In Situ Kinetic Studies of Rh(II)-Catalyzed Asymmetric Cyclopropanation with Low Catalyst Loadings.

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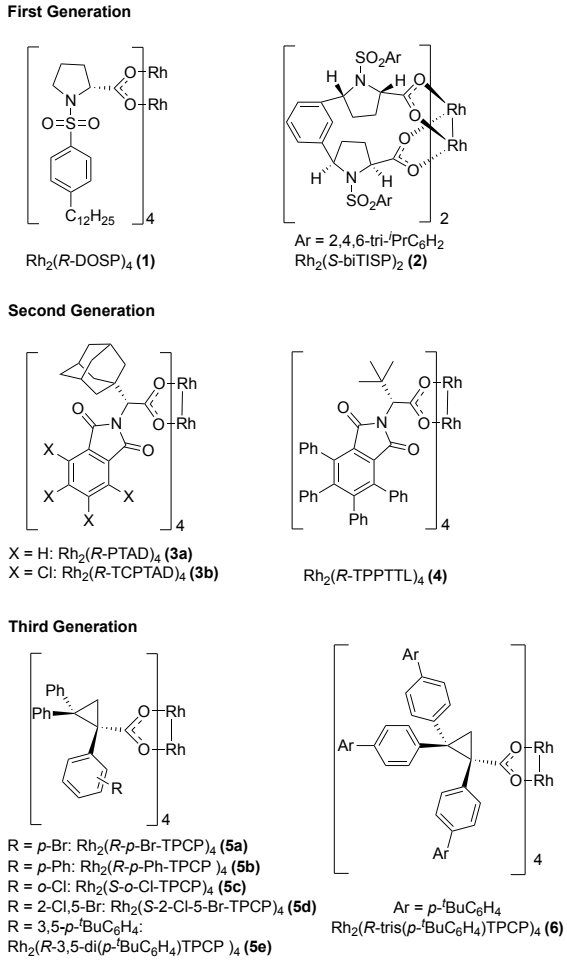
Supporting Information Placeholder

ABSTRACT: Dirhodium tetracarboxylates are versatile catalysts for the reactions of donor/acceptor carbenes. They catalyze a variety of transformations, including enantioselective intermolecular cyclopropanations. This study is focused on understanding the kinetics of the rhodium-catalyzed cyclopropanation and this information was used to develop conditions for conducting the reactions with very low catalyst loadings. The enantioselective cyclopropanation of styrenes can be conducted with a catalyst loading of 0.001 mol % and still maintain high levels of enantioselectivity (86-99% ee). A triarylcyclopropanecarboxylate (TPCP) catalyst, Rh_2(*p*-Ph-TPCP)$_4$ was the optimum catalyst for maintaining high enantioselectivity with very low catalyst loading. The reaction also benefitted from using dimethyl carbonate as solvent, an environmentally benign and nontoxic material.

Key-words: dirhodium tetracarboxylate, donor/acceptor carbene, enantioselective cyclopropanation, Reaction Progress Kinetic Analysis, low catalyst loadings.

INTRODUCTION

Dirhodium tetracarboxylates have revolutionized the chemistry of transition-metal-catalyzed reactions of diazo compounds.[1-4] Under mild reaction conditions, they cause the extrusion of nitrogen and generation of transient metal carbene intermediates capable of undergoing a variety of synthetically useful reactions. We have been particularly interested in developing chiral dirhodium catalysts for enantioselective reactions of donor/acceptor carbenes (Scheme 1).[5] The first generation of catalysts we developed were the chiral *N*-arylsulfonylprolinates, exemplified by Rh_2(*R*-DOSP)$_4$ (**1**), which were found to be particularly suited for the reactions of donor/acceptor



Scheme 1. Chiral dirhodium catalysts

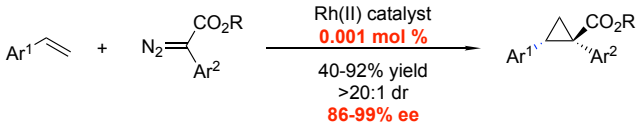
carbenes.[6, 7] They have been shown to be effective in a wide range of transformations, including cyclopropanation,[8-10] tandem cyclopropanation/Cope rearrangement,[11] cyclopropenation,[12] various ylide transformations,[13, 14] C—H functionalization[1] and the combined C—H functionalization/Cope rearrangement.[15] Rh_2(*S*-biTISP)$_2$ (**2**), a chiral bridged N-arylsulfonylprolinate catalyst, which has also been shown to also be effective in these reactions and is more robust than Rh_2(*R*-DOSP)$_4$ (**1**).[16-18]

The second generation catalysts are related to the phthalimido catalysts developed by Hashimoto.[19] The chiral adamantyl phthalimido catalyst Rh_2(*R*-PTAD)$_4$ (**3a**) was the first catalyst we developed of this class.[20] This catalyst tends to give enhanced enantioselectivity with cyclopropanation involving donor-acceptor carbenes compared to the Hashimoto catalysts, which contain smaller alkyl groups.[19, 21] Since then, two other phthalimido-derived catalysts have been developed for the donor/acceptor carbenes, Rh_2(*R*-TCPTAD)$_4$ (**3b**) and Rh_2(*R*-TPPTTL)$_4$ (**4**), and both are capable of site selective C—H functionalization reactions.[22-24]

The third generation catalysts are the triarylcyclopropanecarboxylates (TPCP). These catalysts were designed to be more sterically crowded than the earlier chiral catalysts. The original catalysts were Rh_2(*R*-*p*-Br-TPCP)$_4$ (**5a**) and Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**5b**).[25-28] Since then a variety of even more sterically demanding derivatives have been prepared. The most notable of these are Rh_2(*S*-*o*-Cl-TPCP)$_4$ (**5c**), Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$ (**5d**), Rh_2(*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$ (**5e**), and Rh_2(*R*-tris(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$ (**6**).[29-32]

Considering the high cost of rhodium catalysts and the broad utility of donor/acceptor carbenes, we have had a long-standing interest to perform these reactions with very low catalyst loadings. It was found that use of the bridged catalyst, Rh_2(*S*-biTISP)$_2$ (**2**), enabled the cyclopropanation of styrene to be conducted with 0.001 mol % catalyst loading in 85% ee. This catalyst, however, is difficult to synthesize on scale,[32] which has limited its general utility. Even lower catalyst loadings could be achieved for reactions catalyzed by Rh_2(*R*-DOSP)$_4$ (**1**) and Rh_2(*R*-PTAD)$_4$ (**3a**) in the absence of solvent, but the enantioselectivity dropped dramatically under these conditions.[33] Furthermore, reactions of diazo compounds under neat conditions on large scale would have significant safety issues because of the high energy associated with the diazo compounds.[34, 35]

The earlier high turnover number (TON) studies on the cyclopropanation of styrene were conducted with Rh_2(*R*-DOSP)$_4$ (**1**), Rh_2(*S*-biTISP)$_2$ (**2**), and Rh_2(*R*-PTAD)$_4$ (**3a**) because these were the available chiral catalysts at the time.[17, 33] With several new chiral dirhodium catalysts now available, we decided to carry out a systematic study to determine if the newer catalysts have beneficial properties for asymmetric cyclopropanation under extremely low catalyst loadings. Detailed kinetic studies were undertaken to determine the relative reactivity of these catalysts and their performance as the reaction progresses. These studies have resulted in the optimization of reaction conditions for highly enantioselective cyclopropanation (86-99% ee) which can be achieved with a range of substrates at a catalyst loading of 0.001 mol % (Scheme 2).

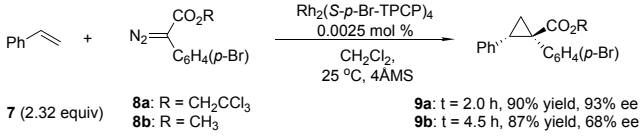


Scheme 2. Current studies: asymmetric cyclopropanation under low catalyst loading

RESULTS AND DISCUSSION

The first stage of the project was to determine the relative reactivity of the various catalysts in a standard cyclopropanation of styrene (**7**) with *p*-bromophenyldiazoacetate (**8**) to form the cyclopropane

(**9**). Recently, we have shown that the trichloroethyl ester (**8a**) offers advantages compared to the traditional methyl ester (**8b**) in terms of site selectivity in C—H functionalization reactions, reaction efficiency and, at least under thermal conditions, faster reactions.[10, 36] Therefore, we began by comparing the highly selective Rh_2(*S*-*p*-Br-TPCP)$_4$-catalyzed reaction of **8a** and **8b** using a catalyst loading of 0.0025 mol % (Scheme 3). The trichloroethyl ester **8a** was found to be more reactive and gave significantly higher enantioselectivity (93% ee versus 68% ee). Therefore, **8a** was used as the standard substrate to explore the relative reactivity of the different catalysts.



