Guide to Enantioselective Dirhodium(II)-Catalyzed Cyclopropanation with Aryldiazoacetates

Kathryn M. Chepiga, Changming Qin, Joshua S. Alford, Spandan Chennamadhavuni, Timothy M. Gregg, Jeremy P. Olson, and Huw M. L. Davies

Huw M. L. Davies: hmdavie@emory.edu

Department of Chemistry, Emory University, (404)727-6839, 1515 Dickey Drive, Atlanta, Georgia 30322, USA

bDepartment of Chemistry and Biochemistry, Canisius College, Buffalo, NY 14208, USA

Abstract
Catalytic enantioselective methods for the generation of cyclopropanes has been of longstanding pharmaceutical interest. Chiral dirhodium(II) catalysts prove to be an effective means for the generation of diverse cyclopropane libraries. Rh$_2$(R-DOSP)$_4$ is generally the most effective catalyst for asymmetric intermolecular cyclopropanation of methyl aryldiazoacetates with styrene. Rh$_2$(S-PTAD)$_4$ provides high levels of enantioinduction with ortho-substituted aryldiazoacetates. The less-established Rh$_2$(R-BNP)$_4$ plays a complementary role to Rh$_2$(R-DOSP)$_4$ and Rh$_2$(S-PTAD)$_4$ in catalyzing highly enantioselective cyclopropanation of 3-methoxy-substituted aryldiazoacetates. Substitution on the styrene has only moderate influence on the asymmetric induction of the cyclopropanation.

Keywords
Asymmetric cyclopropanation; Cyclopropanes; Donor/acceptor carbenoids; Dirhodium catalysis; Phenyldiazoacetate

1. Introduction
The metal-catalyzed decomposition of diazo compounds in the presence of alkenes is a general method for the stereoselective synthesis of cyclopropanes.\textsuperscript{1,2} We have previously shown the rhodium-catalyzed cyclopropanation of donor/acceptor carbenoids to be effective for the enantioselective synthesis of cyclopropanes with one or more quaternary stereogenic centers.\textsuperscript{3-6} As many cyclopropyl amines are known to have significant CNS activity,\textsuperscript{7,8} we have initiated a program to use our cyclopropanation methodology to access novel diarylcyclopropylamines as potential therapeutic agents (Scheme 1). For the methodology to be broadly useful in drug discovery, access to a range of diarylcyclopropyl derivatives...
with high levels of enantioenrichment is required. Herein, we define the optimal catalysts for the cyclopropanation with various types of methyl aryl diazoacetates.

Three chiral dirhodium-(II) catalysts were selected for this study (Figure 1). The first catalyst, Rh$_2$(R-DOSP)$_4$, is considered to be the optimal catalyst for the reactions of donor/acceptor carbenoids when the acceptor group is a methyl ester. The substrate scope of Rh$_2$(R-DOSP)$_4$-catalyzed cyclopropanation is quite broad in terms of both the trapping agent and the donor group on the carbenoid. However, a detailed study on the influence of the aryl substituent of the aryldiazoacetate on Rh$_2$(R-DOSP)$_4$-catalyzed cyclopropanation has not been conducted. The second catalyst, Rh$_2$(S-PTAD)$_4$, is the optimal chiral catalyst when the acceptor group in the donor/acceptor carbenoid is a phosphonate, trifluoromethyl, cyano, or keto group. Due to the perceived superiority of Rh$_2$(R-DOSP)$_4$ in the reactions of aryldiazoacetates, Rh$_2$(S-PTAD)$_4$ has not been thoroughly evaluated in the reactions of this class of carbenoid precursor. The third catalyst, Rh$_2$(R-BNP)$_4$, is an interesting catalyst of $D_4$-symmetry that has been applied to a number of carbenoid reactions, but has not been previously evaluated in the cyclopropanation of donor/acceptor carbenoids.

2. Results and Discussion

The study began by exploring the effect of aryl substitution on the enantioselectivity in the cyclopropanation of styrene by aryldiazoacetates. The results for a series of aryldiazoacetates (1a-l) using the three chiral dirhodium catalysts Rh$_2$(R-DOSP)$_4$, Rh$_2$(S-PTAD)$_4$ and Rh$_2$(R-BNP)$_4$ are summarized in Table 1. Excellent levels of diastereoselectivity were achieved in all cases (>95:5 dr) and the isolated yields of the cyclopropanes were generally high, ranging from 63-98%. The absolute configuration of the major isomer of the cyclopropanes is tentatively assigned as 1S,2R.

Rh$_2$(R-DOSP)$_4$ provided high levels of enantioinduction when unsubstituted (1a) or 4-substituted (1b-e) methyl aryldiazoacetates were employed as substrates (Table 1, entries 1-5, 87-90% ee). In general, Rh$_2$(S-PTAD)$_4$ and Rh$_2$(R-BNP)$_4$ gave <60% ee in the cyclopropanation reactions of unsubstituted or 4-substituted aryldiazoacetates with these same substrates. The one exception, however, is the reaction of 4-methoxyphenyldiazoacetate (1e) with Rh$_2$(S-PTAD)$_4$, which gave the cyclopropane 3e in exceptionally high enantioselectivity (entry 5, 96% ee).

