5,7-dioxaspiro[2.5]octane-4,8-dione[59]. White Solid; mp 137°C; $R_f = 0.33$ (1:3 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralpak IB column, 25 x 0.46 cm, 10% ethyl acetate in *n*-hexane; 0.5 mL/min. 254 nm, $\tau_1 = 26$ min, $\tau_2 = 31$ min). The spectroscopic data are consistent with previously reported data.[59]

6,6-dimethyl-1-naphthyl-5,7-dioxaspiro[2.5]octane-4,8-dione[59]. Yellowish solid; mp 120°C; $R_f = 0.68$ (1:3 ethyl acetate: *n*-hexane); Enantiomer separation by HPLC (Chiralpak IB column, 25 x 0.46 cm, 10% ethyl acetate in *n*-hexane; 0.5 mL/min. 254 nm, $\tau_1 = 46$ min, $\tau_2 = 56$ min). The spectroscopic data are consistent with previously reported data.[59]

RESULTS AND DISCUSSION

Synthesis of Dirhodium (II) Tetracarboxylate Catalytic Series

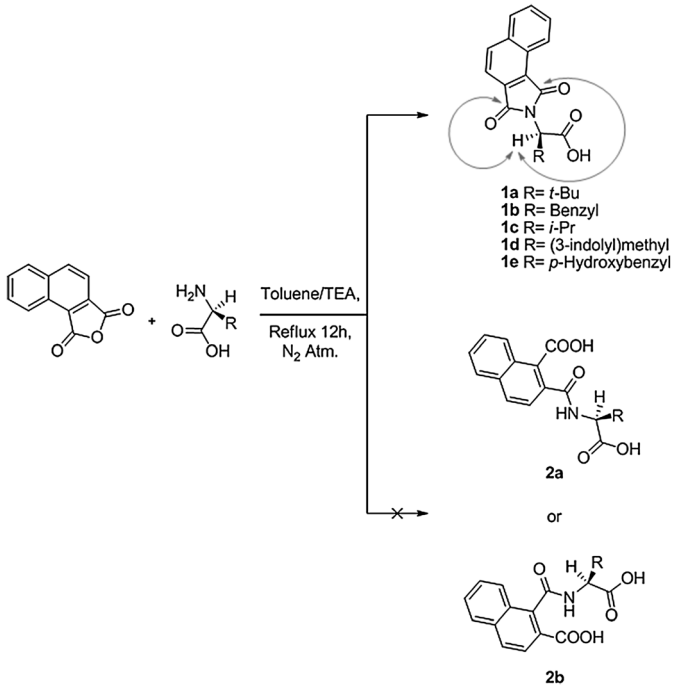
Unlike the previously reported trends used in the development of chiral dirhodium(II) catalysts where the modifications in the dirhodium paddlewheel catalysts mostly focused on the use of symmetrical *N*-protecting group (Fig. 1), we are introducing ligands with a lower symmetry *N*-protecting group. As a starting point, we thought about a protecting group that can retain the *N*-phthaloyl rings of Hashimoto's catalytic series along with the horizontal naphthalene rings of Müller's catalytic series (Fig. 2) for intermolecular cyclopropanation reactions. Thus, chiral carboxylate ligands derived from *N*-1,2-naphthaloyl-(*S*)-amino acids were synthesized. The ligands **1a–e** were prepared via the condensation of 1,2-naphthalic anhydride and (*S*)-amino acids in toluene/TEA solvent mixture (Scheme 2). The structures elucidation of the prepared ligands was confirmed on the basis of their 1D-, 2D-NMR, and MS spectral data. The HMBC spectra for **1a**, **1b**, **1c,** and **1d** revealed a long-range chemical shift correlation between the chiral hydrogen and both carbonyl carbons of the imide. This long-range ^1H-^{13}C correlation provided evidence for the formation of the cyclic imide structures (**1a–e**) and not the open chain amides **2a–b** (Scheme 2).