Scheme 3. Influence of ester functionality

The vast majority of the reported studies on rhodium-catalyzed reactions of donor/acceptor carbenes have not attempted to conduct the reactions at the lowest catalyst loadings possible.[37, 38] The typical conditions use a catalyst loading of 0.5-1.0 mol % at rt, and under these conditions all the catalysts are very effective for cyclopropanation. Typically, the reactions are complete in a matter of minutes, although it is very common for the diazo compounds to be added slowly to limit the possibility of carbene dimer formation. The catalysts are so effective that the reactions with reactive trapping substrates can be conducted at temperatures as low as -50 °C.[37] Consequently, prior to this study, information about the relative rates of the different catalysts was limited.[39-41] Therefore, we decided to compare the rates of these catalysts at relatively low loadings (0.0025 mol % of the Rh(II) catalyst) because under such conditions the kinetic difference between the catalysts should be discernable.

The reactions were conducted in dichloromethane to prevent issues with solubility. Additionally, dichloromethane is the established optimum solvent for 8 of the 10 catalysts explored.[3, 25] The two exceptions are the reactions conducted with Rh_2(*R*-DOSP)$_4$ (**1**), and Rh_2(*R*-PTAD)$_4$ (**3a**), which give higher levels of asymmetric induction when hydrocarbon solvents are used.[42] The rates of the reactions are easily determined by ReactIR, following the rate of disappearance of the distinctive signal for the diazo functionality [2103 cm^{-1}]. Control experiments were conducted to show that the rate of disappearance of the diazo signal is directly proportional to the rate of appearance of the signals associated with the cyclopropane product (See Supporting Information for details). The initial studies, however, were inconsistent, giving variable outcomes between experiments. Upon inclusion of activated 4 Å molecular sieves the reactions became reliable and reproducible. This result indicates that trace amounts of water can interfere with the rate of the reaction under low catalyst loadings and rigorously dry conditions are beneficial.

The influence of the various catalysts on the rates of the reaction under the standard conditions are shown in Figure 1. The catalysts displayed an unexpectedly wide range of reactivity with the most active catalyst being over 500 times faster than the slowest. Even so, the majority of the catalysts still completed the reaction in 30 min. The results implied that the Rh(II) catalysts have robust and efficient catalytic cycles, which would be essential for achieving extremely high TON.

The most reactive catalyst is Rh_2(*R*-DOSP)$_4$ (**1**), which had an initial TOF of 2,880,000 per hour and an overall TOF of 1,068,000 per hour. The second-generation catalysts, Rh_2(*R*-PTAD)$_4$ (**3a**), and Rh_2(*R*-TCPTAD)$_4$ (**3b**), were nearly as reactive as Rh_2(*R*-DOSP)$_4$ (**1**), whereas Rh_2(*R*-TPPTTL)$_4$ (**4**), was about four times slower. The third generation catalysts, the TPCP series, tended to be the slowest catalysts. The trend is not that surprising because the third generation catalysts were designed to be more sterically crowded than the first *and* second-generation catalysts. The *o*-chloro-substituted catalysts, Rh_2(*S*-*o*-Cl-TPCP)$_4$ (**5c**), and Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$ (**5d**), were still relatively fast, with an initial TOF of >1,000,000 per hour but Rh_2(*S*-*p*-Br-TPCP)$_4$, Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**5b**), and Rh_2(*R*-tris(*p*-^{t}BuC$_6$H$_4$)-TPCP)$_4$ (**6**) were about 20 times slower. The slowest catalyst of all was Rh_2(*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$ (**5e**), which was a further order of magnitude slower.

We have previously explored the high TON catalysis of Rh_2(*R*-DOSP)$_4$ (**1**), and Rh_2(*R*-PTAD)$_4$ (**3a**), two of the fastest catalysts.[33] Even though impressive overall TON could be obtained, we found that the enantioselectivity of cyclopropanation with these catalysts dropped precipitously between 0.01-0.001 mol % catalyst loading. Therefore, we decided to explore whether some of the slower and more sterically constrained catalysts would be better suited to maintain the enantioselectivity under low catalyst loading conditions. In this regard, we became interested in exploring further the Rh_2(*S*-*p*-Br-TPCP)$_4$-catalyzed reaction because it gave the highest level of enantioselectivity (93% ee) in the standard test reaction. Even though it is one of the slower catalysts, Rh_2(*S*-*p*-Br-TPCP)$_4$ is still capable of completing cyclopropanation at 0.0025 mol % catalyst loading in under 2 h at rt, and therefore has the potential to achieve very high TONs, especially if the reaction is conducted under elevated temperatures

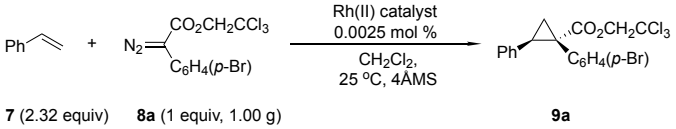
In order to understand better the behavior of Rh_2(*S*-*p*-Br-TPCP)$_4$, we conducted kinetic studies on the cyclopropanation reaction. Using the Variable Time

Normalization Analysis (VTNA) methodology reported by Burés,[43] we determined the reaction order of the catalyst through a series of 1.0 g scale reactions with a diazo-compound **8a** at a concentration of 0.1M. The reaction was performed at various catalyst loadings: 0.02 mol %, 0.01 mol %, and 0.0025 mol % and the diazo compound concentration [**8a**] was plotted against a normalized time scale $t[cat]_T^n$ (t = time, T = total) (Figure 2a), revealing that the reaction was 1st order in Rh_2(*S*-*p*-Br-TPCP)$_4$ (See Supporting Information for detail). After determining the reaction order of the catalyst, the robustness of the catalyst was evaluated using Reaction Progress Kinetic Analysis (RPKA) methodology[44, 45] by conducting "same excess" experiments.

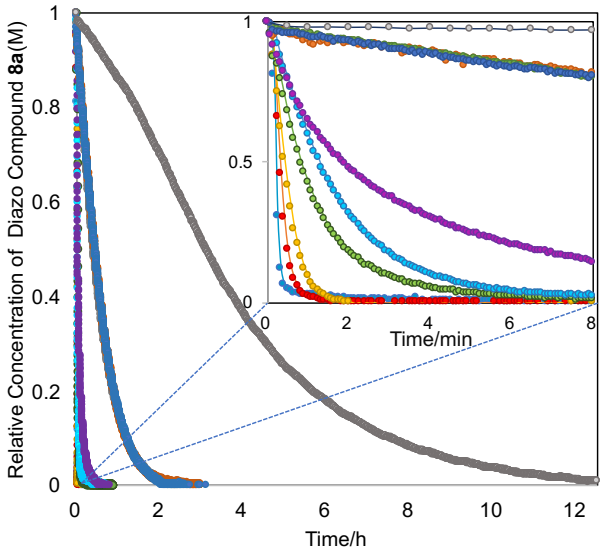
Herein, the [excess] is invariable over the course of the reaction and defined as shown in the eq 1.

$$[\text{excess}]=[\mathbf{7}]_0-[\mathbf{8a}]_0=[\mathbf{7}]-[\mathbf{8a}] \qquad (1)$$

The kinetics of two reactions were determined: one according to the "standard condition" as shown in Scheme 3 and the other is "same excess" with half the normal loading on the diazo compound **8a** (0.5 equiv) but the same [excess] of the styrene (**7**). When the "standard condition" reaction reaches 50% conversion, if the catalyst is robust and does not show deactivation or product inhibition, then the reaction rate should be equal to that of the "same excess" reaction. When tested, the kinetic profile of the "same excess" reaction and the "standard reaction" after 50% conversion show good overlap between the data sets (Figure 2b) (See Supporting Information for details). This result suggests that the Rh_2(*S*-*p*-Br-TPCP)$_4$ performance did not degrade during the reaction through the first 20,000 turnovers, and there was no catalyst inhibition due to product.

