In-situ Kinetic Studies of Rh(II)-Catalyzed C—H Functionalization to Achieve High Catalyst Turnover Numbers

Bo Wei,[a,#] Jack C. Sharland,[a] Donna G. Blackmond,[b] Djamaladdin G. Musaev[a,c] and Huw M. L. Davies[a,*]

[a]Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322, United States

[b]Department of Chemistry, The Scripps Research Institute, La Jolla, California, 92037, United States

[c]Cherry L. Emerson Center for Scientific Computation, Emory University, 1521 Dickey Drive, Atlanta, Georgia 30322, United States

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Supporting information Placeholder

ABSTRACT: Detailed kinetic studies on the functionalization of unactivated hydrocarbon sp^3 C—H bonds by dirhodium-catalyzed reaction of aryldiazoacetates revealed that the C—H functionalization step is rate-determining. The efficiency of this step was increased by using the hydrocarbon as solvent and using donor/acceptor carbenes with an electron-withdrawing substituent on the aryl donor group. The optimum catalyst for these reactions is the tetraphenylphthalimido derivative Rh_2(*R*-TPPTTL)$_4$ and a further beneficial refinement was obtained by using *N,N'*-dicyclohexylcarbodiimide as an additive. Under the optimum conditions with a catalyst loading of 0.001 mol %, effective enantioselective C—H functionalization (66-97% yield, 83-97% ee) was achieved of cycloalkanes with a range of aryldiazoacetates as long as the aryldiazoacetate was not to sterically demanding. The reaction with cyclohexane using a catalyst loading of 0.0005 mol % could be recharged twice with additional aryldiazoacetate, resulting in an overall dirhodium catalyst turnover number of 580,000.

Introduction

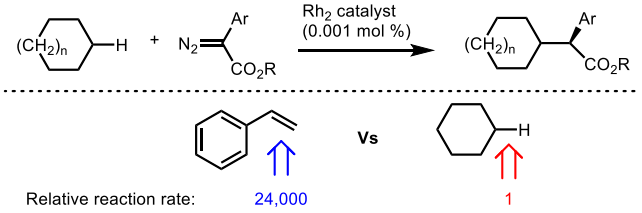
A wide variety of transition metal-catalyzed C—H functionalization methods have been studied in recent years because they offer new strategies to synthesize complex targets.[1-7] With the extensive range of applications, greater focus has been placed on increasing the practicality of this chemistry.[8-14]As the C—H functionalization step is often challenging, the catalytic cycle can be slow and the reactions require forcing conditions with relatively large amounts of the transition metal catalyst.[15-18] In recent years we have focused on the intermolecular site-selective C—H functionalization induced by dirhodium-catalyzed C—H insertion with donor/acceptor carbenes.[19] A variety of chiral catalysts of different shapes and sizes have been developed to control which C—H bond is functionalized.[20] These reactions are catalytically very efficient and typically are conducted at ambient temperature with a catalyst loading of 1 mol %. Even though the catalyst loading compares well with the amount used in many of the other C—H functionalization methods,[21] rhodium is expensive and finding ways to conduct the reactions with much lower catalyst loadings would be beneficial.

The rhodium-catalyzed reactions of diazo compounds have broad applications in organic synthesis.[22-27] Previously, we showed that donor/acceptor carbenes offer new synthetic opportunities because of the attenuating influence of the donor group.[28, 29] They can be used in several different types of enantioselective transformations, such as cyclopropanation, cyclopropenation, C—H and X—H insertions as well as a variety of reactions involving ylide intermediates.[22, 30-34] In the past, questions arose about the feasibility of running large scale reactions with diazo compounds because they are highly energetic and potentially unstable.[35-37] These safety concerns have been greatly alleviated in recent years on account of the advances in generating diazo compounds in flow.[38-43] Considerable efforts have been made to replace the rhodium with cheaper metals, but the dirhodium catalysts have special properties that are difficult to replicate.[21, 43-47] They are kinetically very active at decomposing diazo compounds, yet perfectly stable to air and moisture. Many of the designed chiral ligands self-assemble around the dirhodium core to generate elaborate high symmetry chiral complexes capable of very high levels of asymmetric induction.[19] Furthermore, these catalysts are especially well-suited for intermolecular site-selective C—H functionalization.[20]

As dirhodium tetracarboxylates remain the most effective catalysts for a wide range of carbene reactions, methods have been developed to either recover the catalysts or use very low catalyst loadings.[9, 22, 49-51] The donor group stabilizes donor/acceptor carbenes and consequently, these carbenes are better suited for reactions conducted with low catalyst loadings because they are less likely to destroy the catalyst during multiple catalytic cycles.[52, 53] Previously, we have shown that cyclopropanation can be carried out with low catalyst loadings without loss of enantioselectivity.[22, 54] In carbene-induced C—H functionalization, however, high catalyst turnover number (TON) is more challenging because the activation energy for C—H functionalization is generally much higher than for cyclopropanation causing the reaction to proceed at a considerably slower rate (Scheme 1).[54-57] Thus, the relative rate of catalyst deactivation is likely to be more competitive with the C—H functionalization step. In this manuscript we describe a detailed optimization study that led to a high yielding and highly enantioselective process for the C—H functionalization (Scheme 1) that can be conducted with a catalyst loading as low as 0.0005 mol %. In order to achieve these results, a detailed kinetic study was required, which lead to the unexpected

finding that carbodiimides can play a pivotal role in enhancing the efficiency of the catalyst.

Scheme 1. Carbene-induced C—H functionalization and the challenges associated with low loading.[56,57]

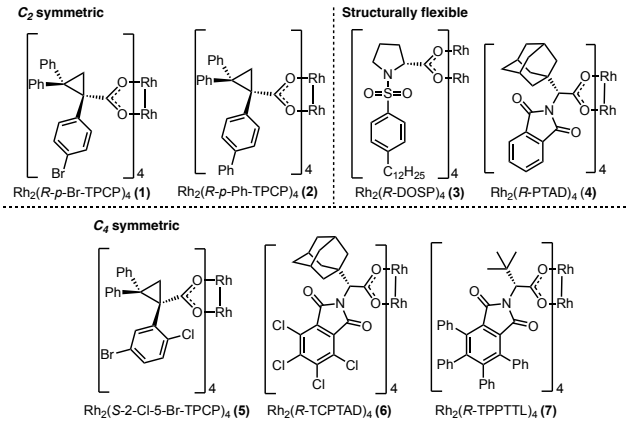


Results and Discussion

Computational studies have indicated that the kinetics of the dirhodium-catalyzed C—H functionalization with aryldiazoacetates are likely to be different from the cyclopropanation chemistry.[52, 58] The barrier for the cyclopropanation step has been calculated to be very small and hence the nitrogen extrusion to form the carbene was predicted to be the rate determining step, and this was confirmed by means of kinetic studies.[22] In contrast, the transition state for the functionalization of an unactivated C—H bond, such as those in cyclohexane, has been calculated to be much higher energy than for the cyclopropanation, and the C—H functionalization step was calculated to be the rate determining step.[52] This could add a further challenge to achieving high TON in C—H functionalization reactions because it was expected that ineffective capture of the rhodium carbene would increase the likelihood for the carbene to destroy the dirhodium catalyst.