High-temperature ligand exchange was then carried out using the prepared chiral carboxylic acid ligands and rhodium acetate ($Rh_2(OAc)_4$).[60] Ligand exchange proceeded successfully, affording the corresponding dirhodium(II,II) tetrakis[*N*-(1,2-naphthoyl)-(*S*)-amino acid] complexes (**3a–e**) (Scheme 3). Their structures were confirmed on the basis of their ^1H and ^{13}C NMR spectra.

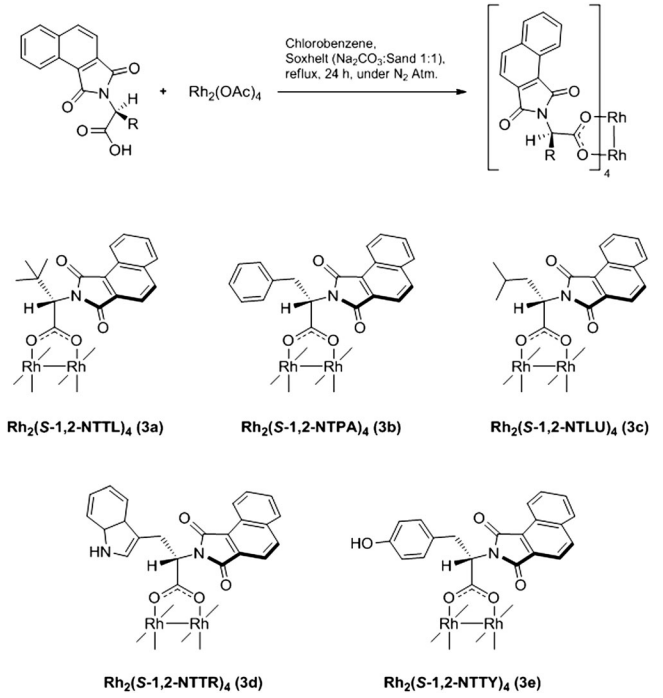
Screening for Asymmetric Cyclopropanation With Donor-Acceptor Diazophoshonate Substrates

With the new catalytic series in hand (**3a–e**), their efficiencies were evaluated in standard donor-acceptor cyclopropanation reactions using dimethyl α-diazobenzylphosphonate **4** (as carbene precursor) and styrene (as olefin substrate) in 2,2-dimethylbutane (2,2-DMB) as reaction solvent. The previously reported Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-NTTL)$_4$ catalysts (Fig. 1) were included in the screening as well-established catalysts in the enantioselective cyclopropanation reactions (Table 1). All catalysts revealed high levels of diastereoselectivities where the diastereomeric ratios (dr) >20:1 for the resulted cyclopropane products.

The results in Table 1 were in agreement with the previously reported trend by Hashimoto in regard to the steric bulk at the α-position and the selectivity of the catalyst.[41,61] From the illustrated results, it can be concluded that the



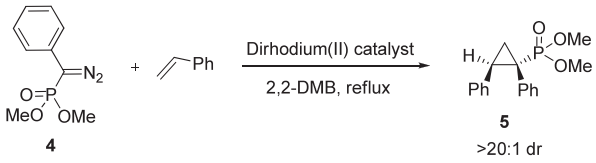
Scheme 2. Preparation of chiral ligands.



Scheme 3. Preparation and structure of new catalysts.

catalyst bearing the bulky *tert*-butyl group (**3a**) was the best catalyst among the series. This was followed by those bearing the *iso*-butyl (**3c**) and benzyl (**3b**) groups and finally those carrying the (3-indolyl)methyl (**3d**) and the 4-hydroxylbenzyl (**3e**) groups. The cyclopropanation reaction catalyzed by Rh_2(*S*-1,2-NTTL)$_4$ (**3a**) generated the cyclopropane product in 92% *ee* (Fig. 3), which is similar to the same reaction catalyzed by Rh_2(*S*-PTTL)$_4$ and slightly better than the one catalyzed by Rh_2(*S*-NTTL)$_4$ (90% *ee*).