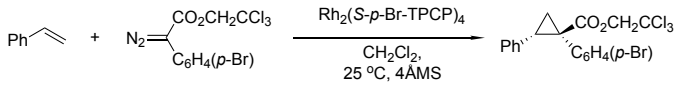


7 (2.32 equiv) **8a** (1 equiv, 1.00 g) **9a**



catalyst	ee (**9a**, %)	reaction time	initial TOF/h
Rh_2(*R*-DOSP)$_4$	73	2 min	2,880,000
Rh_2(*R*-PTAD)$_4$	-63	2 min	1,920,000
Rh_2(*R*-TCPTAD)$_4$	66	2 min	1,920,000
Rh_2(*R*-TPPTTL)$_4$	83	8 min	1,440,000
Rh_2(*S*-*o*-ClTPCP)$_4$	37	8 min	1,440,000
Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$	43	30 min	1,152,000
Rh_2(*S*-*p*-Br-TPCP)$_4$	-93	2 h	57,600
Rh_2(*R*-*p*-Ph-TPCP)$_4$	90	2 h	58,775
Rh_2(*R*-tris(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$	87	2 h	57,600
Rh_2(*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$	31	12.5 h	5,549

Figure 1. Reaction rates of various catalysts in the cyclopropanation reaction with 0.1 M concentration of diazo compound **8a** and 0.0025 mol % catalyst loading. The catalyst was added in one portion to the reaction mixture and the rate of disappearance of the signal for the diazo group was followed by ReactIR. (-) indicates that the opposite enantiomer was obtained *The initial turnover frequency (TOF) is measured according to the initial rate of the reactions up to 20% conversion. All reactions give the quantitative yield according to crude ^{1}H NMR, and the overall TOF calculated by isolated yield. (See Supporting Information for details).



7 **8a** **9a**

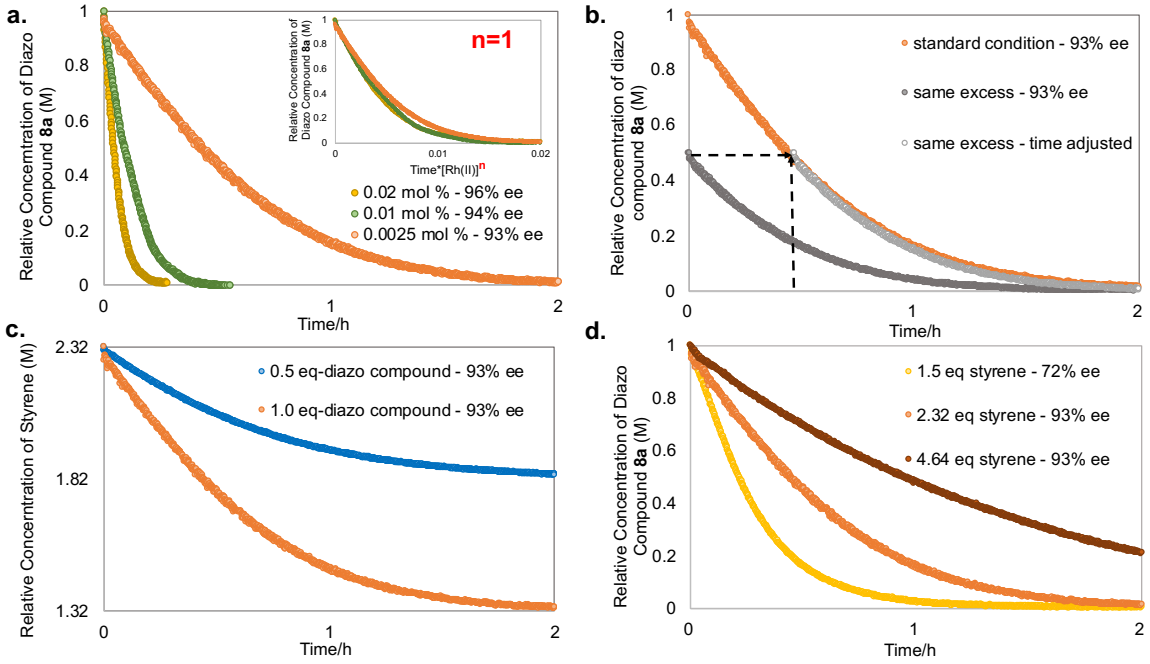


Figure 2. Kinetic profile of cyclopropanation reaction with Rh_2(*S*-*p*-Br-TPCP)$_4$ **a.** The Variable Time Normalization Analysis determined the catalyst is 1st order. **b.** Same excess reaction carried out with [excess] = 0.132 M. "standard condition": [**7**]$_0$ = 0.232 M, [**8a**]$_0$ = 0.1 M; "same excess": [**7**]$_0$ = 0.182 M, [**8a**]$_0$ = 0.05 M. **c**. Different excess reaction determined positive reaction order of diazo compound **8a**. **d**. Different excess reaction determined negative reaction order of styrene **7**.

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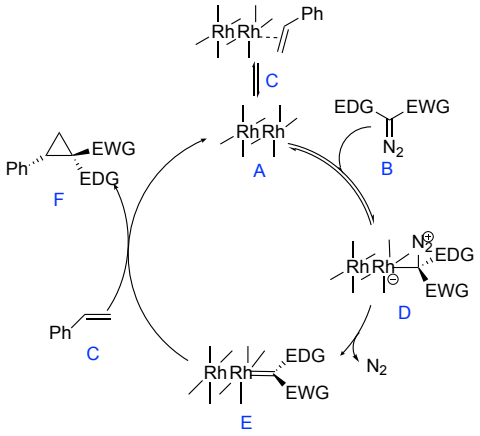
After confirming the robustness of the catalyst, we moved forward to determine the concentration dependences of the diazo compounds and the styrene. To achieve this goal, "different excess" experiments were performed. In these experiments, the amount of the diazo compound **8a** was decreased (0.5 equiv) and the concentrations of styrene (2.32 equiv) and the Rh(II) catalyst (0.0025 mol %) were kept constant (Figure 2c). We found that while the reaction rate (represented by change in the concentration of styrene) became slower, high enantioselectivity was maintained. The positive correlation data demonstrated that the reaction was positive order in diazo compound **8a**. The data was also in agreement with earlier computational studies,[46] which showed that the energy barrier for diazo decomposition is much higher than the cyclopropanation and therefore, is the rate determining step in this reaction. Concentration dependence of styrene was also determined by the same method (Figure 2d). Importantly, a higher concentration of styrene (4.64 equiv) led to slower reaction rate, whereas lower concentration of styrene (1.5 equiv) gave faster reaction rate but diminished enantioselectivity. These results suggest that although styrene may reduce the TOF, possibly by competing coordination to the Rh(II) catalyst, this coordination may also help to stabilize the catalyst and maintain high enantioselectivity. Based on this analysis, a rate law for the cyclopropanation reaction was determined (eq 2, see Supporting information for detailed derivation).

$$\text{rate} = k[\mathbf{8a}]^1\,[\mathbf{7}]^{-1}\,[\text{Rh(II)}]^1 \qquad (2)$$

A catalytic cycle that is consistent with the kinetic studies is shown in Scheme 4. The rhodium carboxylate (**A**) coordinates to the aryldiazoacetate (**B**) in competition with styrene (**C**) coordination. This interaction would explain why the rate of the reaction has a reverse relationship to the concentration of styrene. The rate determining step is the extrusion of nitrogen from the rhodium diazo complex **D** to form the rhodium carbene **E**. Reaction of the rhodium carbene **E**. with styrene (**C**) would then generate the final product **F** and recovered catalyst **A**. This mechanism is consistent with computational studies that have been carried out on the cyclopropanation reaction. These studies showed that the formation of the carbene is the rate determining step and the barrier for the cyclopropanation step is very small.[46] Rhodium tetracarboxylates are very stable complexes. They can be chromatographed and are stable in the open air for years. However, the rhodium carbene intermediate is likely not to be particularly stable and needs to react quickly to prevent catalyst degradation. Hence an excess of styrene, despite its ability to decrease the reaction rate, is better for maintaining the high enantioselectivity under very low catalyst loadings. The X-ray structure of the catalyst always have molecules coordinating to the axial positions (water, ethyl acetate,

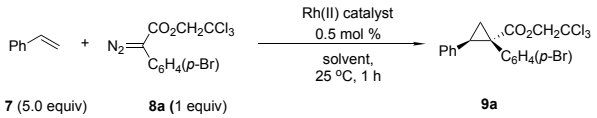
etc.)[5, 30, 47,] These axially coordinating ligands must be displaced for the catalytic reaction to proceed. However, our studies suggest that the kinetic barrier for the loss of the axial ligand must be small since we rarely see a delay before the reaction begins. However, dry conditions are required for reproducible reactions at exceedingly low catalyst loading, presumably because excess water would interfere with the small amount of catalyst present.