The first stage of this study was to evaluate the catalytic efficiency of the most prominent chiral dirhodium catalysts to see whether they have similar reactivity profiles to what had been observed in the cyclopropanation reactions (Scheme 2). The evaluated catalysts were the C_2 symmetric catalysts, Rh_2(*R*-*p*-Br-TPCP)$_4$ (**1**)[59] and Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**2**),[60] the relatively flexible catalysts, Rh_2(*R*-DOSP)$_4$ (**3**) and Rh_2(*R*-PTAD) (**4**),[61] and the C_4 symmetric bowl-shaped catalysts, Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$ (**5**),[62] Rh_2(*R*-TCPATD)$_4$ (**6**),[63,64] and Rh_2(*R*-TPPTTL)$_4$ (**7**).[65]

Scheme 2. Dirhodium(II) catalysts used in this study



The C—H functionalization of cyclohexane (**9**) with 2,2,2-trichloroethyl aryldiazoacetate **8a** was used as the reference reaction to evaluate the effectiveness of the catalysts (Figure 1). The trichloroethyl ester was used in **8a** because it has been shown to result in much more effective reactions with nonactivated C—H bonds compared to the corresponding methyl ester derivative.[66] The initial evaluation was conducted in CH_2Cl_2 under reflux with 0.1 mol % catalyst loading and 2.5 equiv of cyclohexane. The rates of the reactions were monitored by ReactIR following the disappearance of the diazo signal of compound **8a** as the reactions progresses. Rh_2(*R*-*p*-Br-TPCP)$_4$ (**1**) and Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**2**) were the first catalysts to be tested because they had been shown to be the best catalysts for high TONs in the cyclopropanation reaction, routinely giving excellent results at 0.001 mol % catalyst loading.[22] However, as shown in Figure 1, the reactions with Rh_2(*R*-*p*-Br-TPCP)$_4$ (**1**) and Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**2**) both showed slow reaction rates (~20% conversion after 30 min) and moderately low levels of enantioselectivity (56-71% ee). Both of these catalysts are considered to be sterically demanding and capable of high asymmetric induction when conducted with 1 mol % catalyst loading. Hence, it is assumed that the rhodium carbene intermediate is not trapped quickly enough with cyclohexane, leading to the poor performance at 0.1 mol % catalyst loading. The kinetically most active catalysts in the cyclopropanation study were Rh_2(*R*-DOSP)$_4$ (**3**) and Rh_2(*R*-PTAD)$_4$ (**4**), but neither performed well here.[22] Rh_2(*R*-PTAD)$_4$ (**4**) achieved ~40% conversion after 30 min, whereas Rh_2(*R*-DOSP)$_4$ (**3**) started fast but the reaction stopped after 10 min with ~40% conversion. Much more promising results were obtained with the C_4 symmetric dirhodium(II) catalysts, which have become some of the dominant catalysts in our recent C—H functionalization studies. All three catalysts, Rh_2(*S*-2-Cl-5-Br-TPCP)$_4$ (**5**), Rh_2(*R*-TCPATD)$_4$ (**6**) and Rh_2(*R*-TPPTTL)$_4$ (**7**), resulted in complete conversion in 20 min. By far the most impressive catalyst of the three is Rh_2(*R*-TPPTTL)$_4$ (**7**), which completed the reaction in only 2 min and generated **10a** in 94% yield and with 95% ee.

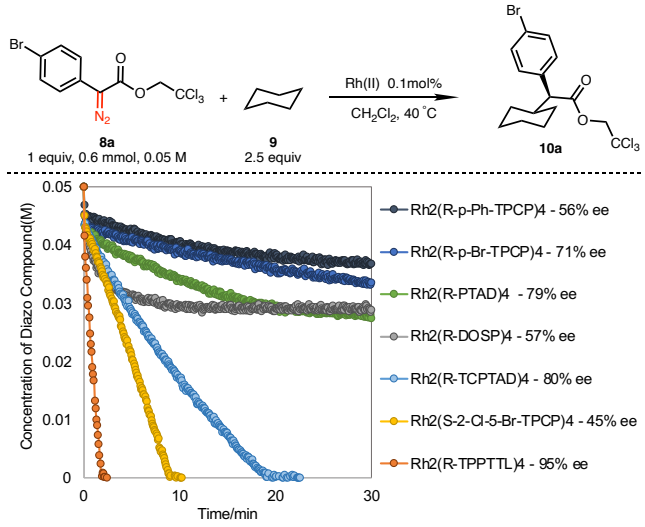


Figure 1. Kinetic profiles of C—H insertion of cyclohexane catalyzed by dirhodium(II) catalysts with various symmetric structures.

In order to have a solid foundation for the further optimization of Rh_2(*R*-TPPTTL)$_4$ (**7**), detailed kinetic studies were conducted on the cyclohexane C—H functionalization reaction.[67] The critical data are summarized in Figure 2 (see the Supporting Information for complete details). Reaction progress kinetic analysis (RPKA) was chosen for this purpose. A "same excess" was performed which enabled us to evaluate the robustness of the catalyst by replicating the reaction product and starting material concentrations at 50% conversion but with fresh catalyst. This analysis revealed that the catalyst after completing 500 cycles still reacts similarly as fresh catalyst

(Figure 2a). This result shows that catalyst deactivation is minimal at standard condition with 0.1 mol % catalyst loading. A series of "different excess" experiments were then conducted to determine the overall kinetics of the reaction. In these experiments, the concentration of each reagent is individually varied keeping all other conditions constant to determine the reaction order with respect to each reaction component. Figure 2b shows that the rate of the reaction increases with a higher concentration of cyclohexane, indicating a positive order of cyclohexane in the reaction.[67] The experiments with various equiv of diazo compound **8a**, keeping the other reaction conditions constant, were then performed (Figure 2c). The kinetic profiles showed the reactions with different diazo compound concentration gave the same initial reaction rates, which suggested zero-order rate influence of the diazo compound **8a**. The variable time normalization analysis (VTNA) method was further