Interestingly, Rh$_2$(R-DOSP)$_4$ fails to provide high levels of enantioinduction when the aryldiazoacetate contains a 3-methoxysubstituent (1l) (entries 9-12), especially when the ring is polysubstituted (1l). In these cases, the cyclopropanes 3i, k-l are produced in 28-56% ee (entries 9, 11-12). Rh$_2$(S-PTAD)$_4$ is an effective catalyst only in the case of 3,4-dimethoxyphenyldiazoacetate (1i), generating the cyclopropane 3i in 94% ee (entry 9). In contrast, Rh$_2$(R-BNP)$_4$ is an extremely effective catalyst with all of the 3-methoxy substituted aryldiazoacetates (1l), generating the cyclopropanes 3i-l in 88-97% ee (entries 9-12).

One of the most attractive features of Rh$_2$(R-DOSP)$_4$ and Rh$_2$(S-PTAD)$_4$ as chiral catalysts is that they are capable of operating at low catalyst loadings. As Rh$_2$(R-BNP)$_4$ was found to be the optimal catalyst for 3-methoxyaryl diazoacetate derivatives, we investigated...
whether it could also operate at low catalyst loading. Reactions of aryldiazoacetate $\text{1i}$, with successively lower loadings of $\text{Rh}_2(\text{R-BNP})_4$ are summarized in Table 2. $\text{Rh}_2(\text{R-BNP})_4$ was effective at catalyzing highly enantioselective cyclopropanation with catalyst loadings of 1.0 and 0.5 mol%, providing $\text{3i}$ with virtually the same level of enantioselectivity (entry 1 vs. 2, 97% ee vs. 96% ee). When the catalyst loading was decreased further to 0.1 mol% a more significant drop in the level of enantioselectivity was observed (entry 3, 91% ee). Further decreasing the catalyst loading to 0.01 mol%, however, caused a dramatic decrease in enantioinduction (entry 4, 40% ee). These results suggest that, although $\text{Rh}_2(\text{R-BNP})_4$ is capable of moderately high turnover numbers (TONs), it may not be as robust a catalyst as $\text{Rh}_2(\text{R-DOSP})_4$ or $\text{Rh}_2(\text{S-PTAD})_4$, which are capable of TONs as high as 850,000 and 1,800,000 respectively in asymmetric intermolecular cyclopropanation.29.

At the onset of this study, the asymmetric induction of the cyclopropanation was not expected to be heavily influenced by the functionality on the aryldiazoacetate. Having observed considerable variation in enantioselectivity depending on the nature of the aryl group, we decided to explore the effect of modifying the substitution on the styrene. These studies were focused on $\text{Rh}_2(\text{R-BNP})_4$-catalyzed cyclopropanation with the 3, 4-dimethoxyphenyldiazoacetate $\text{1i}$ (Table 3), because $\text{Rh}_2(\text{R-BNP})_4$ had not been previously evaluated as a catalyst for this transformation. The levels of enantioselectivity in the cyclopropanation under $\text{Rh}_2(\text{R-BNP})_4$-catalyzed conditions were found to be moderately influenced by the functionality on the styrene, as the cyclopropanes $\text{5a-g}$ were obtained with uniformly high levels of enantioinduction (80-90% ee). Previous studies have shown that $\text{Rh}_2(\text{R-DOSP})_4$-catalyzed cyclopropanation is also not especially influenced by the nature of the styrene3,4,9 and the $\text{Rh}_2(\text{R-DOSP})_4$-catalyzed cyclopropanation of a range of styrenes (4a-g) with $\text{1i}$ gave 5a-g with modest levels of enantioselectivity (48-67% ee).

These studies reveal subtle differences in the ability of the chiral dirhodium tetracarboxylate catalysts to induce high enantioselectivity in the cyclopropanation of styrenes, as summarized in Table 4. The previous expectation that $\text{Rh}_2(\text{R-DOSP})_4$ would give high asymmetric induction for all aryldiazoacetates was found not to be true, although it was found to be the most effective catalyst for the broadest range of substituted methyl aryldiazoacetates. In spite of the fact that $\text{Rh}_2(\text{S-PTAD})_4$ is the most consistent catalyst when the acceptor group of the donor/acceptor carbenoid is modified,19-22 the level of enantioselectivity was found to be highly variable when aryl substitution of the aryldiazoacetate was modified. In particular, $\text{Rh}_2(\text{S-PTAD})_4$ was very effective with 2-chlorophenyl aryldiazoacetate derivative. $\text{Rh}_2(\text{R-BNP})_4$ becomes the best catalyst for 3-methoxyphenyl-substituted aryldiazoacetate derivatives. The cause for these subtle variations, at this stage, is not well understood. There is no clear steric or electronic trend to define which catalyst will perform best in a given system, which suggests the asymmetric induction may involve a combination of factors including π-stacking interactions. Computational studies are in progress to develop a rational model to explain these trends.

3. Conclusion

This study provides guidelines for choosing the optimal chiral dirhodium-(II) catalyst for cyclopropanation of aryldiazoacetates. The nature of the aryl group on the aryldiazoacetate strongly affects the asymmetric induction imparted by the three catalysts studied. Depending on the aryl substituent, $\text{Rh}_2(\text{R-DOSP})_4$, $\text{Rh}_2(\text{S-PTAD})_4$, or $\text{Rh}_2(\text{R-BNP})_4$ can be utilized to obtain the desired cyclopropane with a high level of enantioinduction. In contrast, the functionality on the styrene has only moderate influence on the level of asymmetric induction in cyclopropanation reactions. These studies set the chemical foundation for our ongoing studies to develop the raptually useful diarylcyclopropylamines, the results of which will be reported in due course.
4. Experimental Section