Scheme 4. Catalytic cycle for cyclopropanation of Styrene

Having established an understanding of the catalytic system at 0.0025 mol % loading, we then explored how the catalyst would perform at lower catalyst loadings. When it was conducted at 0.001 mol % loading, the reaction went to completion, but the enantioselectivity decreased from 93% ee to 79% ee. The drop in enantioselectivity as one attempts to push the reaction to ultra-low catalyst loading is similar to what was observed in earlier studies.[17, 33] Therefore, we decided to explore what other factors could be used to maintain the enantioselectivity under lower catalyst loadings. In the original studies with Rh_2(*S*-biTISP)$_2$ (**2**) we had found that high enantioselectivity was maintained only when one equivalent of methyl benzoate was added to the reaction mixture.[17] It was reasoned that methyl benzoate was weakly interacting with the carbene and thus increasing its stability. Therefore, we decided to explore whether the reaction could be benefit from a solvent switch, with particular emphasis on solvents containing ester groups. Furthermore, we desired to explore the possibility of using higher boiling solvents, so that we would have the option to conduct the reactions with relatively slow catalysts, such as Rh_2(*S*-*p*-BrTPCP)$_4$, at higher temperatures in a reasonable amount of time.

In order to evaluate quickly the effect of solvent on the enantioselectivity of the reaction, a series of reactions were performed using a robotic system (Figure 3). The small-scale reactions were conducted using a robotic system in the open-air and without stirring. Control experiments showed that the reactions were effective, giving reproducible levels of diastereoselectivity and enantioselectivity, however, under these conditions the isolated yields were low and not truly representative. Each reaction was conducted for 1 h at rt with a catalyst loading on 0.5 mol %, which is sufficient for all catalysts to complete the cyclopropanation in dichloromethane. Despite the sensitivity of both the catalyst and the carbene to atmospheric water in C—H insertion reactions, the cyclopropanations are sufficiently favorable and robust that no diazo dimer or O-H insertion products were observed. The results of the high throughput screening were tabulated and transposed into a heat map to demonstrate the enantioselectivity of the reaction in each solvent for each of the catalyst tested.



Catalyst	EtOAc	CH_2Cl_2	TFT	*i*-PrOAc	$(MeO)_2CO$	$(EtO)_2CO$	Pentane
Rh_2(*R*-DOSP)$_4$	78.1	63.1	77.9	83.9	67.1	66.7	77
Rh_2(*R*-PTAD)$_4$*	90.9	56.6	56.9	53.5	40.5	47.1	58.9
Rh_2(*R*-TCPTAD)$_4$	90.7	71.5	72.9	66.7	68.1	90.7	
Rh_2(*R*-TPPTTL)$_4$	95.6	88.5	90.5	91.3	91.9	87.9	
Rh_2(*S*-*o*-ClTPCP)$_4$	60.3	44.8	37.5	42.1	35.1	71.3	
Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$	39.7	72.2	70.9	77.9	63.5	70.2	
Rh_2(*S*-*p*-Br-TPCP)$_4$*	> 99	92	85.1	94.7	94.7	92.5	89.6
Rh_2(*R*-*p*-Ph-TPCP)$_4$	> 99	96.7	78.5	> 99	>99	97.7	
Rh_2(*S*-tris(*p*-^{t}BuC_6H_4)TPCP)$_4$*	98.9	95.9	89.9	96.5	93.7	> 99	
Rh_2(*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP)$_4$	87.1	73.3	91.3	82.7	61.8	89.5	

>99 %

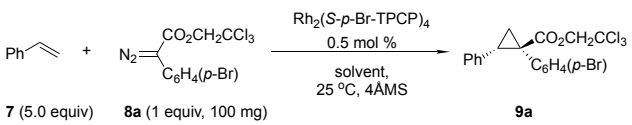
% ee

0 %

Figure 3. High throughput cyclopropanation in a variety of solvents and chiral catalysts. Color gradient proceeds from red to blue via white middle color which denotes middling % ee. The solvents tested in the screen were ethyl acetate (EtOAc), dichloromethane (CH_2Cl_2), trifluorotoluene (TFT), isopropyl acetate (*i*-PrOAc) dimethyl carbonate ($(MeO)_2CO$), and diethyl carbonate ($(EtO)_2CO$). The majority of the catalysts were insoluble in pentane. *These catalysts provided the opposite enantiomer to the structure depicted in the representative reaction diagram above.

Several solvents emerged as promising candidates for further evaluation under high turnover conditions. Particularly interesting were ethyl acetate, isopropyl acetate, and dimethyl carbonate [$(MeO)_2CO$], which provided significant increases in enantioselectivity compared to dichloromethane. Before deciding which solvent would be best suited for low catalyst loading studies, laboratory-scale (100 mg) reactions using 0.5 mol % of catalyst were performed to both validate results obtained from the high throughput screen and determine the solvent impact on the yield. Rh_2(*S*-*p*-Br-TPCP)$_4$ was chosen as the catalyst for these reactions because it had been shown to be the optimal catalyst during low-loading kinetic studies in dichloromethane. These lab scale reactions offered some interesting insight into the effect of the solvent on the cyclopropanation. The enantioselectivity enhancements observed in the high throughput screen were confirmed, however, some of the more selective solvents, such as ethyl acetate and isopropyl acetate, had significantly negative impacts on the yield of the reaction (Table 1).

TABLE 1. Lab scale cyclopropanation in a variety of solvents with Rh_2(*S*-*p*-Br-TPCP)$_4$



7 (5.0 equiv) **8a** (1 equiv, 100 mg) **9a**

solvent	yield, %	ee, %
CH_2Cl_2	95	91
$(MeO)_2CO$	91	94
EtOAc	66	95
n-hexane	34	87
TFT	88	89
^{t}BuCN	49	97
i-PrOAc	52	91
$(EtO)_2CO$	89	86

Previous work with ethyl acetate revealed that the ester group can coordinate to the rhodium-carbene leading to side products.[48] Additionally, ^{t}BuCN, a solvent preferred for Rh-nitrene chemistry in the DuBois lab was shown to increase enantioselectivity but was significantly detrimental to the yield.[49] Importantly, dimethyl carbonate maintained high yield for the transformation while significantly enhancing the enantioselectivity over dichloromethane. Dimethyl carbonate is a green, high-boiling, environmentally benign solvent that has become widely used as an alternative to potentially hazardous options like dichloromethane and diethyl ether.[50, 51] Though previous work has shown that ester solvents like isopropyl acetate can engage the rhodium carbene to form ylides,[48] we theorize that carbonates would be more compatible with our chemistry due to the lack of labile alpha-hydrogens. Hence as a highly enantioselective, high-boiling, green solvent, dimethyl carbonate was identified as a good candidate for optimizing cyclopropanation at low catalyst loading.

The Rh_2(*S*-*p*-Br-TPCP)$_4$-catalyzed reaction of diazo compound **(8a)** with styrene was then examined under high TON conditions using dimethyl carbonate as solvent. The reaction rate in dimethyl carbonate at rt was much slower (incomplete conversion after 10 h at 0.0025 mol % catalyst loading) compared to 2 h in dichloromethane, which is indicative of strong interactions between the solvent and the catalyst either through coordination to the carbene or the dirhodium complex.[52-54] Even so, the level of enantioselectivity was greatly improved (97% ee compared to 93% ee in dichloromethane). Control experiments revealed that **8a** underwent only about 3% decomposition over 10 h, on warming to 60 °C in dimethyl carbonate in the absence of catalyst (See Supporting Information for details). Consequently, we decided to increase the temperature of the reaction to accelerate the reaction rate and achieve higher TON, hopefully while retaining high enantioselectivity. At 0.0025 mol % catalyst loading the cyclopropanation was finished within 6 h at 40 °C, and 2 h at 60 °C. Even more promising was the observation that the enantioselectivity of the reaction remained around 96% ee (Figure 4a). Therefore, we continued to explore the lowest possible catalyst loading using dimethyl carbonate as solvent. As shown in Figure 4b, when the catalyst loading was decreased to 0.001 mol %, the reaction maintained enantioselectivity at 94% ee. The reaction also went to completion with 0.00025 mol % catalyst but the enantioselectivity dropped to 90% ee. The reaction at 0.0001 mol % catalyst was still incomplete after 24 h and the enantioselectivity further dropped to 81% ee.