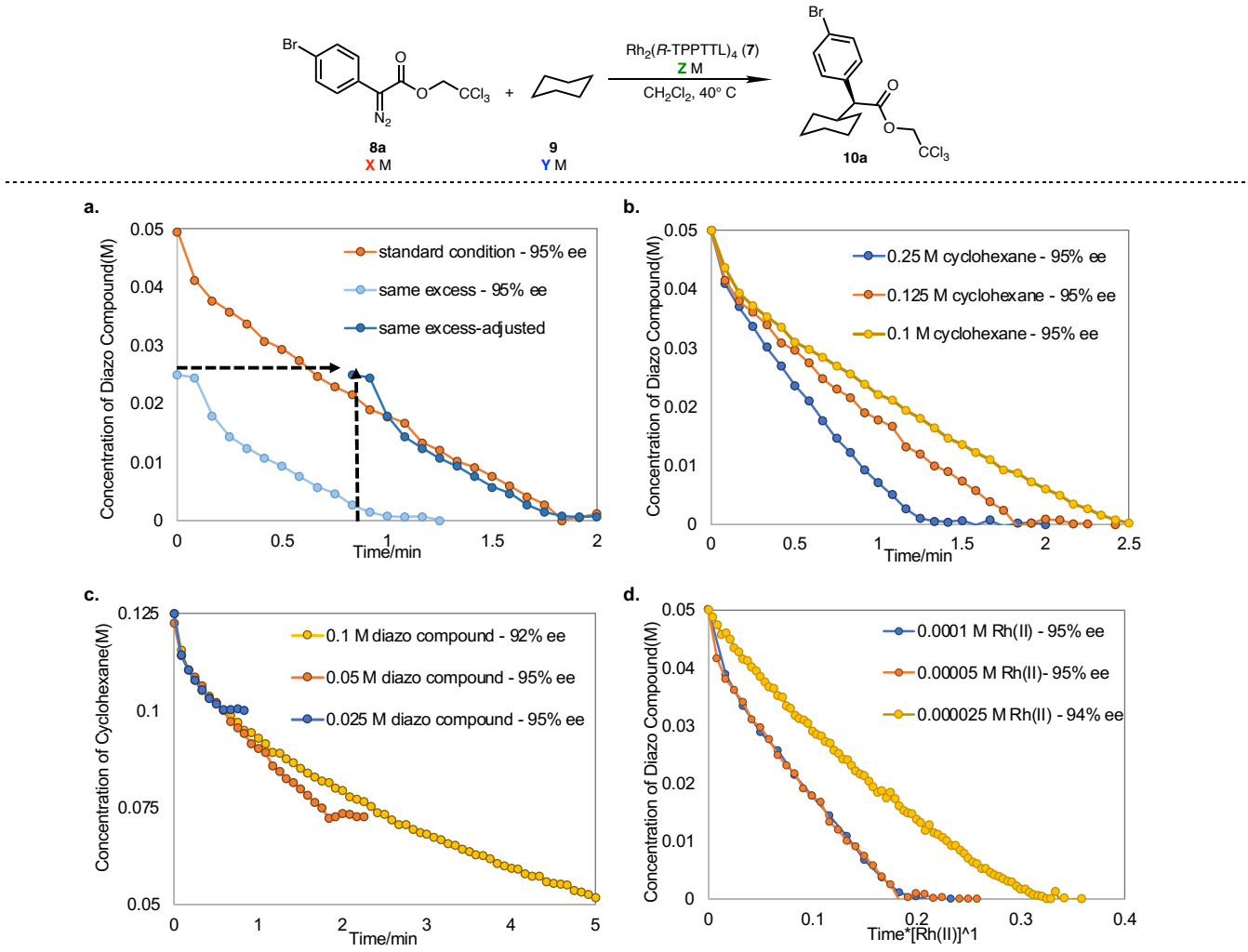
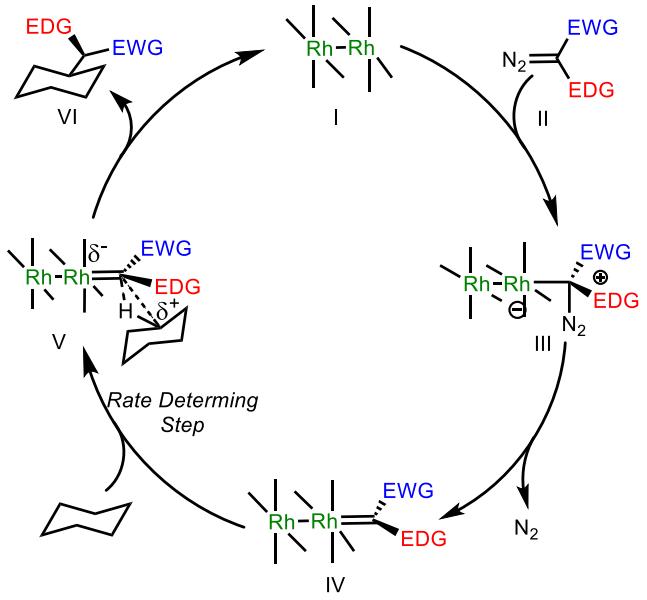


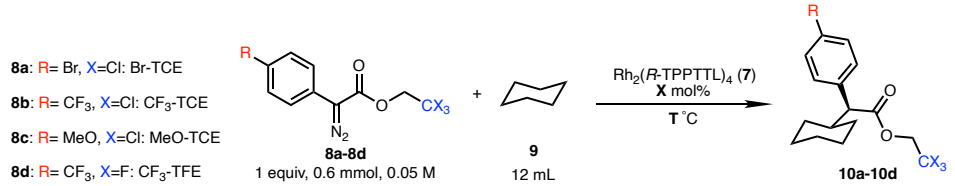
Figure 2. Kinetic profiles of RPKA studies for Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyzed C—H insertion of cyclohexane **a.** Same excess experiments at 0.1 mol % catalyst loading were carried out with [excess] = 0.075 M. Standard condition: $[diazo]_0$ = 0.05 M, $[cyclohexane]_0$ = 0.125 M; Same excess condition: $[diazo]_0$ = 0.025 M, $[cyclohexane]_0$ = 0.1 M. **b.** Different excess experiments determined a positive reaction order of cyclohexane ($[diazo]_0$ = 0.05 M, at 0.1 mol % catalyst loading). **c.** Different excess experiments determined a zero-order of diazo compound **8a** ($[cyclohexane]_0$ = 0.125 M, at 0.1 mol % catalyst loading). **d.** The variable time normalization analysis (VTNA) determined that the dirhodium(II) catalyst **7** was first order($[diazo]_0$ = 0.025 M, $[cyclohexane]_0$ = 0.1 M). (see the Supporting Information for details)

Scheme 3. Proposed catalytical cycle of the dirhodium(II) catalyzed C—H insertion of cyclohexane.



applied to obtain the dirhodium(II) catalyst order (Figure 2d).[68] The result indicated that, the Rh_2(*R*-TPPTTL)$_4$ (**7**) displayed first order kinetics at 0.2 and 0.1 mol % catalyst loading. When the catalyst loading was 0.05 mol %, catalyst deactivation was considerably more evident (see the Supporting Information for details). Thus, the kinetic studies revealed the reaction had a positive order in catalyst and cyclohexane but zero-order in the diazo compound. These results would be consistent with the catalytic cycle shown in Scheme 3, in which the carbene insertion to cyclohexane is the rate determining step. The zero-order influence of the diazo compound is because the reaction is operating under Michaelis-Menten conditions[69] with the diazo compound in vast excess to the catalyst, and hence, not influencing the overall rate of the reaction. On the basis of these kinetic studies, the further optimization of the reaction conditions focused on how to enhance the carbene insertion step because this rate-determining step was considered to be the weak link in the catalytic cycle.

The first adjustment was to increase the likelihood of an effective trap of the carbene by using cyclohexane as solvent. This caused a dramatic enhancement of the reaction, allowing the reactions to be routinely conducted with an order of magnitude lower catalysts loading. The reaction using cyclohexane as solvent at 40 °C with only 0.01 mol % catalyst loading generated the product in under 1 min in essentially quantitative yield and 98% ee (Figure 3a). Increasing the temperature to 60 °C further enhanced the reaction. With even less catalyst loading (0.005 mol %) the reaction took only 20 sec and gave the C—H functionalization product in 96% ee. However, the reaction with 0.0025 mol % catalyst loading did not go to completion at 60 °C and further increasing the temperature (80 °C) did not help the reaction (see the Supporting Information for details). In the case of the cyclopropanation reaction, electron rich donor groups on the diazo compound, such as *p*-methoxyphenyl enhanced the rate of the reaction because the rate-determining carbene formation step would be accelerated.[22] In the current study, the carbene insertion step is rate determining and so we reasoned that a more electrophilic carbene would be advantageous. In order to test this hypothesis, the aromatic ring of the aryldiazoacetate was modified. As shown in Figure 3b the reaction with *p*-(trifluoromethyl)phenyldiazoacetate **8b** was more effective compared to the reaction with *p*-bromophenyldiazoacetate **8a**. Now at the 0.0025 mol % catalyst loading the reaction did go to completion in 1 min, giving essentially a quantitative yield of **10a** in 95% ee. As a negative control, the *p*-methoxyphenyl derivative **8c** was also tested, and as predicted, virtually no reaction occurred. A slight further improvement was obtained with the trifluoroethyl ester derivative **8d**. It gave similar enantioselectivity to the trichloroethyl ester **8a** at 0.0025 mol % catalyst loading, and it was still competent at 0.001 mol % catalyst loading, giving essentially quantitative yield of the product but with slightly diminished enantioselectivity (91% ee). However, the reaction with even lower Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst loading (0.0005 mol %) only proceeded to about 5% completion(Figure 3c).