4.1 General

All reactions were conducted under anhydrous conditions in oven-dried glassware under an inert atmosphere of dry argon, unless otherwise stated. Hexanes, pentane, and toluene were dried by a solvent purification system (passed through activated alumina columns). All solvents were degassed by bubbling argon through the solvent for a minimum of 10 minutes prior to use. Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. $^1$H Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz or 600 MHz. Data presented as follows: chemical shift (in ppm on the $\delta$ scale relative to $\delta^H$ 7.27 for the residual protons in CDCl$_3$), coupling constant (J/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. $^{13}$C NMR spectra were recorded at 100 MHz and all chemical shift values are reported in ppm on the $\delta$ scale, with an internal reference of $\delta^C$ 77.23 for CDCl$_3$. Mass spectral determinations were carried out by using APCI as ionization source. Melting points are uncorrected. Infrared spectral data are reported in units of cm$^{-1}$. Analytical TLC was performed on silica gel plates using UV light. Flash column chromatography was performed on silica gel 60Å (230-400 mesh). Optical rotations were measured on a Jasco polarimeter. Analytical enantioselective chromatographies were measured on a Varian Prostar instrument and used isopropanol:hexane as gradient. Chiral HPLC conditions were determined by obtaining separation of the racemic product. Rh$_2$(R/S-DOSP)$_4$ was employed as the catalyst in the racemic reactions. Styrene (2) and substituted styrenes (4a-f) were commercially available and purified by pushing through a silica-filled pipette prior to use. Rh$_2$(R-DOSP)$_4$,$^3$ Rh$_2$(S-PTAD)$_4$,$^{19}$ Rh$_2$(R-BNP)$_4$,$^{23}$ aryldiazoacetates 1a-1 and styrene 4g$^{30}$ were all synthesized according published procedures.

4.2 General Procedure for the Synthesis of Methyl Phenyl Diazooacetates$^{31}$

The methyl arylacetate (1 equiv.) and p-ABSA (1.3 equiv.) were dissolved in acetonitrile and cooled to 0 °C using an ice bath under an argon atmosphere. 1, 8-Diazabicycloundec-7-ene (DBU, 1.3 equiv.) was then added to the stirring mixture over the course of 5 minutes. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for an additional 15 minutes. Once this allotted time had passed, the ice bath was removed and the reaction mixture was stirred for 24 hours at room temperature. The resulting orange solution was quenched with saturated NH$_4$Cl and the aqueous layer was extracted with diethyl ether (3×). The organic layer was then washed with deionized H$_2$O to remove any residual salts. The combined organic layers were dried over MgSO$_4$ and filtered. The organic layer was then concentrated under reduced pressure. The residue was purified via flash chromatography on silica gel (10:1 Hexanes:EtOAc).

4.3 General Procedure for the Synthesis of Methyl Phenylcyclopropanecarboxylates with Rh$_2$(R-DOSP)$_4$

In a 25-mL round bottom flask (Flask A) equipped with a magnetic stir bar, styrene (5 equiv.) and p-ABSA (1.3 equiv.) were dissolved in acetonitrile and cooled to 0 °C using an ice bath under an argon atmosphere. 1, 8-Diazabicycloundec-7-ene (DBU, 1.3 equiv.) was then added to the stirring mixture over the course of 5 minutes. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for an additional 15 minutes. Once this allotted time had passed, the ice bath was removed and the reaction mixture was stirred for 24 hours at room temperature. The resulting orange solution was quenched with saturated NH$_4$Cl and the aqueous layer was extracted with diethyl ether (3×). The organic layer was then washed with deionized H$_2$O to remove any residual salts. The combined organic layers were dried over MgSO$_4$ and filtered. The organic layer was then concentrated under reduced pressure. The residue was purified via flash chromatography on silica gel column chromatography (increasing gradient starting at 10:1 Hexanes:EtOAc).
4.4 General Procedure for the Synthesis of Methyl Phenylcyclopropanecarboxylates with Rh$_2$(S-PTAD)$_4$

In a 25-mL round bottom flask (Flask A) equipped with a magnetic stir bar, styrene (5 equiv.) and Rh$_2$(S-PTAD)$_4$ (0.005 equiv.) were dissolved in dry, degassed pentane (3 mL). The reaction mixture was then degassed using vacuum/argon cycles ($\times$3). In a separate 25-mL round bottom flask (Flask B), the methyl phenyldiazoacetate (0.5 mmol, 1 equiv.) was dissolved in dry, degassed pentane (5 mL) and degassed using vacuum/argon cycles ($\times$3). The contents in Flask B were then added to Flask A using a syringe pump for the duration of 1 hour. After the addition, the reaction mixture continued to stir for 1 additional hour. Once the allotted time had passed, the reaction mixture was concentrated under reduced pressure and purified using silica gel column chromatography (increasing gradient starting at 10:1 Hexanes:EtOAc).

4.5 General Procedure for the Synthesis of Methyl Phenylcyclopropanecarboxylates with Rh$_2$(R-BNP)$_4$

In a 25-mL round bottom flask (Flask A) equipped with a magnetic stir bar, styrene (5 equiv.) and Rh$_2$(R-BNP)$_4$ (0.01 equiv.) were dissolved in dry, degassed toluene (3 mL). The reaction mixture was then degassed using vacuum/argon cycles ($\times$3). In a separate 25-mL round bottom flask (Flask B), the methyl phenyldiazoacetate (0.5 mmol, 1 equiv.) was dissolved in dry, degassed pentane (5 mL) and degassed using vacuum/argon cycles ($\times$3). The contents in Flask B were then added to Flask A using a syringe pump for the duration of 1 hour. After the addition, the reaction mixture continued to stir for 1 additional hour. Once the allotted time had passed, the reaction mixture was concentrated under reduced pressure and purified using silica gel column chromatography (increasing gradient starting at 10:1 Hexanes:EtOAc).