After the solvent optimization, an RPKA study was conducted at 0.001 mol % catalyst loading in dimethyl carbonate at 60 °C to demonstrate the robustness of the catalyst in this new system. (see Supporting Information for details) The kinetic profile of the reaction in dimethyl carbonate mirrored that of the reaction in dichloromethane but maintained routinely higher level of enantioselectivity. We hypothesize that dimethyl carbonate may be weakly coordinating to the dirhodium complex in a way similar to that of methyl benzoate as posited in our previous study on Rh_2(*S*-biTISP)$_2$ (**2**).[17] To further investigate the robustness of the catalyst and practically demonstrate a high number of turnovers, we conducted a multiple addition experiment.[55] Multiple additions of diazo compound **8a** (1 equiv, 0.5 g per addition) into a solution of Rh_2(*S*-*p*-Br-TPCP)$_4$ (0.0025 mol %) and styrene (7.32 eq) were carried out. A new batch of diazo compound **8a** was added to the reaction upon consumption of the previous batch, as determined by ReactIR trace (Figure 5). Seven additions were performed over 20 h consistently giving 90% ee after consumption of each addition. Rh_2(*S*-*p*-Br-TPCP)$_4$ remains robust throughout the seven cycles although there is a slight increase in the maximum diazo signal and time for completion of each cycle, suggesting a slight decrease in catalyst performance.

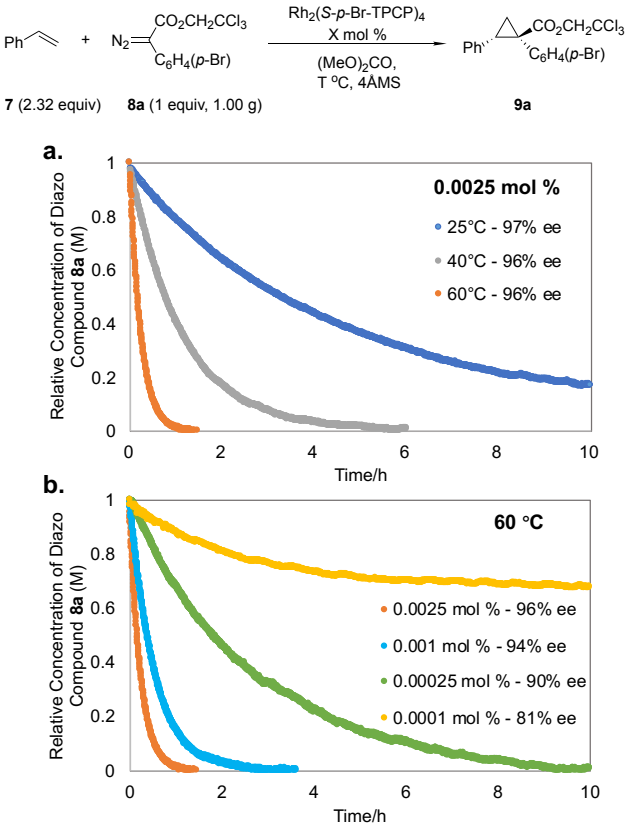
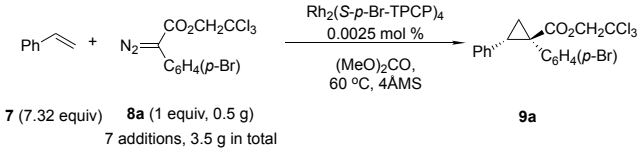


Figure 4. Kinetic profile of cyclopropanation in dimethyl carbonate. a. Reaction rate at different temperatures (0.0025 mol % catalyst loading). b. Reaction rate at 60 °C with different catalyst loadings.



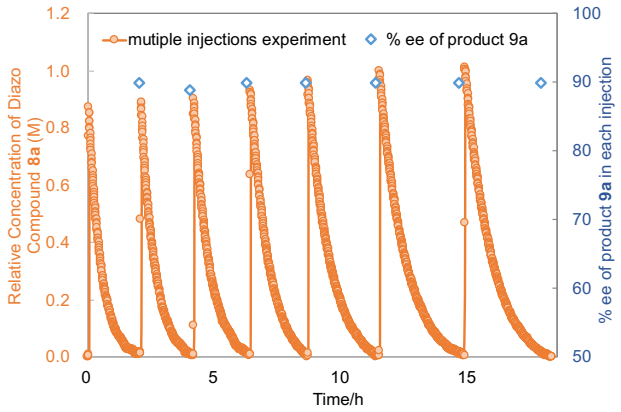
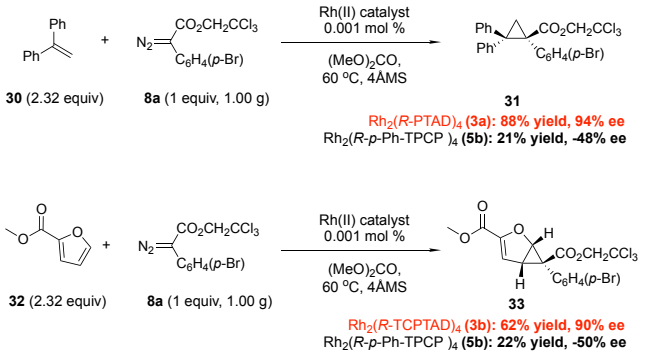


Figure 5. Kinetic profile of multiple addition experiment of the benchmark cyclopropanation. Seven successive additions of diazo compound **8a** (1 equiv) are added into a solution of styrene **7** (7.32 equiv) and Rh_2(*S*-*p*-Br-TPCP)$_4$ (0.0025 mol %) in dimethyl carbonate at 60 °C.

The scope of the low catalyst loading cyclopropanation was then examined with a range of aryldiazoacetates. Unfortunately, while the Rh_2(*S*-*p*-Br-TPCP)$_4$ / dimethyl carbonate system gave high enantioselectivity for some substrates, some substrates resulted in enantioselectivities well below 90% ee. During the high throughput screen, Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**5b**) performed extremely well in dimethyl carbonate, giving very high asymmetric induction. Therefore, we decided to examine Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**5b**) further and at low catalyst loading in dimethyl carbonate, its kinetic profile was identical to Rh_2(*S*-*p*-Br-TPCP)$_4$ but it routinely gave higher levels of enantioselectivity. (See Supporting Information) Based on these results, the full study on the scope of the asymmetric cyclopropanation at low catalyst loading was conducted with Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**5b**) as the catalyst (Figure 6). High enantioselectivity and yield was preserved across a broad substrate scope of aryldiazoacetates and styrene derivatives. In some cases, the reactions did not go to completion in 12 h and in those cases, the reactions were repeated using 0.003 mol % catalysts loading. Some of the more intriguing examples are the boronate derivative **16**, the styryl derivative **19**, and the heterocyclic derivatives **21** and **22**.

Extension of the triarylcyclopropanecarboxylate-catalyzed cyclopropanation to certain substrates was not as successful. 1,1-diphenylethylene (**30**), a key substrate for the enantioselective synthesis of the third generation (TPCP) ligands, did not perform very well and the cyclopropane **31** was obtained in only 48% ee with Rh_2(*R*-*p*-Ph-TPCP)$_4$ **(5b)**. Therefore, it was necessary to test some of the other catalysts in order to optimize the system further. Rh_2(*R*-PTAD)$_4$ (**3a**) and dimethyl carbonate were used as the optimal system for this transformation, furnishing the cyclopropane **31** in 94% ee at 0.001 mol % catalyst loading. Additionally, in the cyclopropanation of methyl-2-furoate (**32**), the enantioselectivity of the cyclopropane **33** increased from 50% ee with Rh_2(*R*-*p*-Ph-TPCP)$_4$ **(5b)** to 90% ee with Rh_2(*R*-TCPTAD)$_4$ (**3b**) in dimethyl carbonate. at 0.001 mol % catalyst loading.[56] (Scheme 5) The requirement for Rh_2(*R*-PTAD)$_4$ (**3a**) and Rh_2(*R*-TCPTAD)$_4$ (**3b**) rather than the third-generation catalyst (TPCP) to achieve high enantioselectivity, is presumably because the phthalimido series of catalysts **3a** and **3b** are better suited for reactions of more crowded substrates such as 1,1-diphenylethylene (**30**) and methyl-2-furoate (**32**). The steric trend was previously observed in C—H functionalization reactions using these catalysts. [5, 22, 26.] The third generation catalysts like Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**5b**) are selective for only the most accessible primary or secondary C—H bonds due to the extreme crowding of the TPCP catalytic pocket. In contrast, Rh_2(*R*-TCPTAD)$_4$ (**3b**) is an established catalysts as a highly selective functionalization of tertiary C—H bonds.