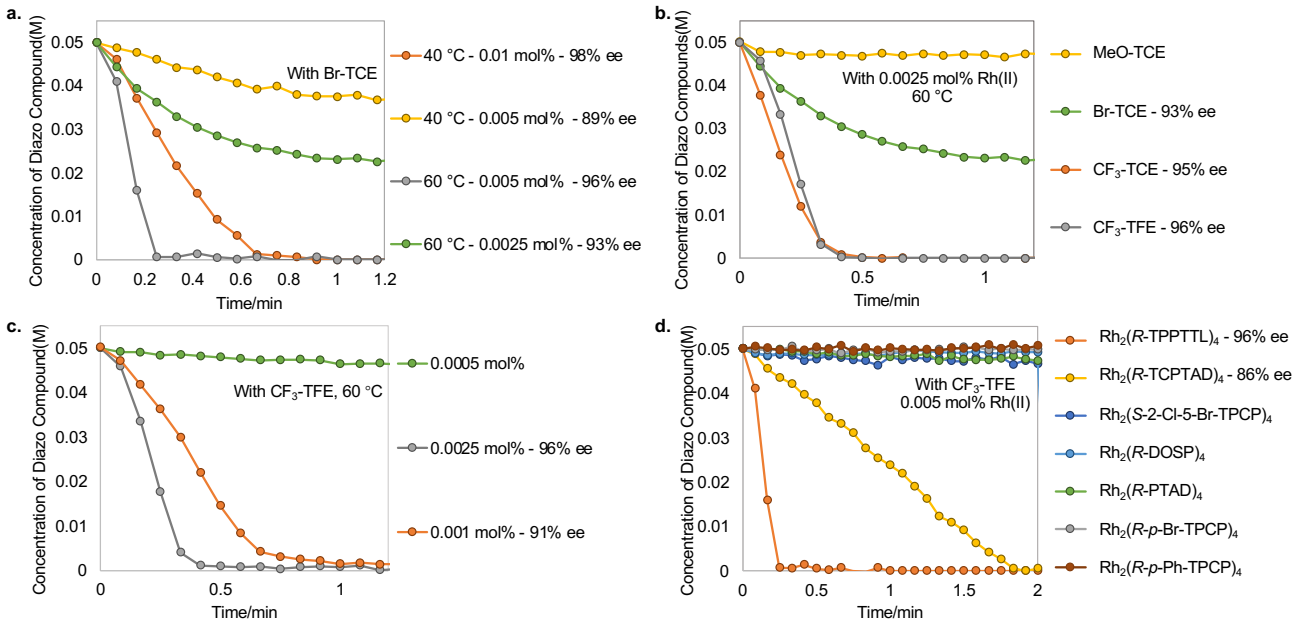


Figure 3. Kinetic Profiles of condition optimization of C—H insertion of cyclohexane. **a.** Applying neat condition with various temperature and Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst loading when R = Br, X = Cl. **b.** Effect of different aryldiazoacetates **8** structure on the reaction rate at 60 °C, 0.0025 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst loading **c.** Effect of Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst loading on the reaction rate when R = CF_3, X = F at 60 °C. **d.** Kinetic profiles of C—H insertion of cyclohexane catalyzed by various dirhodium(II) catalysts under neat condition, 0.005 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst loading, when R = CF_3, X = F at 60 °C.

Having completed the optimization studies, the seven catalysts were reevaluated (Figure 3d) to determine if the catalysts performed differently in these optimized conditions. The only catalysts that resulted in an effective transformation at the 0.005 mol % catalyst loading were the bowl-shaped catalysts, Rh_2(*R*-TCPTAD)$_4$ (**6**) and Rh_2(*R*-TPPTTL)$_4$ (**7**), with Rh_2(*R*-TPPTTL)$_4$ (**7**) being clearly superior, completing the reactions in under 20 sec in essentially quantitative yield and 96% ee.

The Davies group had recently developed a series of new C_4 symmetric catalysts derived from bulky *N*-phthalimido amino acids. As they are related to Rh_2(*R*-TPPTTL)$_4$ (**7**), one of these newer catalysts, Rh_2(*S-tetra*-Br-TPPTTL)$_4$ (**11**), was examined in this study, but the initial results were irreproducible. The first test reaction with Rh_2(*S-tetra*-Br-TPPTTL)$_4$ (**11**) with **8d** and cyclohexane was very promising, completing the reaction in 3 min with only 0.0005 mol % catalyst loading and forming the C—H functionalization product **10d** in essentially quantitative yield and 95% ee (Figure 4). However, the result could not be reproduced when a new batch of the aryldiazoacetate **8d** was used (repeated 7 times). After checking the purity of the starting material, it became clear that the original sample of diazo compound **8d** was contaminated with a small amount of *N,N′*-dicyclohexylcarbodiimide (DCC), a residue from an earlier esterification step (see the Supporting Information for details). The unexpected discovery that DCC had a major influence on maintaining the catalyst performance under high TON conditions, motivated us to study this phenomenon further.

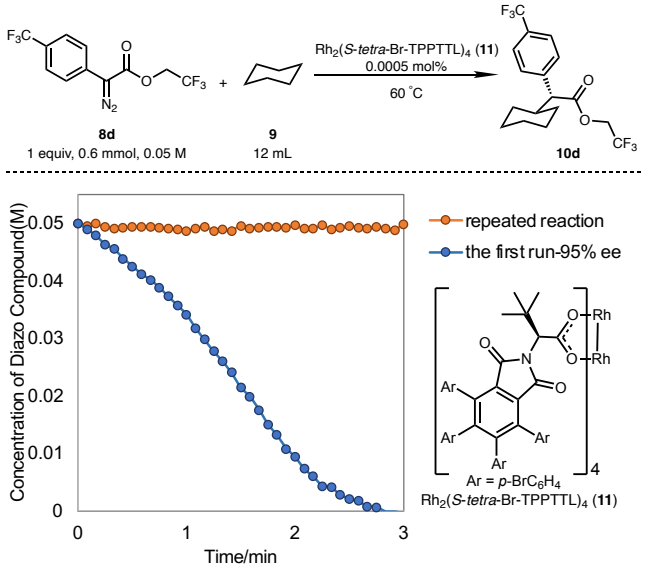


Figure 4. Rh_2(*S-tetra*-Br-TPPTTL)$_4$ (**11**) catalyzed unreproducible C—H insertion reaction. **blue:** Rh_2(*S-tetra*-Br-TPPTTL)$_4$ (**11**) catalyzed C—H insertion reaction succeed at 0.0005 mol % loading. **orange:** The repeated experiment showed the results were unreproducible.

The evaluation of the influence of carbodiimides was conducted on Rh_2(*R*-TPPTTL)$_4$ (**7**) to maintain consistency with the kinetic studies to date. As shown in Figure 5, the addition of 1 mol % of DCC had a similar beneficial effect on the Rh_2(*R*-TPPTTL)$_4$ (**7**)-catalyzed reactions. The reaction with 0.0005 mol % of Rh_2(*R*-TPPTTL)$_4$ (**7**) was complete in 2.5 min and gave the C—H functionalization product in essentially quantitative yield and 96% ee. When the reaction was conducted with 0.1 mol % of DCC, the rate

of the reaction was even faster but the enantioselectivity was lower (91% ee). The use of 2 mol % of DCC slowed the reaction rate, but the reaction was still complete in 5 min and the high asymmetric induction was retained. In contrast, the C—H functionalization without DCC additive showed very little reaction progress when 0.0005 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst was applied. A similar enhancement in performance was seen when *N,N′*-diisopropylcarbodiimide was used as an additive but *N,N′*-di-*tert*-butylcarbodiimide had no effect. The reaction at the 0.0005 mol % catalyst loading was also explored in the presence of other additives such as *N,N′*-dicyclohexylurea, tetramethylurea, pyridine, 2-chloropyridine, and pyrimidine but no conversion was observed (see the Supporting Information for details).