TABLE 1. Asymmetric cyclopropanation with dimethyl α-diazobenzylphosphonate (donor-acceptor substrate)



Entry	Catalyst	Code	Reaction Time (h)	Yield (%)	*ee* (%)
1	Rh_2(*S*-PTAD)$_4$[47]	-	8	86	99
2	Rh_2(*S*-PTTL)$_4$	-	10	83	92
3	Rh_2(*S*-NTTL)$_4$	-	5	91	90
4	Rh_2(*S*-1,2-NTTL)$_4$	**3a**	5	93	92
5	Rh_2(*S*-1,2-NTPA)$_4$	**3b**	5	91	34
6	Rh_2(*S*-1,2-NTLU)$_4$	**3c**	5	94	64
7	Rh_2(*S*-1,2-NTTR)$_4$	**3d**	20	76	22
8	Rh_2(*S*-1,2-NTTY)$_4$	**3e**	20	80	26

Diastereomeric ratios (dr) were determined by 1H NMR of the crude mixture. Enantiomeric excess (*ee* %) were determined by chiral HPLC using Chiralcel OJ column, 2% 2-propanol in *n*-hexane (*v/v*%), 1 mL/min., 220 nm, $\tau_1 = 18$ min., $\tau_2 = 21$ min. See Materials and Methods section for more details.

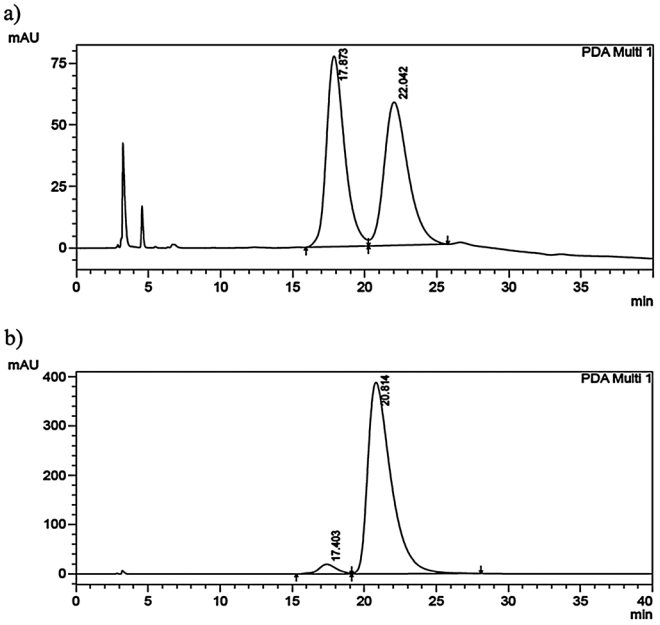
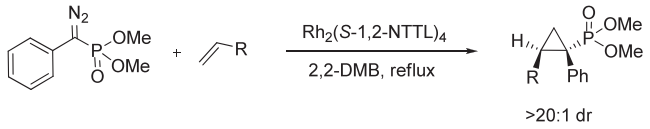
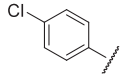
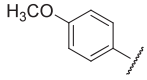
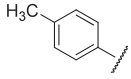
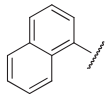


Fig. 3. Chiral HPLC trace of (1*S*,2*R*)-Dimethyl 1,2-diphenylcyclopropylphosphonate (**5**) (a) prepared using $Rh_2(OAc)_4$ (Racemic sample) (b) prepared using Rh_2(*S*-1,2-NTTL)$_4$. Chromatographic conditions: Chiralcel OJ column, 2% 2-propanol in *n*-hexane (*v/v*%), 1 mL/min., 220 nm.