Scheme 5. Alternative catalysts applied to more sterically crowded substrates

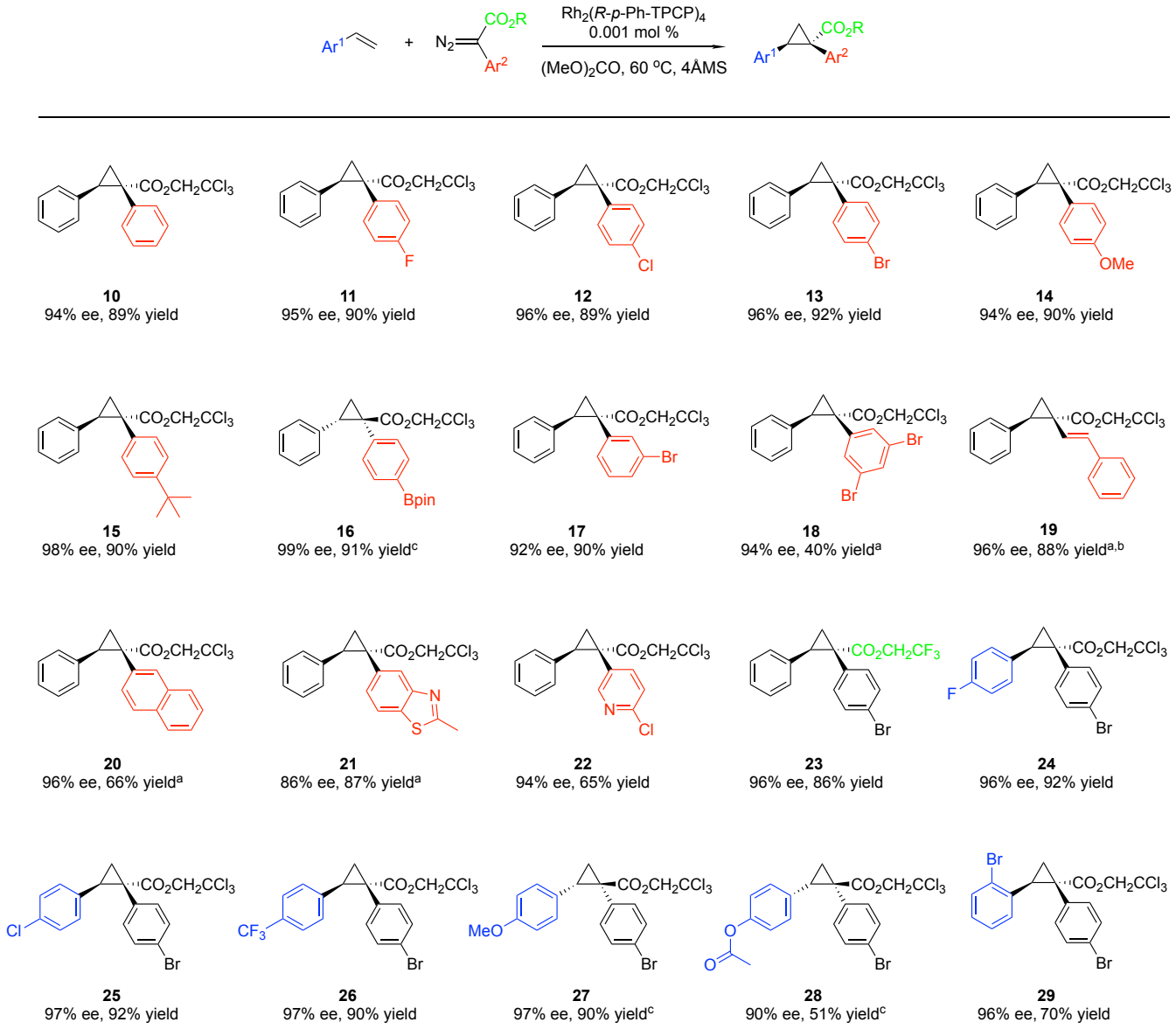
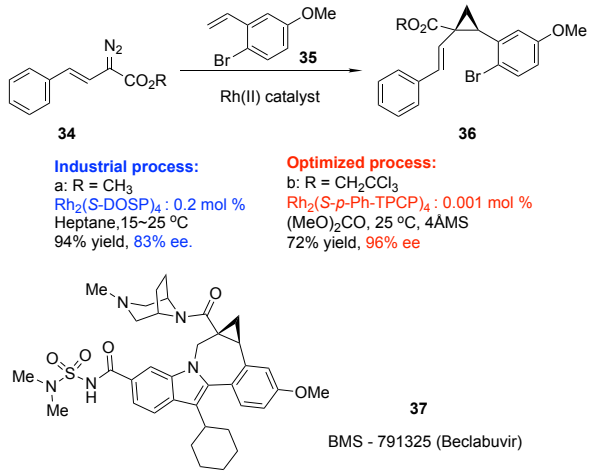


Figure 6. Scope of asymmetric cyclopropanation with 2.7 mmol of diazo compound at low catalyst loading (0.001 mol %) with Rh_2(*R*-*p*-Ph-TPCP)$_4$ **(5b)** at 60 °C in dimethyl carbonate. Compounds **10-23** illustrate scope of aryldiazoacetates. Compounds **24-29** show a variety of styrene derivatives. a: Reaction was conducted at 0.003 mol % catalyst loading to ensure reaction proceeds to completion. b: Reaction was conducted at 25 °C to avoid thermal rearrangement of the styryldiazoacetate to a pyrazole. c: Reaction was conducted with Rh_2(*S*-*p*-Ph-TPCP)$_4$.

Cyclopropanation is an important reaction for the construction of complex molecular architectures including key drug molecules.[57, 58] To demonstrate the utility of the optimized conditions for low catalyst loading cyclopropanation, we decided to re-examine the previously published synthesis of the cyclopropane **36**, a key step in the kilogram scale synthesis of the Hepatitis C drug, Beclabuvir **(37)**.[59] (Scheme 6) The previous synthesis was conducted *via* a Rh_2(*S*-DOSP)$_4$ -catalyzed reaction of methyl styryldiazoacetate **34a** with the styrene **35**. Using 0.2 mol % of Rh_2(*S*-DOSP)$_4$ to afford the desired cyclopropane **36a** in 94% yield and 83% ee. Under our low catalyst loading conditions using trichloroethyl styryldiazoacetate **34b**, the reaction was carried out with 1/200th the amount of catalysts with much higher asymmetric induction. The Rh_2(*R*-*p*-Ph-TPCP)$_4$ **(5b)**-catalyzed reaction of **34b** using 0.001 mol % catalyst loading at 25 °C with dimethyl carbonate as solvent, generated the cyclopropane **36b** in 72% yield and 96% ee.



Scheme 6. Asymmetric cyclopropanation in a key step in the synthesis of Beclabuvir

CONCLUSION

Over the course of this comprehensive study, the effect of the ligand on the performance of dirhodium catalysts was investigated under *in-situ* monitoring by ReactIR. Poor selectivity among a variety of scaffolds led us to choose Rh_2(*S*-*p*-Br-TPCP)$_4$, a highly enantioselective catalyst for further optimization at low catalyst loading. Detailed studies under the RPKA model determined the rate law of the cyclopropanation reaction and revealed that the catalyst was stable though 20,000 TON. However, the reactions failed maintain high enantioselectivity in dichloromethane for reactions with over 40,000 catalyst TON's. Further optimization studies identified dimethyl carbonate as a superior solvent for achieving 100,000 catalyst TON's with consistently high enantioselectivity. During these studies, the related catalyst Rh_2(*R*-*p*-Ph-TPCP)$_4$ **(5b)** was found to give slightly higher enantioselectivity than Rh_2(*S*-*p*-Br-TPCP)$_4$, and it was applied to a series of aryldiazoacetates and styrenes. The study culminated in the optimization of a key step in the synthesis of the Hepatitis C drug Beclabuvir **(37)** at 200-fold lower catalyst loading than the published procedure with higher enantioselectivity. In the future, these high TON conditions and kinetic analyses will be applied to other donor/acceptor carbene reactions, such as C—H functionalization, tandem cyclopropanation/Cope rearrangement, and ylide-induced cascade reactions.[60]

ASSOCIATED CONTENT

SUPPORTING INFORMATION

The Supporting Information includes complete experimental procedures, compound characterization, and derivations of relevant kinetic equations.
This material is available free of charge via the internet at http://pubs.acs.org.