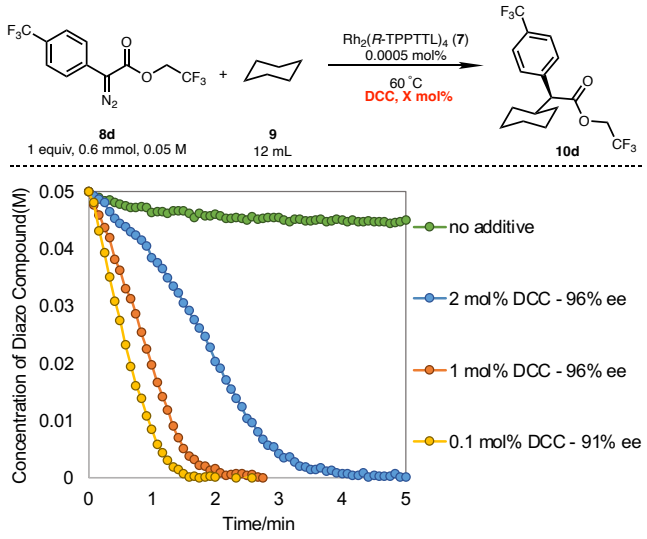


Figure 5. Effect of different concentration of DCC additive on the reaction kinetic profiles at 60 °C with 0.0005 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst loading.

Further experiments were conducted to gain additional information about the role of DCC in the reaction. As shown in Figure 6, the repeat reaction with 0.0005 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst showed little progress. When 1 mol % DCC was added to the reaction, no further conversion was observed, which suggests that the original batch of catalyst has been destroyed. However, when a second batch of 0.0005 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) was added, the reaction reinitiated and went to completion. These control experiments indicate that the catalyst loses its reactivity at a faster rate without protection from DCC and gave limited TONs. At this stage we suspect that the presence of DCC coordination prevents the rhodium-carbene intermediate from destroying the dirhodium catalyst under high TON conditions.

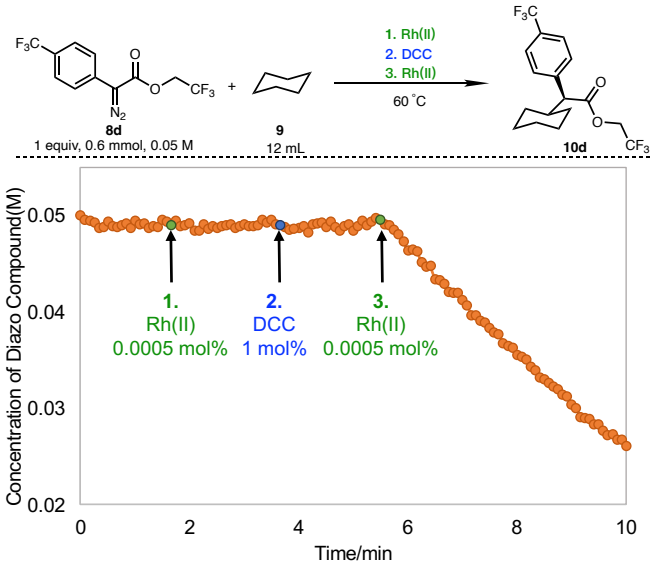


Figure 6. The reaction with 0.0005 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst loading gives no progress until 1 mol % DCC and another 0.0005 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst added.

The beneficial influence of DCC was a surprise because we would have expected it to poison the catalyst or react with the carbene to form an ylide.[34,70] To gain a deeper understanding of the role of DCC, DFT calculations were conducted. In these calculations we explored DCC (which promotes the reaction as shown above) and pyridine (a nucleophilic additive that poisons the catalyst) as additives (Figure 7). After extensive validation of the used density functionals and basis sets (see the Supporting Information), here, we discuss only the results acquired at the most practical [B3LYP-D3(BJ)]/BS1 level of theory, where BS1 = 6-31(d,p) split-valence basis sets for main group atoms and LANL2DZ basis sets and effective core potentials for Rh.[71-74] All presented calculations include solvent effects at the PCM level. The CH_2Cl_2 was selected as a solvent.[75]

As these calculations show, pyridine coordinates strongly to $Rh_2(OAc)_4$ catalyst (ΔG=-12.7 kcal/mol, not shown in Figure 7), which may hinder the diazo coordination to the Rh-centers, a necessary step for the formation of the catalytic active rhodium carbene intermediate.[76] Even if changes in experimental conditions, like high temperature, makes it possible to generate a rhodium carbene, the presence of pyridine may still prevent the reaction of carbene with alkanes because of the highly energetically favorable formation of a formal ylide (see Figure 7A, ΔG=-22.3 kcal/mol). As seen in Figure 7A, the pyridine's axial coordination to the $Rh_2(OAc)_4$(Carbene) is only slightly favorable (ΔG=-1.9 kcal/mol).

In contrast, DCC relatively weakly coordinates to the dirhodium catalyst and the dirhodium carbene intermediate: the calculated (DCC)–$Rh_2(OAc)_4$ (not shown in Figure 7) and (DCC)–$Rh_2(OAc)_4$(Carbene) bond energies are ΔG=-9.3 kcal/mol, and ΔG=-1.9 kcal/mol, respectively (see also Figure 7B). Interestingly, the coordination energy of DCC and pyridine to the open rhodium site of the carbene complex is the same (ΔG=-1.9 kcal/mol). However, the interaction of DCC with the carbene of the Rh-carbene complex is less energetically favorable (ΔG=-0.9 kcal/mol). Therefore, the presence of DCC in proximity to the rhodium carbene does not initiate ylide formation as pyridine does, to the difference in electronics of the *N*-donor centers of pyridine and DCC, and the presence of the sterically bulky cyclohexyl groups in DCC. Instead, the

performed calculations enabled us to hypothesize that DCC's weak coordination to the axial site of the dirhodium complex destabilizes the Rh-carbene bond (elongating it by 0.03Å), modifying the nature of the Rh-carbene bond, and changing the energy of the HOMO and LUMO (and other frontier orbitals. See the Supporting Information). One should emphasize that similar conclusions have been made by Darko and coworkers in their study of the dirhodium catalysts with tethered axial coordinating groups, thioethers in particular.[77-80] Therefore, we explain the observed rate acceleration upon reaction of the carbene and unactivated traps in our studies through axial coordination to the rhodium carbene.

The above presented discussion provides the impression that the presence of any axially coordinating additive in dirhodium tetracarboxylate catalyzed carbene insertion would accelerate the reaction. However, one should not forget that many of such nucleophiles, like pyridine, may also poison the catalyst, preventing formation of the catalytically active Rh-carbene, or react with the carbene leading to undesired side-products. One should emphasize that the unique ability of DCC to enhance reactivity of the rhodium carbene insertion into the C—H bond derive not only by the unique electronics of the N-donor centers, but also by the steric bulky nature of its cyclohexyl groups which prohibit ylide formation. More work will be done in future studies to further explore the role of DCC and other additives in greater detail.