4.1.1. (1R,2S)-methyl 1,2-diphenylcyclopropanecarboxylate (3a)—Title compound was prepared by general procedure and obtained as a white solid. 85% yield for Rh$_2$(R-DOSP)$_4$; 87% yield for Rh$_2$(S-PTAD)$_4$; 72% yield for Rh$_2$(R-BNP)$_4$; HPLC: (Chiralcel SS-WHELK, 1% $i$-PrOH in hexane, 1.0 mL/min, 1 mg/mL, 30 min, $\lambda$ = 254 nm) retention times of 8.62 min (major) and 10.22 min (minor), 88% ee for Rh$_2$(R-DOSP)$_4$; 21% ee for Rh$_2$(S-PTAD)$_4$; 42% ee for Rh$_2$(R-BNP)$_4$; $R_f$ = 0.25 (hexane: ethyl acetate 10:1); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.12-7.11 (m, 3H), 7.05-7.01 (m, 5H), 6.77-6.75 (m, 2H), 3.70 (s, 3H), 3.11 (dd, J = 7.2, 9.3, 1H), 2.13 (dd, J = 4.8, 9.3, 1H), 1.88 (dd, J = 4.8, 7.2, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.5, 136.5, 134.9, 132.1, 128.2, 127.9, 127.2, 126.5, 52.8, 37.6, 33.3, 20.7; Data are consistent with the literature$^{5,6}$.

4.1.2. (1S,2R)-methyl 2-phenyl-1-(p-tolyl)cyclopropanecarboxylate (3b)—Title compound was prepared by general procedure and obtained as a white solid. 84% yield for Rh$_2$(R-DOSP)$_4$; 77% yield for Rh$_2$(S-PTAD)$_4$; 69% yield for Rh$_2$(R-BNP)$_4$; HPLC: (Chiralcel SS-WHELK, 1% $i$-PrOH in hexane, 1.0 mL/min, 1 mg/mL, 30 min, $\lambda$ = 254 nm) retention times of 10.57 min (major) and 14.13 min (minor), 87% ee for Rh$_2$(R-DOSP)$_4$; 46% ee for Rh$_2$(S-PTAD)$_4$; 51% ee for Rh$_2$(R-BNP)$_4$; $R_f$ = 0.44 (4:1 Hexanes:EtOAc); $[^1]^H$ NMR (400 MHz; CDCl$_3$) $\delta$ 7.11-7.07 (m, 3H), 6.98-6.92 (m, 4H), 6.82-6.80 (m, 2H), 3.69 (s, 3H), 3.12 (dd, J = 9.2 and 7.2 Hz, 1H), 2.16 (dd, J = 9.6 and 4.8 Hz, 1H), 1.88 (dd, J = 7.2 and 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 74.5, 136.5, 134.9, 132.1, 128.2, 127.9, 127.2, 126.5, 52.8, 37.6, 33.3, 20.7; IR (film): 3028, 2950, 1716, 1255; m/z (ESI) 267.1 (100%, M+H), 268.1 (20%); HRMS-ESI m/z 167.138 (C$_{18}$H$_{19}$O$_2$ requires 167.138).

4.1.3. (1S,2R)-methyl 2-phenyl-1-(4-(trifluoromethyl)phenyl)cyclopropanecarboxylate (3c)—Title compound was
4.1.4. (1S,2R)-methyl 1-(4-chlorophenyl)-2-phenylcyclopropanecarboxylate (3d) — Title compound was prepared by general procedure and obtained as a transparent oil. 93% yield for Rh$_2$(R-DOSP)$_4$; 67% yield for Rh$_2$(S-PTAD)$_4$; 80% yield for Rh$_2$(R-BNP)$_4$; HPLC: (Chiralcel OD-H, 0.5% i-PrOH in hexanes, 1.0 mL/min, 1 mg/mL, 30 min, $\lambda_{254}$ nm) retention times of 8.27 min (minor) and 10.34 min (major), 87% ee for Rh$_2$(R-DOSP)$_4$; 77% ee for Rh$_2$(S-PTAD)$_4$; 57% ee for Rh$_2$(R-BNP)$_4$; $R_e = 0.44$ (4:1 Hexanes:EtOAc); $[\Delta]^{20}_D = 19.1$ (c. 1, chloroform); $^1$H NMR (400 MHz; CDC$_3$)$_2$ $\delta$ 7.36 (d, $J = 8$ Hz, 2H), 7.12 (d, $J = 8$ Hz, 2H), 7.06 (m, 3H), 6.74 (m, 2H), 3.66 (s, 3H), 3.14 (dd, $J = 9.6$ and 7.6 Hz, 1H), 2.17 (dd, $J = 9.2$ and 5.2 Hz, 1H), 1.88 (dd, $J = 7.2$ and 5.2 Hz, 1H); $^{13}$C NMR (100 MHz, CDC$_3$)$_2$ $\delta$ 139.2, 135.8, 132.4, 128.1, 126.9, 125.0, 124.9, 124.8, 124.7, 53.0, 37.2, 33.5, 20.4; IR (film): 3032, 2954, 1719, 1501, 1322, 1257; m/z (ESI) 321.1 (100%, M+H)$^+$, 322.1 (21%); HRMS-ESI m/z 321.0979 (C$_{18}$H$_{16}$O$_2$F$_3$ requires 321.1097).