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Notes

HMLD is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued March 10, 2015).

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REFERENCES

(1) Davies, H. M.; Morton, D. Guiding Principles for Site Selective and Stereoselective Intermolecular C—H Functionalization by Donor/Acceptor Rhodium Carbenes. *Chem. Soc. Rev.* **2011**, *40*, 1857-1869.

(2) Ye, T.; McKervey, M. A. Organic Synthesis with Alpha-Diazo Carbonyl Compounds. *Chem. Rev.* **1994**, *94*, 1091-1160.

(3) Doyle, M. P.; Forbes, D. C. Recent Advances in Asymmetric Catalytic Metal Carbene Transformations. *Chem. Rev.* **1998**, *98*, 911-936.

(4) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. Catalytic Carbene Insertion into C–H Bonds. *Chem. Rev.* **2010**, *110*, 704-724.

(5) Davies, H. M. L.; Liao, K. Dirhodium Tetracarboxylates as Catalysts for Selective Intermolecular C—H Functionalization. *Nat. Rev. Chem.* **2019**, *3*, 347-360.

(6) Davies, H. M. L. Asymmetric Synthesis Using Rhodium-Stabilized Vinylcarbenoid Intermediates. *Aldrichim. Acta.* **1997**, *30*, 107-114.

(7) Davies, H. M. L. Dirhodium Tetra(N-arylsulfonylprolinates) as Chiral Catalysts for Asymmetric Transformations of Vinyl- and Aryldiazoacetates. *Eur. J. Org. Chem.* **1999**, 2459-2469.

(8) Davies, H. M. L.; Nagashima, T.; Klino, J. L. Stereoselectivity of Methyl Aryldiazoacetate Cyclopropanations of 1,1-Diarylethylene. Asymmetric Synthesis of a Cyclopropyl Analogue of Tamoxifen. *Org. Lett.* **2000**, *2*, 823-826.

(9) Chepiga, K. M.; Qin, C.; Alford, J. S.; Chennamadhavuni, S.; Gregg, T. M.; Olson, J. P.; Davies, H. M. L.; Guide to Enantioselective Dirhodium(II)-Catalyzed Cyclopropanation with Aryldiazoacetates. *Tetrahedron.* **2013**, *69*, 5765-5771.

(10) Negretti, S.; Cohen, C. M.; Chang, J. J.; Guptill, D. M.; Davies, H. M. L. Enantioselective Dirhodium(II)-Catalyzed Cyclopropanations with Trimethylsilylethyl and Trichloroethyl Aryldiazoacetates. *Tetrahedron.* **2015**, *71*, 7415-7420.

(11) Spangler, J. E.; Lian, Y.; Raikar, S. N.; Davies, H. M. L. Synthesis of Complex Hexacyclic Compounds via a Tandem Rh(II)-Catalyzed Double-Cyclopropanation/Cope Rearrangement/Diels-Alder Reaction. *Org. Lett.* **2014**, *16*, 4794-4797.

(12) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. Highly Enantioselective Rh_2(S-DOSP)$_4$-Catalyzed Cyclopropenation of Alkynes with Styryldiazoacetates. *J. Am. Chem. Soc.* **2010**, *132*, 17211-17215.

(13) Li, Z.; Parr, B. T.; Davies, H. M. L. Highly Stereoselective C-C Bond Formation by Rhodium-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement Between Donor/Acceptor Carbenoids and Chiral Allylic Alcohols. *J. Am. Chem. Soc.* **2012**, *134*, 10942-10946.

(14) Li, Z.; Boyarskikh, V.; Hansen, J. H.; Autschbach, J.; Musaev, D. G.; Davies, H. M. L. Scope and Mechanistic Analysis of the Enantioselective Synthesis of Allenes by Rhodium-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement Between Donor/Acceptor Carbenoids and Propargylic Alcohols. *J. Am. Chem. Soc.* **2012**, *134*, 15497-15504.

(15) Davies, H. M. L.; Lian, Y. The Combined C—H Functionalization/Cope Rearrangement: Discovery and Applications in Organic Synthesis. *Acc. Chem. Res.* **2012**, *45*, 923-935.

(16) Nagashima, T.; Davies, H. M. L. Catalytic Asymmetric Cyclopropanation Using Bridged Dirhodium Tetraprolinates on Solid Support. *Org. Lett.* **2002**, *4*, 1989-1992.

(17) Davies, H. M. L.; Venkataramani, C. Dirhodium Tetraprolinate-Catalyzed Asymmetric Cyclopropanations with High Turnover Numbers. *Org. Lett.* **2003**, *5*, 1403-1406.

(18) Davies, H. M. L.; Panaro, S. A. Novel Dirhodium Tetraprolinate Catalysts Containing Bridging Prolinate Ligands for Asymmetric Carbenoid Reactions. *Tetrahedron Lett.* **1999**, *40*, 5287-5290.

(19) Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. Enhancement of Enantioselectivity in Intramolecular C—H Insertion Reactions of Alpha-Diazo Beta-Keto-Esters Catalyzed by Chiral Dirhodium(II) Carboxylates. *Tetrahedron Lett.* **1993**, *34*, 5109-5112.

(20) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. Dirhodium Tetracarboxylate Derived from Adamantylglycine as a Chiral Catalyst for Carbenoid Reactions. *Org. Lett.* **2006**, *8*, 3437-3440.

(21) Takeda, K.; Oohara, T.; Anada, M.; Nambu, H.; Hashimoto, S. A Polymer-Supported Chiral Dirhodium(II) Complex: Highly Durable and Recyclable Catalyst for Asymmetric Intramolecular C—H Insertion Reactions. *Angew. Chem. Int. Ed.* **2010**, *49*, 6979-6983.

(22) Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. Site-selective and Stereoselective Functionalization of Non-activated Tertiary C—H Bonds. *Nature* **2017**, *551*, 609-613.

(23) Fu, J.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L., Desymmetrization of Cyclohexanes by Site- and Stereoselective C—H Functionalization. *Nature* **2018**, *564*, 395-399.

(24) Yamaguchi, A. D.; Chepiga, K. M.; Yamaguchi, J.; tami, K.; Davies, H. M. L. Concise Syntheses of Dictyodendrins A and F by a Sequential C—H Functionalization Strategy. *J. Am. Chem. Soc.* **2015**, *137*, 644-647.

(25) Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. D_2-Symmetric Dirhodium Catalyst Derived from a 1,2,2-Triarylcyclopropanecarboxylate Ligand: Design, Synthesis and Application. *J. Am. Chem. Soc.* **2011**, *133*, 19198-19204.

(26) Qin, C.; Davies, H. M. Role of Sterically Demanding Chiral Dirhodium Catalysts in Site-Selective C—H Functionalization of Activated Primary C—H Bonds. *J. Am. Chem. Soc.* **2014**, *136*, 9792-9796.

(27) Fleming, G. S.; Beeler, A. B. Regioselective and Enantioselective Intermolecular Buchner Ring Expansions in Flow. *Org. Lett.* **2017**, *19*, 5268-5271.

(28) Dong, K.; Pei, C.; Zeng, Q.; Wei, H.; Doyle, M. P.; Xu, X. Selective C(sp^3)–H Bond Insertion in Carbene/Alkyne Metathesis Reactions. Enantioselective Construction of Dihydroindoles. *ACS Catalysis.* **2018**, *8*, 9543-9549.

(29) Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L., Site-selective and Stereoselective Functionalization of Unactivated C—H Bonds. *Nature.* **2016**, *533*, 230-234.

(30) Liao, K.; Liu, W.; Niemeyer, Z. L.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Sigman, M. S.; Davies, H. M. L. Site-Selective Carbene-Induced C–H Functionalization Catalyzed by Dirhodium Tetrakis(triarylcyclopropanecarboxylate) Complexes. *ACS Catalysis.* **2017**, *8*, 678-682.