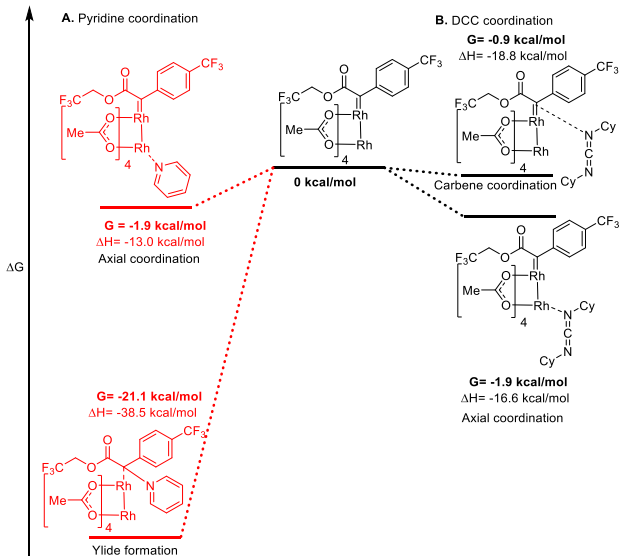
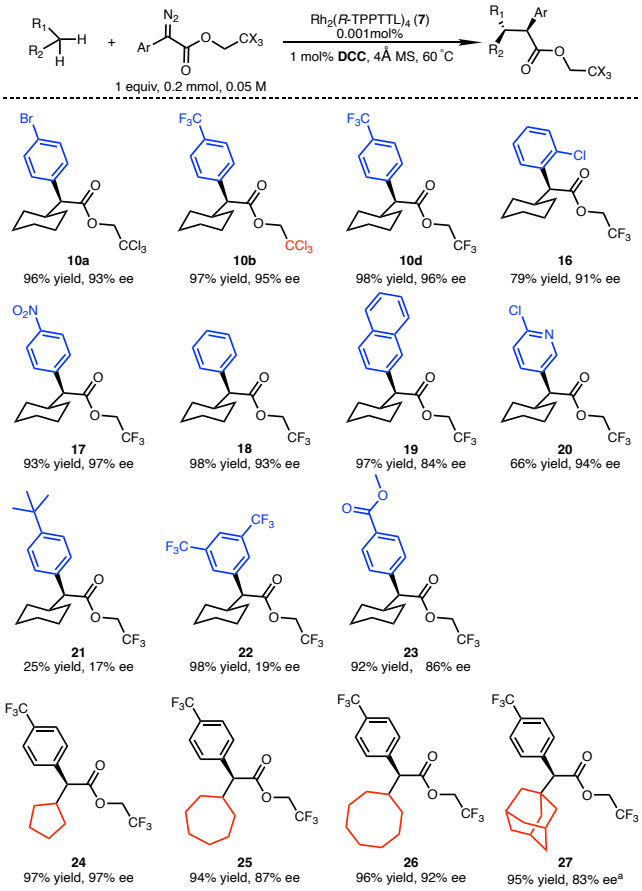


Figure 7. *In silico* comparison between pyridine(A) and DCC(B) coordination to a rhodium carbene.

Having established that the high TON reactions benefit from the addition of 1 mol % DCC, the scope of the reaction with a 0.001 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) catalyst loading was examined. As shown in Scheme 4, the C—H functionalization of cyclohexane could be carried out with a range of aryldiazoacetates to form the C—H

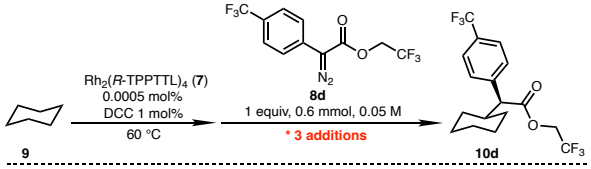
Scheme 4. Scopes of asymmetric C—H functionalization with 0.001 mol % Rh_2(*R*-TPPTTL)$_4$ (7) catalyst.



[a]The reaction was conducted with 10 equiv of adamantane in 4 mL $CHCl_3$.

functionalization products in very high yield and enantioselectivity. The notable exceptions are the *tert*-butyl derivative **21** and the 3,5-trifluoromethyl derivative, **22**, which results in low levels of enantioselectivity and in the case of **21**, low yield as well. Rh_2(*R*-TPPTTL)$_4$ (**7**) is known to adopt a bowl-shaped structure and there could be limitation to what fits well into the bowl. Both **21** and **22** are relatively bulky aryldiazoacetates and may not be accommodated well by the catalyst leading to the poor enantioselectivity. It is likely that the poor yield of **21** is due to the electron-donating nature of the *tert*-butyl group considering that groups like *p*-MeO lead to significantly slower and less competent reactions (Figure 3).

The turnover potential of Rh_2(*R*-TPPTTL)$_4$ (**7**) was further explored in a multiple substrate addition experiment. As showed in Figure 8, cyclohexane, 0.0005 mol % Rh_2(*R*-TPPTTL)$_4$ (**7**) and 1 mol % DCC were added first into the reaction flask. 1 equiv of diazo compound **8d** as a solid was subsequently added to the reaction in one potion and the reaction reached completion in 2.5 min. Two consecutive additional batches of diazo compound **8d** were then added. The reaction rate for the second batch appears very similar to the first batch, but the reaction is somewhat slower for the third batch. The enantioselectivity after each addition remained the same at 96% ee, and the overall catalyst TON was 580,000.



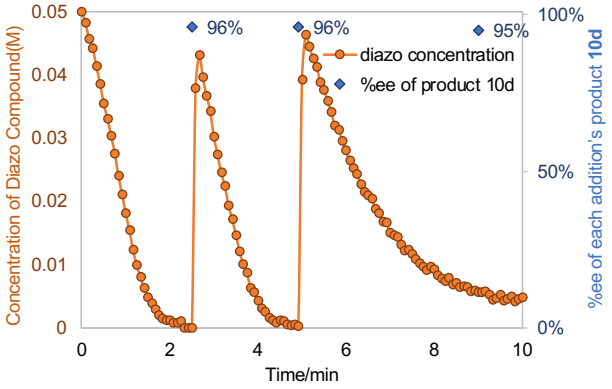


Figure 8. Kinetic profile of multiple-addition experiment of the C—H insertion reaction. Three consecutive additions of diazo compound **8d** were added into a solution of cyclohexane, DCC (1 mol %) and Rh_2(*R*-TPPTTL)$_4$ (**7**) (0.0005 mol %) at 60 °C.

Conclusion

A comprehensive kinetic investigation of dirhodium(II)-catalyzed C—H functionalization of cyclohexane provided a solid understanding of the reaction process. The rate law demonstrated carbene insertion was the rate determining step. Accordingly, rational optimization studies for higher catalyst TONs were conducted. Neat conditions, higher temperature, more electrophilic carbene intermediates were applied to help the dirhodium(II) catalysts effectively deliver the desired product under extremely low catalyst loading. Unexpectedly, DCC (1 mol %) as an additive was found to significantly promote the reaction. The coordination effect of DCC to the carbene intermediate was proposed to stabilize the carbene, blocking undesirable reactions that would deactivate the catalyst. Under the optimized conditions, Rh_2(*R*-TPPTTL)$_4$ (**7**) with 0.001 mol % loading was applied to a range of C—H functionalization reactions and showed great efficiency. By using a multiple diazo compound addition sequence, Rh_2(*R*-TPPTTL)$_4$ (**7**) can achieve C—H functionalization of cyclohexane with 580,000 TONs and in 96% ee. This study provided detailed insights into the C—H functionalization mechanism. The kinetic profiles demonstrated the great reactivity and selectivity of the C_4 dirhodium(II) catalyzed C—H functionalization. The DCC coordination has an unexpected capability to enhance the catalyst robustness under extremely high TONs. The above results will motivate further studies to extend the high TON C—H functionalization to a wider range of substrates and develop new methods to avoid the need of a vast excess of trapping agents. This would require further understanding of the role of additives and the design of even better dirhodium(II) bowl-shaped catalysts.

AUTHOR INFORMATION

Corresponding Author

Huw M. L. Davies – Department of Chemistry, Emory University, Atlanta, Georgia 30322, United States; orcid.org/0000-0001-6254-9398; Email: hmdavie@emory.edu

Authors

Bo Wei – Department of Chemistry, Emory University, Atlanta, Georgia 30322, United States; orcid.org/0000-0002-6376-6762

Jack C. Sharland – Department of Chemistry, Emory University, Atlanta, Georgia 30322, United States; orcid.org/0000-0003-0895-6659

Donna G. Blackmond – Department of Chemistry, Emory University, Atlanta, Georgia 30322, United States; orcid.org/0000-0001-9829-8375

Djamaladdin G. Musaev – Department of Chemistry, Emory University, Atlanta, Georgia 30322, United States; Cherry L. Emerson Center for Scientific Computation, Emory University, 1521 Dickey Drive, Atlanta, Georgia 30322, United States; orcid.org/0000-0003-1160-6131

Present Address:

[#]B. W.: Incyte Research Institute, Incyte Corporation, Wilmington, Delaware 19803, United States

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Complete experimental procedures, compound characterization, kinetic studies, and computational modeling details are described in the Supporting Information. (PDF)

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REFERENCES

(1) Zheng, C.; You, S.-L. Recent development of direct asymmetric functionalization of inert C—H bonds. *RSC Adv.* **2014,** *4*, 6173-6214.