The yields of the cyclopropane product **5** were generally high for all catalysts, ranging from 76% to 93%. The observed yield of the product resulting from the reaction catalyzed by Rh_2(*S*-1,2-NTTL)$_4$ was slightly higher than those resulting from reactions catalyzed by Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-NTTL)$_4$ (Table 1). This can be rationalized to the ligand's larger aromatic moiety, which offers a relatively higher solubility of Rh_2(*S*-1,2-NTTL)$_4$ in nonpolar solvents. Its better solubility also offered a quicker conversion into products resulting in a shorter reaction time when compared to Rh_2(*S*-PTTL)$_4$.

TABLE 2. Scope of Rh_2(*S*-1,2-NTTL)$_4$ (3a) with respect to the alkene



Entry	R group	Product	Yield (%)	*ee* (%)
1		**6**	92	94
2		**7**	93	>99
3		**8**	90	95
4		**9**	86	>98

Diastereomeric ratios (dr) were determined by 1H NMR of the crude mixture. Enantiomeric excess (*ee* %) were determined by chiral HPLC. See Materials and Methods section for more details.

The scope of the Rh_2(*S*-1,2-NTTL)$_4$ catalyst was further investigated with respect to the alkene (Table 2). The reactions proceeded smoothly, resulting in the formation of cyclopropylphosphonate products with very high yields (86–93%), diasteroselectivity (>20:1 dr), and enantioselectivity (94- > 99% *ee*).

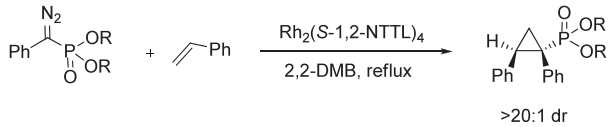
The effect of diazophosphonate ester size on the enantioselectivity of the Rh_2(*S*-1,2-NTTL)$_4$ - catalyzed reaction was next examined (Table 3). The diastereoselectivity is independent on the size of the phosphonate group and not greatly influenced by the ester size. However, both yield and enantioselectivity were decreasing with increasing the ester group size and the highest levels of enantioselectivity were observed with dimethyl phenyldiazophosphonate (Entry 1, Table 3).

Screening for Asymmetric Cyclopropanations With Other Donor-Acceptor Substrates

Encouraged by the cyclopropanation results illustrated in Tables 1–3, the scope of the new catalysts was further investigated by looking into more donor-acceptor carbenoid cyclopropanations. To study the influence of replacing the phosphonate ester group of the carbenoid with a carboxylate ester group on the catalyst enantioselectivity, the next series of experiments were carried out using methyl α-phenyldiazoacetate **12** (Table 4).

As illustrated in Table 4, all catalysts afforded the cyclopropane product **13** in excellent to good yields (89–65%) with high diastereoselectivity (>18:1 dr). However, the asymmetric induction deteriorated dramatically with the replacement

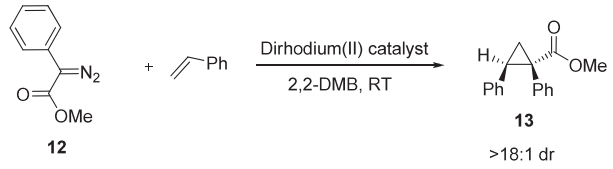
TABLE 3. Effect of the ester group size on the enantiomeric induction of Rh_2(*S*-1,2-NTTL)$_4$



Entry	R group	Product	Yield (%)	*ee* (%)
1	Me	**5**	93	92
2	Et	**10**	69	60
3	*i*-Pr	**11**	43	68[a]

[a]After reflux for 3 days. Diastereomeric ratios (dr) were determined by 1H NMR of the crude mixture. Enantiomeric excess percents (*ee* %) were determined by chiral HPLC. See Materials and Methods section for more details.