4.1.5. (1S,2R)-methyl 1-(4-methoxyphenyl)-2-phenylcyclopropanecarboxylate (3e) — Title compound was prepared by general procedure and obtained as a white solid. 66% yield for Rh$_2$(R-DOSP)$_4$; 93% yield for Rh$_2$(S-PTAD)$_4$; 84% yield for Rh$_2$(R-BNP)$_4$; HPLC: (Chiralcel OD-H, 0.7% i-PrOH in hexanes, 1.0 mL/min, 1 mg/mL, 30 min, $\lambda_{254}$ nm) retention times of 11.97 min (major) and 17.71 min (minor), 90% ee for Rh$_2$(R-DOSP)$_4$; 96% ee for Rh$_2$(S-PTAD)$_4$; 57% ee for Rh$_2$(R-BNP)$_4$; $R_e = 0.39$ (4:1 Hexanes:EtOAc); $[\Delta]^{20}_D = +5.1$° (c = 1, chloroform); $^1$H NMR (400 MHz; CDC$_3$)$_2$ $\delta$ 7.10-7.07 (m, 3H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.80-6.77 (m, 2H), 6.68 (d, $J = 8.8$ Hz, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.09 (dd, $J = 9.2$ and 7.6 Hz, 1H), 2.14 (dd, $J = 9.2$ and 4.8 Hz, 1H), 1.84 (dd, $J = 7.2$ and 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDC$_3$)$_2$ $\delta$ 174.1, 136.1, 133.7, 133.4, 133.2, 132.8, 128.3, 128.1, 126.8, 52.9, 36.9, 33.4, 20.6; IR (film): 3031, 2951, 1717, 1493, 1255; m/z (ESI) 287.1 (100%, M+H)$^+$, 288.1 (16.42%), 289.1 (29.3%); HRMS-ESI m/z 287.0833 (C$_{17}$H$_{16}$O$_2$CI requires 287.0833).

4.1.6. (1S,2R)-methyl 1-(2-chlorophenyl)-2-phenylcyclopropanecarboxylate (3f) — Title compound was prepared by general procedure and obtained as a transparent oil. 89% yield for Rh$_2$(R-DOSP)$_4$; 71% yield for Rh$_2$(S-PTAD)$_4$; 89% yield for Rh$_2$(R-BNP)$_4$; HPLC: (Chiralcel OJ-H, 1% i-PrOH in hexanes, 1.0 mL/min, 1 mg/mL, 30 min, $\lambda_{254}$ nm) retention times of 8.62 min (minor) and 12.58 min (major), 88% ee for Rh$_2$(R-DOSP)$_4$; 48% ee for Rh$_2$(S-PTAD)$_4$; 57% ee for Rh$_2$(R-BNP)$_4$; $R_e = 0.56$ (4:1 Hexanes:EtOAc); $[\Delta]^{20}_D = +1.0$° (c = 1, chloroform); $^1$H NMR (400 MHz; CDC$_3$)$_2$ $\delta$ 7.18-7.02 (m, 5H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.79-6.76 (m, 2H), 3.67 (s, 3H), 3.12 (dd, $J = 9.3$ and 7.5 Hz, 1H), 2.15 (dd, $J = 9.3$ and 4.8 Hz, 1H), 1.85 (dd, $J = 7.2$ and 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDC$_3$)$_2$ $\delta$ 173.6, 137.5, 133.5, 129.6, 128.9, 128.2, 127.6, 126.6, 126.4, 52.9, 33.5, 29.9, 21.7; IR (film): 3031, 2950, 1718, 1251, 694; m/z (ESI) 287.1 (100%, M+H)$^+$, 288.1 (17%), 289.1 (32%); HRMS- m/z 287.0833 (C$_{17}$H$_{16}$O$_2$CI requires 287.0833).
4.1.7. (1S,2R)-methyl 1-(2-methoxyphenyl)-2-phenylcyclopropanecarboxylate (3g)—Title compound was prepared by general procedure and obtained as a white solid. 92% yield for Rh2(R-DOSP); 87% yield for Rh2(S-PTAD); 69% yield for Rh2(R-BNP); HPLC: (SS-WHELK column, 1% i-PrOH in hexanes, 1.0 mL/min, 1mg/mL, 30 min, 254 nm) retention times of 11.65 min (minor) and 14.00 min (major); 86% ee for Rh2(R-DOSP); 80% ee for Rh2(S-PTAD); 27% ee for Rh2(R-BNP); \( R_f = 0.45 \) (1: Hexanes:EtOAc); [\( \lambda_{20D}^{D} \] + 133.3° (c. 1, chloroform); \( ^1\)HNMR (400 MHz, CDCl3) \( \delta \) 7.19-7.10 (m, 2H), 7.04-6.98 (m, 3H), 6.86 (td, \( J = 7.6 \) and 1.1 Hz, 1H), 1.84 (dd, \( J = 7.6 \) and 4.8 Hz, 1H); \( ^{13}\)C NMR (100 MHz, CDCl3) \( \delta \) 147.8, 136.4, 127.9, 126.8, 123.9, 121.5, 115.3, 110.5, 55.2, 52.7, 34.3, 32.6, 20.8; IR (film): 3089, 2950, 2835, 1716, 1496, 1242; m/z (ESI) 283.1 (100%, M+H), 284.1 (19%); HRMS-ESI m/z requires 283.1329.}