(2) Brady, P. B.; Bhat, V. Recent applications of Rh- and Pd-catalyzed C(sp3)-H functionalization in natural product total synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 5179-5190.

(3) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J. Recent applications of C—H functionalization in complex natural product synthesis. *Chem. Soc. Rev.* **2018**, *47*, 8925-8967.

(4) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016**, *45*, 546-576.

(5) Gutekunst, W. R.; Baran, P. S. C—H functionalization logic in total synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976-1991.

(6) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New strategies for the transition-metal catalyzed synthesis of aliphatic amines. *Chem. Rev.* **2020**, *120*, 2613-2692.

(7) Achar, T. K.; Maiti, S.; Jana, S.; Maiti, D. Transition metal catalyzed enantioselective C(sp^2)—H bond functionalization. *ACS Catal.* **2020**, *10*, 13748-13793.

(8) Yoo, C. J.; Rackl, D.; Liu, W.; Hoyt, C. B.; Pimentel, B.; Lively, R. P.; Davies, H. M. L.; Jones, C. W. An immobilized-dirhodium hollow-fiber flow reactor for scalable and sustainable C—H functionalization in continuous flow. *Angew. Chem. Int. Ed.* **2018**, *57*, 10923-10927.

(9) Hatridge, T. A.; Liu, W.; Yoo, C. J.; Davies, H. M. L.; Jones, C. W. Optimized immobilization strategy for dirhodium(II) carboxylate catalysts for C—H functionalization and their implementation in a packed bed flow reactor. *Angew. Chem. Int. Ed.* **2020**, *59*, 19525-19531.

(10) Salazar, C. A.; Flesch, K. N.; Haines, B. E.; Zhou, P. S.; Musaev, D. G.; Stahl, S. S. Tailored quinones support high-turnover Pd catalysts for oxidative C—H arylation with O_2. *Science* **2020**, *370*, 1454-1460.

(11) Govaerts, S.; Nyuchev, A.; Noel, T. Pushing the boundaries of C—H bond functionalization chemistry using flow technology. *J. Flow Chem.* **2020**, *10*, 13-71.

(12) Gage, J. R.; Chen, F.; Dong, C.; Gonzalez, M. A.; Jiang, Y.; Luo, Y.; McLaws, M. D.; Tao, J. Semicontinuous process for GMP manufacture of a carbapenem intermediate via carbene insertion using an immobilized rhodium catalyst. *Org. Process Res. Dev.* **2020**, *24*, 2025-2033.

(13) 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. Process Res. Dev.* **2018**, *22*, 1393-1408.

(14) Anthes, R.; Bello, O.; Benoit, S.; Chen, C. K.; Corbett, E.; Corbett, R. M.; DelMonte, A. J.; Gingras, S.; Livingston, R.; Sausker, J.; Soumeillant, M. Kilogram Synthesis of a selective serotonin reuptake inhibitor. *Org. Process Res. Dev.* **2008**, *12*, 168-177.

(15) Gandeepan, P.; Muller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition metals for C—H activation. *Chem. Rev.* **2019**, *119*, 2192-2452.

(16) Zheng, Q. Z.; Jiao, N. Ag-catalyzed C—H/C—C bond functionalization. *Chem. Soc. Rev.* **2016**, *45*, 4590-4627.

(17) Liu, L.; Zhang, J. Gold-catalyzed transformations of *alpha*-diazocarbonyl compounds: Selectivity and diversity. *Chem. Soc. Rev.* **2016**, *45*, 506-516.

(18) Schafer, A. G.; Blakey, S. B. Ir-Catalyzed enantioselective group transfer reactions. *Chem. Soc. Rev.* **2015**, *44*, 5969-5980.

(19) Davies, H. M. L. Finding opportunities from surprises and failures. Development of rhodium-stabilized donor/acceptor Carbenes and Their Application to Catalyst-Controlled C—H Functionalization. *J. Org. Chem.* **2019**, *84*, 12722-12745.

(20) Davies, H. M. L.; Liao, K. Dirhodium tetracarboxylates as catalysts for selective intermolecular C—H functionalization. *Nat. Rev. Chem.* **2019**, *3*, 347-360.

(21) Caballero, A., Díaz-Requejo, M.M., Trofimenko, S., Belderraín, T.R. and Pérez, P.J. The Effect of Catalyst Loading in Copper-Catalyzed Cyclohexane Functionalization by Carbene Insertion. *Eur. J. Inorg. Chem.* **2007**, 2848-2852.

(22) Wei, B.; Sharland, J. C.; Lin, P.; Wilkerson-Hill, S. M.; Fullilove, F. A.; McKinnon, S.; Blackmond, D. G.; Davies, H. M. L. In situ kinetic studies of Rh(II)-catalyzed asymmetric cyclopropanation with low catalyst loadings. *ACS Catal.* **2020**, *10*, 1161-1170.

(23) Xu, X.; Deng, Y.; Yim, D. N.; Zavalij, P. Y.; Doyle, M. P. Enantioselective cis-beta-lactam synthesis by intramolecular C—H functionalization from enoldiazoacetamides and derivative donor-acceptor cyclopropenes. *Chem. Sci.* **2015**, *6*, 2196-2201.

(24) Miyazawa, T.; Minami, K.; Ito, M.; Anada, M.; Matsunaga, S.; Hashimoto, S. Enantio- and diastereoselective desymmetrization of *alpha*-alkyl- α -diazoesters by dirhodium(II)-catalyzed intramolecular C—H insertion. *Tetrahedron* **2016**, *72*, 3939-3947.

(25) Lamb, K. N.; Squitieri, R. A.; Chintala, S. R.; Kwong, A. J.; Balmond, E. I.; Soldi, C.; Dmitrenko, O.; Castineira Reis, M.; Chung, R.; Addison, J. B.; Fettinger, J. C.; Hein, J. E.; Tantillo, D. J.; Fox, J. M.; Shaw, J. T. Synthesis of benzodihydrofurans by asymmetric C—H insertion reactions of donor/donor rhodium carbenes. *Chem. Eur. J.* **2017**, *23*, 11843-11855.

(26) Marichev, K. O.; Doyle, M. P. Catalytic asymmetric cycloaddition reactions of enoldiazo compounds. *Org. Biomol. Chem.* **2019**, *17*, 4183-4195.

(27) Murai, T.; Lu, W.; Kuribayashi, T.; Morisaki, K.; Ueda, Y.; Hamada, S.; Kobayashi, Y.; Sasamori, T.; Tokitoh, N.; Kawabata, T.; Furuta, T. Conformational control in dirhodium(II) paddlewheel catalysts supported by chalcogen-bonding interactions for stereoselective intramolecular C—H insertion reactions. *ACS Catal.* **2020**, *11*, 568-578.

(28) Davies, H. M. L.; Walji, A. M. Rhodium(II)-stabilized carbenoids containing both donor and acceptor substituents. In *Modern Rhodium-Catalyzed Organic Reactions,* **2005**, 301-340.

(29) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. Effect of diazoalkane structure on the stereoselectivity of rhodium(II) (S)-N-(arylsulfonyl)prolinate catalyzed cyclopropanations. *Tetrahedron Lett.* **1996**, *37*, 4133-4136.