(31) Liu, W.; Ren, Z.; Bosse, A. T.; Liao, K.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stoltz, B. M.; Davies, H. M. L. Catalyst-Controlled Selective Functionalization of Unactivated C—H Bonds in the Presence of Electronically Activated C—H Bonds. *J. Am. Chem. Soc.* **2018**, *140*, 12247-12255.

(32) Liao, K.; Yang, Y. F.; Li, Y.; Sanders, J. N.; Houk, K. N.; Musaev, D. G.; Davies, H. M. L., Design of Catalysts for Site-Selective and Enantioselective Functionalization of Non-Activated Primary C—H Bonds. *Nature Chem.* **2018**, *10*, 1048-1055.

(33) Pelphrey, P.; Hansen, J.; Davies, H. M. L. Solvent-Free Catalytic Enantioselective C–C Bond Forming Reactions with Very High Catalyst Turnover Numbers. *Chem. Sci.* **2010**, *1*, 254-257.

(34) Maas, G. New Syntheses of Diazo Compounds. *Angew. Chem. Int. Ed.* **2009**, *48*, 8186-8195.

(35) Mix, K. A.; Aronoff, M. R.; Raines, R. T., Diazo Compounds: Versatile Tools for Chemical Biology. *ACS Chem. Bio.* **2016**, *11*, 3233-3244.

(36) Guptill, D. M.; Davies, H. M. L. 2,2,2-Trichloroethyl Aryldiazoacetates as Robust Reagents for the Enantioselective C—H Functionalization of Methyl Ethers. *J. Am. Chem. Soc.* **2014**, *136*, 17718-17721.

(37) Davies, H. M. L.; Antoulinakis, E. G. Intermolecular Metal-Catalyzed Carbenoid Cyclopropanations. *Org. React.* **2001** *57*, 1-326.

(38) Davies, H. M. L.; Pelphrey, P. M. Intermolecular C—H Insertions of Carbenoids. *Org. React.* **2011**, *75*, 75-211.

(39) Pirrung, M. C.; Morehead, A. T. Electronic Effects in Dirhodium(II) Carboxylates. Linear Free Energy Relationships in Catalyzed Decompositions of Diazo Compounds and CO and Isonitrile Complexation. *J. Am. Chem. Soc.* **1994**, *116*, 8991-9000.

(40) Pirrung, M. C.; Morehead, A. T. Saturation Kinetics in Dirhodium(II) Carboxylate-Catalyzed Decompositions of Diazo Compounds. *J. Am. Chem. Soc.* **1996**, *118*, 8162-8163.

(41) Pirrung, M. C.; Liu, H.; Morehead, A. T. Rhodium Chemzymes: Michaelis-Menten Kinetics in Dirhodium(II) Carboxylate-Catalyzed Carbenoid Reactions. *J. Am. Chem. Soc.* **2002**, *124*, 1014-1023.

(42) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. Asymmetric Cyclopropanations by Rhodium(II) N-(Arylsulfonyl)prolinate Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Alkenes. Practical Enantioselective Synthesis of the Four Stereoisomers of 2-Phenylcyclopropan-1-amino Acid. *J. Am. Chem.. Soc.* **1996**, *118*, 6897-6907.

(43) Nielsen, C. D.; Bures, J. Visual Kinetic Analysis. *Chem. Sci.* **2019**, *10*, 348-353.

(44) Blackmond, D. G. Kinetic Profiling of Catalytic Organic Reactions as a Mechanistic Tool. *J. Am. Chem. Soc.* **2015**, *137*, 10852-10866.

(45) Blackmond, D. G. Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions. *Angew. Chem. Int. Ed.* **2005**, *44*, 4302-4320.

(46) Hansen, J.; Autschbach, J.; Davies, H. M. L. Computational Study on the Selectivity of Donor/Acceptor-Substituted Rhodium Carbenoids. *J. Org. Chem.* **2009**, *74*, 6555-6563.

(47) Lindsay, V. N. G.; Lin, W.; Charette, A. B. Experimental Evidence for the All-Up Reactive Conformation of Chiral Rhodium(II) Carboxylate Catalysts: Enantioselective Synthesis of cis-Cyclopropane α-Amino Acids. *J. Am. Chem. Soc.* **2009**, *131*, 16383-16385.

(48) Fu, L.; Hoang, K.; Tortoreto, C.; Liu, W.; Davies, H. M. L. Formation of Tertiary Alcohols from the Rhodium-Catalyzed

Reactions of Donor/Acceptor Carbenes with Esters. *Org. Lett.* **2018**, *20*, 2399-2402.

(49) Chiappini, N. D.; Mack, J. B. C.; Du Bois, J. Intermolecular C(sp^3)–H Amination of Complex Molecules. Angew. Chem. Int. Ed. **2018**, *57*, 4956-4959.

(50) Miao, X. Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. Dimethyl Carbonate: an Eco-Friendly Solvent in Ruthenium-Catalyzed Olefin Metathesis Transformations. *Chem. Sus. Chem.* **2008**, *1*, 813-816.

(51) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Robert McElroy, C.; Sherwood, J. Tools and Techniques for Solvent Selection: Green Solvent Selection Guides. *Sus. Chem. Proc.* **2016**, *4*. 1-24

(52) Trindade, A. F.; Coelho, J. A. S.; Afonso, C. A. M.;Veiros, L. F.; Gois, P. M. P. Fine Tuning of Dirhodium(II) Complexes: Exploring the Axial Modification. *ACS Catalysis.* **2012**, *2*, 370-383.

(53) Aguirre, J. D.; Lutterman, D. A.; Angeles-Boza, A. M.; Dunbar, K. R.; Turro, C. Effect of Axial Coordination on the Electronic Structure and Biological Activity of Dirhodium(II,II) Complexes. *Inorg. Chem.* **2007**, *46*, 7494-7502.

(54) Nelson, T. D.; Song, Z. J.; Thompson, A. S.; Zhao, M.; DeMarco, A.; Reamer, R. A.; Huntington, M. F.; Grabowski, E. J. J.; Reider, P. J. Rhodium-Carbenoid-Mediated Intermolecular O–H Insertion Reactions: a Dramatic Additive Effect. Application in the Synthesis of an Ascomycin Derivative. *Tetrahedron Lett.* **2000**, *41*, 1877-1881.

(55) Blackmond, D.; Schultz, T.; Mathew, J.; Loew, C.; Rosner, T.; Pfaltz, A. Comprehensive Kinetic Screening of Palladium Catalysts for Heck Reactions. *Synlett.* **2006**, 3135-3139.

(56) Lehner, V.; Davies, H. M. L.; Reiser, O., Rh(II)-Catalyzed Cyclopropanation of Furans and Its Application to the Total Synthesis of Natural Product Derivatives. *Org. Lett.* **2017**, *19*, 4722-4725.

(57) Chi, Y.; Qiu, L.; Xu, X. Highly Enantioselective Synthesis of Spirocyclopropyloxindoles via a Rh(II)-Catalyzed Asymmetric Cyclopropanation Reaction. *Org. Biomol. Chem.* **2016**, *14*, 10357-10361.

(58) Talele, T. T. The “Cyclopropyl Fragment” is a Versatile Player That Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59*, 8712-8756.

(59) Bien, J.; Davulcu, A.; DelMonte, A. J.; Fraunhoffer, K. J.; Gao, Z.; Hang, C.; Hsiao, Y.; Hu, W.; Katipally, K.; Littke, A.; Pedro, A.; Qiu, Y.; Sandoval, M.; Schild, R.; Soltani, M.; Tedesco, A.; Vanyo, D.; Vemishetti, P.; Waltermire, R. E. The First Kilogram Synthesis of Beclabuvir, an HCV NS5B Polymerase Inhibitor. *Org. Proc. Res. Dev.* **2018**, *22*, 1393-1408.

(60) During the review process of this article, a comprehensive study has been published concerning the stability of aryldiazoacetates. Green, S. P; Wheelhouse, K. M.; Payne; A. D.; Hallett, J. P.; Miller, P. W.; & Bull, J. A. Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents. *Org. Proc. Res. Dev.* **2019**. Even though we have not experienced any hazardous decomposition over many years working with these compounds, they are high energy compunds that need to be handled wih caution. Care should be taken to minimize the amount of heating needed to concentrate solutions of the diazo compounds and reactions should be conducted behind a blast shield.

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