4.1.8. (1S,2R)-methyl 1-(3,4-dichlorophenyl)-2-phenylcyclopropanecarboxylate (3h)—Title compound was prepared by general procedure and obtained as a clear oil; 88% yield for Rh2(R-DOSP); 82% yield for Rh2(S-PTAD); 63% ee for Rh2(R-BNP); HPLC: (Chiralcel OD-H, 6% i-PrOH in hexane, 1 mL/min, 1 mg/mL, 30 min, \( \lambda = 254 \) nm) retention times of 13.99 min (minor) and 17.97 min (major); 96% ee for Rh2(R-DOSP); 94% ee for Rh2(S-PTAD); 97% ee for 1 mol% Rh2(R-BNP); 96% ee for 0.5 mol% Rh2(R-BNP); 40% ee for 0.1 mol% Rh2(R-BNP); \( R_f = 0.20 \) (hexane: ethyl acetate 4:1); mp 88-89°C; \( [\lambda]_{D}^{20} +28.4^\circ \) (c = 1.51, CHCl3); \( ^1\)HNMR (400 MHz, CDCl3) \( \delta \) 7.09-7.03 (m, 4H), 7.03-6.97 (m, 3H), 6.86 (td, \( J = 7.6 \) and 1.1 Hz, 1H), 1.84 (dd, \( J = 7.6 \) and 4.8 Hz, 1H); \( ^{13}\)C NMR (100 MHz, CDCl3) \( \delta \) 174.5, 147.8, 136.4, 127.9, 126.8, 52.8, 36.3, 33.3, 20.2; IR (film): 2925, 1719, 1257, 1163, 695; HRMS (ESI) calc'd for C_{18}H_{19}O_{3} found 283.14398.}

4.1.9. (1S,2R)-methyl 1-(3,4-dimethoxyphenyl)-2-phenylcyclopropanecarboxylate (3i)—Title compound was prepared by general procedure and obtained as a yellow oil. 78% yield for Rh2(R-DOSP); 72% yield for Rh2(S-PTAD); 82% yield for Rh2(R-BNP); HPLC: (Chiralcel OD-H, 0.7% i-PrOH in hexanes, 1 mL/min, 1 mg/mL, 30 min, \( \lambda = 254 \) nm) retention times of 9.50 min (major) and 11.38 min (minor); 79% ee for Rh2(R-DOSP); 16% ee for Rh2(S-PTAD); 88% ee for Rh2(R-BNP); \( R_f = 0.25 \) (hexane: ethyl acetate 9:1); \( [\lambda]_{D}^{20} +21.1^\circ \) (c = 1.25, CHCl3); \( ^1\)HNMR (400 MHz, CDCl3) \( \delta \) 7.09-7.03 (m, 4H), 6.81-6.79 (m, 2H), 6.69-6.63 (m, 2H), 6.53-6.52 (m, 1H), 3.67(s, 3H), 3.59 (s, 3H), 3.12 (s, 3H); IR (film): 3089, 2950, 2835, 1716, 1496, 1242; m/z (ESI) 283.1 (100%, M+H), 284.1 (19%); HRMS-ESI m/z 283.1329 (C_{18}H_{19}O_{3} requires 283.1329).
(dd, J = 9.6, 7.2 Hz, 1H), 2.12 (dd, J = 9.2, 4.8 Hz, 1H), 1.87 (dd, J = 7.6, 5.2 Hz, 1H); 13C
NMR (100MHz, CDCl3): δ 74.2, 158.8, 136.4, 136.2, 128.5, 127.9, 127.7, 126.3, 124.4,
117.5, 112.9, 55.0, 52.6, 37.3, 33.1, 20.6; IR (film): 2925, 1717, 1602, 1454, 1439, 1368,
1347, 1249, 1103, 1057, 1043, 750; HRMS (ESI) calcd for C24H21O3 (M+H) + 348.14827 found 348.14835.

4.1.14. (1S,2R)-methyl 1-(3,4-dimethoxyphenyl)-2-phenylcyclopropanecarboxylate (5b)—Prepared by general procedure with methyl 2-
(3,4-dimethoxyphenyl)cyclopropanecarboxylate (3l)—Title compound was prepared by general
procedure and obtained as a yellow oil. 98% yield for Rh(R-BNP).

4.1.14. (1S,2R)-methyl 1-(3,4-dimethoxyphenyl)-2-(p-
(3,4-dimethoxyphenyl)cyclopropanecarboxylate (5b)—Prepared by general procedure with methyl 2-
(3,4-dimethoxyphenyl)cyclopropanecarboxylate (3l)—Title compound was prepared by general
procedure and obtained as a yellow oil. 98% yield for Rh(R-BNP).
diazoy-2-(3,4-dimethoxyphenyl)acetate (118 mg, 0.5 mmol, 1 equiv), 4-methylstyrene (148 mg, 1.25 mmol, 2.5 equiv), and Rh₂(R-BNP)₄ (4 mg, 0.0025 mmol, 0.005 equiv). The remaining residue was purified on silica gel eluting with hexanes: ethyl acetate (5:1) to afford a yellow/green oil (147 mg, 90% yield). Rₛ = 0.12 (hexane: ethyl acetate 5:1); [α]D²⁰ +27.7° (c = 1.24, CHCl₃); ¹H NMR (400 MHz, CDC₁₃) δ 8.88 (d, J = 8.0 Hz, 2H), 6.69-6.67 (m, 4H), 6.37 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.57 (s, 3H), 3.05 (dd, J = 9.2, 7.6 Hz, 1H), 2.22 (s, 3H), 2.11 (dd, J = 9.2, 4.8 Hz, 1H), 1.80 (dd, J = 7.6, 4.8 Hz, 1H); ¹³C NMR (100 MHz, CDC₁₃) δ 174.7, 147.9, 136.0, 133.5, 128.6, 128.0, 127.6, 124.1, 115.9, 113.7, 110.7, 56.1, 55.6, 53.1, 37.1, 33.2, 21.3; IR (film): 2951, 1711, 1611, 1589, 1515, 1463, 1435, 1413, 1315, 1250, 1228, 1155, 1027; HRMS (APCI) calcd for C₆H₉NO₂₂F₂ (M+H)+ 342.14618 found 342.14589; HPLC: (Chiralcel OD-H, 6% i-PrOH in hexane, 1 mL/min, 1 mg/mL, 30 min, [α]D²⁰ = 254 nm) retention times of 17.3 min (minor) and 20.1 min (major), 88% ee for Rh₂(R-BNP)₄, 67% ee for Rh₂(R-DOSP)₄.