TABLE 4. Asymmetric cyclopropanation with methyl *α*-diazophenylacetate (donor-acceptor substrate)



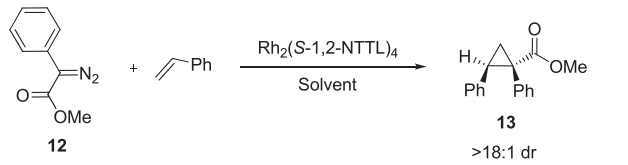
Entry	Catalyst	Code	Yield (%)	*ee* (%)
1	Rh_2(*S*-PTAD)$_4$[57]	-	87[a]	21[a]
2	Rh_2(*S*-PTTL)$_4$	-	87	20
3	Rh_2(*S*-NTTL)$_4$	-	88	8
4	Rh_2(*S*-1,2-NTTL)$_4$	**3a**	89	30
5	Rh_2(*S*-1,2-NTPA)$_4$	**3b**	86	18
6	Rh_2(*S*-1,2-NTLU)$_4$	**3c**	86	14
7	Rh_2(*S*-1,2-NTTR)$_4$	**3d**	63	20
8	Rh_2(*S*-1,2-NTTY)$_4$	**3e**	65	16

[a]In toluene. Diastereomeric ratios (dr) were determined by 1H NMR of the crude mixture. Enantiomeric excess (*ee* %) were determined by chiral HPLC using Chiralcel® OJ column, 0.5% 2-propanol in *n*-hexane (*v*/*v*%), 1 mL/min., 220 nm, τ_1 = 14 min., τ_2 = 20 min. See Materials and Methods section for more details.

of the phosphonate ester group with a carboxylate ester group. The enantiomeric induction of the catalysts did not exceed 30% *ee,* which was exhibited by Rh_2(*S*-1,2-NTTL)$_4$ **(3a)** (Entry 4, Table 4). Although the enantiomeric induction of Rh_2(*S*-1,2-NTTL)$_4$ was not significantly high, it was still considerably higher than those exhibited by Rh_2(*S*-PTAD)$_4$, Rh_2(*S*-NTTL)$_4$, and Rh_2(*S*-PTTL)$_4$ for the same reaction (Entries 1, 2, and 3, Table 4).

As an attempt to enhance the enantioselectivity of Rh_2(*S*-1,2-NTTL)$_4$ catalyst, the effects of changing the reaction conditions (e.g., solvent and temperature) were investigated (Table 5). Using methylene chloride as a reaction solvent rather than 2,2-DMB resulted in slight decrease in enantioselectivity of Rh_2(*S*-1,2-NTTL)$_4$ (Entry 4, Table 5). The enantioselectivity decreased dramatically when toluene or pentane was used (Entries 3 and 5, Table 5). Furthermore, the variation of temperature had a little influence on the

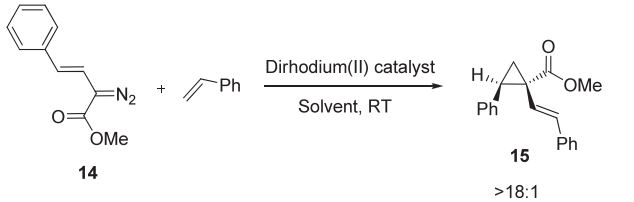
TABLE 5. Effect of solvent and temperature on the stereoselectivity of Rh_2(*S*-1,2-NTTL)$_4$ with methyl *α*-diazophenylacetate substrate



Entry	Solvent	Temperature (°C)	Yield (%)	*ee* (%)
1	2,2-DMB	23	89	30
2	2,2-DMB	-20	82	28
3	Toluene	23	88	-2
4	CH_2CL_2	23	90	26
5	Pentane	23	87	18

Diastereomeric ratios (dr) were determined by 1H NMR of the crude mixture. Enantiomeric excess (ee %) were determined by chiral HPLC using Chiralcel® OJ column, 0.5% 2-propanol in *n*-hexane (*v*/*v*%), 1 mL/min., 220 nm, τ_1 = 14 min., τ_2 = 20 min. See Materials and Methods section for more details.