4.1.15. (1S,2R)-methyl 1-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (5c)—Prepared by general procedure with methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (118 mg, 0.5 mmol, 1 equiv), 4-methoxy styrene (168 mg, 1.25 mmol, 2.5 equiv), and Rh₂(R-BNP)₄ (4 mg, 0.0025 mmol, 0.005 equiv). The remaining residue was purified on silica gel eluting with hexanes: ethyl acetate (5:1) to afford a yellow oil (168 mg, 94% yield). Rₛ = 0.20 (hexane: ethyl acetate 3:1); mp 123-125°C; [α]D¹⁶ +27.7° (c = 1.4, CHCl₃); ¹H NMR (400 MHz, CDC₁₃) δ 7.73-6.61 (m, 6H), 6.41 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.60 (s, 3H), 3.03 (dd, J = 9.2, 7.6 Hz, 1H), 2.10 (dd, J = 9.2, 4.8 Hz, 1H), 1.76 (dd, J = 7.6, 4.8 Hz, 1H); ¹³C NMR (100 MHz, CDC₁₃) δ 175.1, 158.6, 148.3, 129.5, 128.9, 127.9, 124.6, 115.9, 113.7, 110.7, 56.1, 55.6, 53.1, 37.1, 33.2, 21.3; IR (film): 2952, 1714, 1611, 1589, 1516, 1435, 1413, 1341, 1315, 1250, 1228, 1177, 1153; HRMS (APCI) calcd for C₂₀H₂₂O₅ (M+H)+ 342.14618 found 342.14589; HPLC: (Chiralcel OD-H, 5% i-PrOH in hexane, 1 mL/min, 1 mg/mL, 30 min, [α]D²⁰ = 254 nm) retention times of 19.2 min (minor) and 22.9 min (major), 90% ee for Rh₂(R-BNP)₄, 62% ee for Rh₂(R-DOSP)₄.

4.1.16. (1S,2R)-methyl 1-(3,4-dimethoxyphenyl)-2-(4-nitrophenyl)cyclopropanecarboxylate (5d)—Prepared by general procedure with methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (118 mg, 0.5 mmol, 1 equiv), 4-nitrostyrene (148 mg, 1.25 mmol, 2.5 equiv), and Rh₂(R-BNP)₄ (4 mg, 0.0025 mmol, 0.005 equiv). The remaining residue was purified on silica gel eluting with hexanes: ethyl acetate (5:1) to afford a yellow oil (148 mg, 98% yield). Rₛ = 0.28 (hexane: ethyl acetate 3:1); [α]D¹⁶ +15.5° (c = 1.07, CHCl₃); ¹H NMR (400 MHz, CDC₁₃) δ 7.94 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.2 Hz, 1H), 6.61 (dd, J = 8.2, 2.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.62 (s, 3H), 3.16 (dd, J = 9.2, 7.6 Hz, 1H), 2.22 (dd, J = 9.2, 5.4 Hz, 1H), 1.91 (dd, J = 7.6, 5.4 Hz, 1H); ¹³C NMR (100 MHz, CDC₁₃) δ 173.9, 148.5, 145.1, 128.7, 126.2, 124.2, 123.0, 115.0, 110.6, 55.9, 55.8, 53.0, 38.4, 32.6, 29.8, 21.8; IR (film): 2924, 1717, 1597, 1515, 1463, 1415, 1342, 1229, 1206, 1156, 1141; HRMS (APCI) calcd for C₁₀H₁₂O₃N₂ (M+H)+ 358.12851 found 358.12836; HPLC: (Chiralcel OD-H, 5% i-PrOH in hexane, 1 mL/min, 1 mg/mL, 60 min, [α]D²⁰ = 254 nm) retention times of 30.4 min (minor) and 41.0 min (major), 80% ee for Rh₂(R-BNP)₄, 50% ee for Rh₂(R-DOSP)₄.

4.1.17. (1S,2R)-methyl 1-(3,4-dimethoxyphenyl)-2-(4-trifluoromethyl)phenyl)cyclopropanecarboxylate (5e)—Prepared by general procedure with methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (118 mg, 0.5 mmol, 1 equiv), styrene (215 mg, 1.25 mmol, 2.5 equiv), and Rh₂(R-BNP)₄ (4 mg, 0.0025 mmol, 0.005 equiv). The remaining residue was purified on silica gel eluting with hexanes: ethyl acetate (6:1) to afford a yellow oil (171 mg, 90% yield); Rₛ = 0.24 (hexane: ethyl acetate

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4.1.18. (1S,2R)-methyl 2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)cyclopropanecarboxylate (5f)—Prepared by general procedure with methyl 2-diazo-2-(3, 4-dimethoxyphenyl)acetate (118 mg, 0.5 mmol, 1 equiv), 4-chlorostyrene (173 mg, 1.25 mmol, 2.5 equiv), and Rh$_2$(R-BNP)$_4$ (4 mg, 0.0025 mmol, 0.005 equiv). The remaining residue was purified on silica gel eluting with hexanes: ethyl acetate (6:1) to afford clear oil (123 mg, 89% yield). $R_f = 0.30$ (hexane: ethyl acetate 3:1); [$\alpha$]$_{20}^D +13.4^\circ$ (c = 1.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.04 (d, J = 8.4 Hz, 2H), 6.72-6.63 (m, 4H), 6.38 (d, J = 1.6 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.61 (s, 3H), 3.04 (dd, J = 9.2, 7.2 Hz, 1H), 2.13 (dd, J = 9.2, 4.8 Hz, 1H), 1.78 (dd, J = 7.2, 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.4, 148.2, 148.2, 135.4, 132.3, 129.4, 128.0, 127.0, 124.2, 115.4, 110.5, 55.9, 55.8, 52.8, 37.2, 32.6, 21.2; IR (film): 2951, 1715, 1589, 1517, 1496, 1435, 1413, 1371, 1341, 1228, 1177, 1155, 1139; HRMS (APCI) calcd for C$_{19}$H$_{19}$ClO$_4$ (M$^+$+H)$^+$ 346.09664 found 346.09632; HPLC: (Chiralcel OD-H, 5% i-PrOH in hexane, 1 mL/min, 1 mg/mL, 30 min, $\Delta = 254$ nm) retention times of 14.9 min (minor) and 18.5 min (major), 89% ee for Rh$_2$(R-BNP)$_4$, 67% ee for Rh$_2$(R-DOSP)$_4$.

4.1.19. (1S,2R)-methyl 2-(3,4-dichlorophenyl)-1-(3,4-dimethoxyphenyl)cyclopropanecarboxylate (5g)—Methyl 2-diazo-2-(3, 4-dimethoxyphenyl)acetate (2.7 g, 11.6 mmol, 1 equiv) in 153 mL dry and degassed toluene was added by syringe pump over 2 h to a solution of 1, 2-dichloro-4-vinylbenzene (2.4 g, 13.9 mmol, 1.2 equiv) and Rh$_2$(R-BNP)$_4$ (92.2 mg, 0.06 mmol, 0.005 equiv) in 77 mL toluene. After addition, the solution was allowed to stir overnight and toluene was removed in vacuo. The remaining residue was purified on silica gel (hexane:ethyl acetate 5:1) to afford a clear oil (3.2 g, 72% yield for Rh$_2$(R-BNP)$_4$ [enantiomer shown above]; 2.3 g, 52% yield for Rh$_2$(S-BNP)$_4$) $R_f = 0.17$ (hexane: ethyl acetate 5:1); [$\alpha$]$_{20}^D +4.1^\circ$ (c = 1.03, CHCl$_3$); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.10 (d, J = 9.0 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.69 (d, J = 9.0 Hz, 1H), 6.33 (dd, J = 9.0, 2.4 Hz, 1H), 6.51 (dd, J = 9.0, 2.4 Hz, 1H), 6.44 (d, J = 1.8 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 3.02 (dd, J = 9.0, 7.2 Hz, 1H), 2.13 (dd, J = 9.0, 5.1 Hz, 1H), 1.78 (dd, J = 7.2, 5.1 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.1, 148.4, 148.3, 137.4, 131.9, 130.5, 130.4, 129.7, 127.0, 126.6, 124.2, 115.2, 110.6, 55.9, 55.8, 52.9, 37.4, 32.1, 21.1; IR (film): 2951, 2836, 1716, 1559, 1516, 1413, 1229, 1178, 1137, 1027, 764; HRMS awaiting results; HPLC: (Chiralcel OD-H, 5% i-PrOH in hexane, 1 mL/min, 1 mg/mL, 30 min, $\Delta = 254$ nm) retention times of 15.4 min (minor) and 17.9 min (major), 86% ee for Rh$_2$(R-BNP)$_4$; retention times of 15.3 min (major) and 19.7 min (minor) 85% ee for Rh$_2$(S-BNP)$_4$, 48% ee for Rh$_2$(R-DOSP)$_4$.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.
Acknowledgments

This work was supported by the National Institutes of Health (DA023224).

References

28. The absolute configuration of the cyclopropanes is tentatively assigned assuming a similar asymmetric induction as was observed with styryldiazoacetates (see Davies HMLHNJS, Cantrell WR Jr, Olive JL. J Am Chem Soc. 1993; 115:9468.)

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Figure 1. Dirhodium-(II) catalysts used in this study
Scheme 1. Route to cyclopropyl amines from aryldiazoacetates
Table 1

Examination of the influence of substitution on aryldiazoacetate

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apentane, btoluene, c0.5 mol% catalyst loading
### Table 2
Examination of Rh$_2$ (R-BNP)$_4$ Loading

![Chemical structures](image)

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*a2.5 equiv. styrene used*
Table 3

Substrate Scope of Styrene with Rh$_2$(R-BNP)$_4$

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Rh$_2$(R-BNP)$_4$  Rh$_2$(R-DOSP)$_4$

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Table 4
A Guide to Chiral Dirhodium-(II) Catalyzed Cyclopropanation

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