TABLE 6. Asymmetric cyclopropanation with methyl *α*-diazostyrylacetate (donor-acceptor substrate)



Entry	Catalyst	Code	Solvent	Yield (%)	*ee* (%)
1	Rh_2(*S*-PTTL)$_4$	-	CH_2Cl_2	83	40
2	Rh_2(*S*-NTTL)$_4$	-	CH_2Cl_2	82	16
3	Rh_2(*S*-1,2-NTTL)$_4$	**3a**	CH_2Cl_2	88	10
4	Rh_2(*S*-1,2-NTTL)$_4$	**3a**	Pentane	87	10
5	Rh_2(*S*-1,2-NTPA)$_4$	**3b**	CH_2Cl_2	82	18
6	Rh_2(*S*-1,2-NTLU)$_4$	**3c**	CH_2Cl_2	89	23
7	Rh_2(*S*-1,2-NTTR)$_4$	**3d**	CH_2Cl_2	65	20
8	Rh_2(*S*-1,2-NTTY)$_4$	**3e**	CH_2Cl_2	67	20

Diastereomeric ratios (dr) were determined by 1H NMR of the crude mixture. Enantiomeric excess percents (*ee* %) were determined by chiral HPLC using Chiralcel OJ column, 1.5% 2-propanol in *n*-hexane (*v*/*v*%), 1 mL/min., 254 nm, τ_1 = 15 min., τ_2 = 21 min. See Materials and Methods section for more details.

enantioselectivity of Rh_2(*S*-1,2-NTTL)$_4$ over a reaction temperature range from 23°C to –20°C (Entries 1 and 2, Table 5).

The final series of experiments were carried out using methyl *α*-styryldiazoacetate **14** with the phenylvinyl functionality as an attempt to enhance the enantioinduction of the catalysts with diazocarboxylates. The reactions were carried out at room temperature using methylene chloride as reaction solvent (Table 6). The desired cyclopropane product **15** was obtained in yield range from 65% to 89% with high levels of diastereoselectivity (>20:1 dr). However, the enantiomeric induction did not exceed 23% *ee* when using Rh_2(*S*-1,2-NTLU)$_4$ (Entry 6, Table 6). Although the

enantioselectivity of Rh_2(*S*-PTTL)$_4$ was the highest (40% *ee*), the enantioselectivity exhibited by Rh_2(*S*-1,2-NTLU)$_4$ (**3c**), Rh_2(*S*-1,2-NTTR)$_4$ (**3d**), Rh_2(*S*-1,2-NTTY)$_4$ (**3e**), and Rh_2(*S*-1,2-NTPA)$_4$ (**3b**) were higher than that observed when using Rh_2(*S*-NTTL)$_4$. Altering the reaction solvent from methylene chloride to pentane did not affect the degree of enantioselectivity (Entries 3 and 4, Table 6).

Screening for Asymmetric Cyclopropanation With Diacceptor Substrates

In order to probe the enantiomeric induction of the prepared catalytic series with diacceptor carbenoid intermediates, the enantioselective cyclopropanation of Meldrum's acid with a variety of alkenes was examined. To facilitate the screening, a previously developed user-friendly one-pot cyclopropanation procedure was used, wherein the phenylidonium ylides are generated and decomposed in situ.[53,60,62,63]. All the reactions were carried out at room temperature in methylene chloride as reaction solvent and the data are summarized in Table 7.

All catalysts revealed moderate isolated yields, except for Rh_2(*S*-1,2-NTTR)$_4$ (**3d**) and Rh_2(*S*-1,2-NTTY)$_4$ (**3e**). The asymmetric induction exhibited by the prepared catalysts ranged from moderate to low (30–7% *ee*) for all substrates. In terms of *ee* of the resulting cyclopropane derivatives, Rh_2(*S*-1,2-NTTL)$_4$ (**3a**) was the best among the series (30-20% *ee*) and it revealed similar enantiomeric induction to Rh_2(*S*-NTTL)$_4$ (32-17% *ee*) but both were lower than Rh_2(*S*-PTTL)$_4$ (37-27% *ee*).

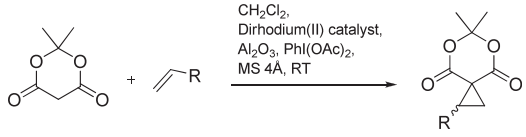
Predictive Model for Asymmetric Induction

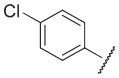
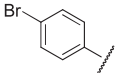
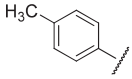
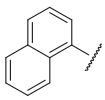
There are some uncertainties about the arrangement of ligands in solution for this family of catalysts which led to some uncertainties about their mode of asymmetric induction during carbenoid transformations. As a consequence, a number of predictive models have appeared to justify the stereoselection in dirhodium(II)-catalyzed reactions.

The first predictive model was proposed by Hashimoto and it was based on the x-ray crystal structure of Rh_2(*S*-PTPA)$_4$. In this model, it was proposed that dirhodium(II) carboxylates derived from *N*-phthalimido amino acid ligands preferentially exist in C_2-symmetric conformation, at which two adjacent *N*-phthalimido groups are positioned on the top face of the complex and the other two are positioned on the bottom face.[36,61,64] Hashimoto's model was used to successfully predict the stereochemical outcome of asymmetric C-H insertion reactions catalyzed by Rh_2(*S*-PTAD)$_4$.[65]

Later on, Fox and colleagues reported that the Rh_2(*S*-PTTL)$_4$ had C_4-symmetry "all-up" in solid state through its

TABLE 7. Asymmetric cyclopropanation with Meldrum's acid (diacceptor substrate)



	Rh_2(*S*-PTTL)$_4$		Rh_2(*S*-NTTL)$_4$		Rh_2(*S*-1,2-NTTL)$_4$ (3a)		Rh_2(*S*-1,2-NTPA)$_4$ (3b)		Rh_2(*S*-1,2-NTLU)$_4$ (3c)		Rh_2(*S*-1,2-NTTR)$_4$ (3d)		Rh_2(*S*-1,2-NTTY)$_4$ (3e)	
R-group	Yield (%)	*ee* (%)[a]	Yield (%)	*ee* (%)[a]	Yield (%)	*ee* (%)[a]	Yield (%)	*ee* (%)[a]	Yield (%)	*ee* (%)[a]	Yield (%)	*ee* (%)[a]	Yield (%)	*ee* (%)[a]
	45%	37%	38%	32%	60%	30%	47%	12%[b]	54%	16%	18%	18%	14%	13%
	52%	36%	40%	31%[b]	57%	28%[b]	51%	9%[b]	59%	15%[b]	20%	18%	16%	14%[b]
	42%	35%	63%	20%	46%	27%	41%	11%	55%	12%	11%	17%	14%	9%
	33%	29%	36%	23%	32%	22%	30%	8%	47%	8%	13%	17%	13%	12%
	53%	27%	28%	17%[b]	44%	20%	38%	8%[b]	46%	9%[b]	12%	13%	15%	7%

[a]The *R*-enantiomer is the major product. [b]Analyzed as crude mixture. Enantiomeric excesses (*ee* %) were determined by chiral HPLC. See Materials and Methods section for more details.

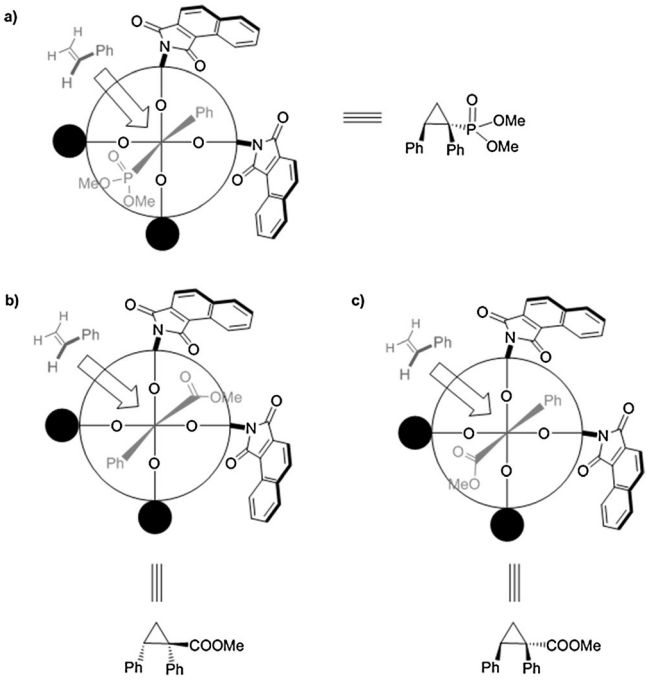


Fig. 4. Model for asymmetric cyclopropanation catalyzed by Rh_2(*S*-1,2-NTTL)$_4$.

x-ray crystal structure, with the four *N*-phthalimido groups on one face of the complex creating a chiral crown cavity.[66,67] Also, other research groups have reported x-ray structures of other catalysts that belong to the same family and all these catalysts were adopting an "all-up" C_4 conformation.[29,51,68–70] According to the Fox model, the bulky *tert*-butyl groups are necessary to limit reactivity to only one of the catalyst faces, whereas the distorted C_4-symmetric chiral crown-like ligand arrangement guides the facial selectivity at the open Rh-face.[50]

Based on the x-ray structure of Rh_2(*S*-1,2-NTPA)$_4$ (**3b**), that revealed an "up, up, down, down" arrangement of the ligands across the rhodium core,[71] Hashimoto's model was adopted for Rh_2(*S*-1,2-NTTL)$_4$. It was hypothesized that the *N*-1,2-naphthaloyl groups are oriented in an "up-up-down-down" arrangement in solution. In the case of dimethyl benzylphosphonate carbenoid, the much bulkier dimethyl phosphonate group (tetrahedral geometry) orients itself away to avoid the steric interaction with the *N*-1,2-napthaloyl walls (Fig. 4a). The alkene is predicted to approach from the front and lead to the observed product. This may justify the high enantiomeric excess of the cyclopropyl derivatives when using carbenoid with bulky phosphonate group (Tables 1 and 2). On the other hand, both the methyl carboxylate and the phenyl groups of methyl benzylcarboxylate carbenoid are almost of the same size (having planner geometry) and can occupy both positions shown in Figure 4b,c. The alkene attacks from the front and may lead to the observed low enantiomeric excess of the corresponding cyclopropyl derivatives (Tables 4–6).

CONCLUSION

In conclusion, we have developed dirhodium(II,II) tetrakis [*N*-(1,2-naphthoyl)-(*S*)-*tert*-leucine] (Rh_2(*S*-1,2-NTTL)$_4$, **3a**) as a new member of the chiral dirhodium catalysts family derived from *N*-protected amino acid ligands. The efficiency and selectivity of this catalyst has been demonstrated in a variety of diastereo- and enantioselective reactions of donor-acceptor and diacceptor carbenoids.

It was demonstrated that Rh_2(*S*-1,2-NTTL)$_4$ (**3a**) is a promising backup catalyst for the cyclopropanation reaction involving donor-acceptor phosphonate carbenoids. However, the results did not provide a clear advantage for the "lower symmetry" approach. Further investigations related to this point are in progress and the results will be reported in due course.

The results also revealed that the nature of the acceptor group in the donor-acceptor carbenoid strongly affects the asymmetric induction imparted by Rh_2(*S*-1,2-NTTL)$_4$. This can provide a guideline for choosing the optimal dirhodium(II) catalyst before attempting an asymmetric cyclopropanation and broadens the range of available catalysts for the synthesis of chiral cyclopropylphosphonate derivatives. Hashimoto's stereochemical model proved to be an excellent model to justify the observed selectivity of the new Rh_2(*S*-1,2-NTTL)$_4$ catalyst. This predictive model raised the importance of considering the conformational mobility of the ligands in solution once the carbene binds to the catalyst.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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