(30) Briones, J. F.; Davies, H. M. L. Gold(I)-catalyzed asymmetric cyclopropenation of internal alkynes. *J. Am. Chem. Soc.* **2012**, *134*, 11916-11919.

(31) Briones, J. F.; Davies, H. M. L. Rh_2(S-PTAD)$_4$-catalyzed asymmetric cyclopropenation of aryl alkynes. *Tetrahedron* **2011**, *67*, 4313-4317.

(32) Davies, H. M. L.; Hansen, T.; Rutberg, J.; Bruzinski, P. R. Rhodium(II) (S)-N-(arylsulfonyl)prolinate catalyzed asymmetric insertions of vinyl- and phenylcarbenoids into the Si—H bond. *Tetrahedron Lett.* **1997**, *38*, 1741-1744.

(33) 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.

(34) Wang, H.; Guptill, D. M.; Alvarez, A. V.; Musaev, D. G.; Davies, H. M. L. Rhodium-catalyzed enantioselective cyclopropanation of electron deficient alkenes. *Chem. Sci.* **2013**, *4*, 2844-2850.

(35) 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. Process Res. Dev.* **2020**, *24*, 67-84.

(36) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. The use of tosylhydrazone salts as a safe alternative for handling diazo compounds and their applications in organic synthesis. *Eur. J. Org. Chem.* **2005**, *2005*, 1479-1492.

(37) Greb, A.; Poh, J. S.; Greed, S.; Battilocchio, C.; Pasau, P.; Blakemore, D. C.; Ley, S. V. A versatile route to unstable diazo compounds via oxadiazolines and their use in aryl-alkyl cross-coupling reactions. *Angew. Chem. Int. Ed.* **2017**, *56*, 16602-16605.

(38) Sheeran, J. W.; Campbell, K.; Breen, C. P.; Hummel, G.; Huang, C.; Datta, A.; Boyer, S. H.; Hecker, S. J.; Bio, M. M.; Fang, Y.-Q.; Ford, D. D.; Russell, M. G. Scalable On-demand production of purified diazomethane suitable for sensitive catalytic reactions. *Org. Process Res. Dev.* **2020**, *25*, 522-528.

(39) Hock, K. J.; Koenigs, R. M. The generation of diazo compounds in continuous-flow. *Chem. Eur. J.* **2018**, *24*, 10571-10583.

(40) Sullivan, R. J.; Freure, G. P. R.; Newman, S. G. Overcoming scope limitations in cross-coupling of diazo nucleophiles by manipulating catalyst speciation and using flow diazo generation. *ACS Catal.* **2019**, *9*, 5623-5630.

(41) Levesque, E.; Laporte, S. T.; Charette, A. B. Continuous flow synthesis and purification of aryldiazomethanes through hydrazone fragmentation. *Angew. Chem. Int. Ed.* **2017**, *56*, 837-841.

(42) Poh, J. S.; Tran, D. N.; Battilocchio, C.; Hawkins, J. M.; Ley, S. V. A versatile room-temperature route to di- and trisubstituted allenes using flow-generated diazo compounds. *Angew. Chem. Int. Ed.* **2015**, *54*, 7920-7923.

(43) Tran, D. N.; Battilocchio, C.; Lou, S. B.; Hawkins, J. M.; Ley, S. V. Flow chemistry as a discovery tool to access sp(2)-sp(3) cross-coupling reactions via diazo compounds. *Chem. Sci.* **2015**, *6*, 1120-1125.

(44) Zhao, X.; Zhang, Y.; Wang, J. Recent developments in copper-catalyzed reactions of diazo compounds. *Chem. Commun.* **2012**, *48*, 10162-10173.

(45) Urbano, J.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J., Functionalization of primary carbon-hydrogen bonds of alkanes by carbene insertion with a silver-based catalyst. *Organometallics* **2005**, *24*, 1528-1532.

(46) Damiano, C.; Sonzini, P.; Gallo, E. Iron catalysts with N-ligands for carbene transfer of diazo reagents. *Chem. Soc. Rev.* **2020**, *49*, 4867-4905.

(47) Batista, V. F.; Pinto, D. C. G. A.; Silva, A. M. S. Iron: A worthy contender in metal carbene chemistry. *ACS Catal.* **2020**, *10*, 10096-10116.

(48) Planas, F.; Costantini, M.; Montesinos-Magraner, M.; Himo, F.; Mendoza, A. Combined experimental and computational study of

ruthenium N-hydroxyphthalimidoyl carbenes in alkene cyclopropanation reactions. *ACS Catal.* **2021**, *11*, 10950-10963.

(49) Poggiali, D.; Homberg, A.; Lathion, T.; Piguet, C.; Lacour, J. Kinetics of Rh(II)-catalyzed α-diazo-β-ketoester decomposition and application to the [3+6+3+6] synthesis of macrocycles on a large scale and at low catalyst loadings. *ACS Catal.* **2016**, *6*, 4877-4881.

(50) Liu, J.; Plog, A.; Groszewicz, P.; Zhao, L.; Xu, Y.; Breitzke, H.; Stark, A.; Hoffmann, R.; Gutmann, T.; Zhang, K.; Buntkowsky, G. Design of a heterogeneous catalyst based on cellulose nanocrystals for cyclopropanation: Synthesis and solid-state NMR characterization. *Chem. Eur. J.* **2015**, *21*, 12414-12420.

(51) Liu, J.; Fasel, C.; Braga-Groszewicz, P.; Rothermel, N.; Lilly Thankamony, A. S.; Sauer, G.; Xu, Y.; Gutmann, T.; Buntkowsky, G. Heterogeneous self-supported dirhodium(II) catalysts with high catalytic efficiency in cyclopropanation – a structural study. *Catal. Sci. Technol.* **2016**, *6*, 7830-7840.

(52) 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.

(53) Lee, M.; Ren, Z.; Musaev, D. G.; Davies, H. M. L. Rhodium-stabilized diarylcarbenes behaving as donor/acceptor carbenes. *ACS Catal.* **2020**, *10*, 6240-6247.

(54) Davies, H. M. L.; Venkataramani, C. Dirhodium tetraprolinate-catalyzed asymmetric cyclopropanations with high turnover numbers. *Org. Lett.* **2003**, *5*, 1403-1406.

(55) 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.

(56) Davies, H.M. and 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.

(57) Davies, H.M., Hansen, T. and Churchill, M.R. Catalytic asymmetric C– H activation of alkanes and tetrahydrofuran. *J. Am. Chem. Soc.* **2000**, *122*, 3063-3070.

(58) Hansen, J.; Li, B.; Dikarev, E.; Autschbach, J.; Davies, H. M. L. Combined experimental and computational studies of heterobimetallic Bi-Rh paddlewheel carboxylates as catalysts for metal carbenoid transformations. *J. Org. Chem.* **2009**, *74*, 6564-6571.

(59) 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.

(60) Qin, C.; Davies, H. M. L. 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.

(61) 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.

(62) 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.

(63) Reddy, R. P.; Davies, H. M. L. Dirhodium tetracarboxylates derived from adamantylglycine as chiral catalysts for enantioselective C—H aminations. *Org. Lett.* **2006**, *8*, 5013-5016.

(64) 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.

(65) 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.

(66) 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.

(67) Blackmond, D. G. Kinetic profiling of catalytic organic reactions as a mechanistic tool. *J. Am. Chem. Soc.* **2015**, *137*, 10852-10866.

(68) Nielsen, C. D.; Bures, J. Visual kinetic analysis. *Chem. Sci.* **2019**, *10*, 348-353.

(69) 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.

(70) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. Highly effective catalytic methods for ylide generation from diazo compounds. Mechanism of the rhodium- and copper-catalyzed reactions with allylic compounds. *J. Org. Chem.* **1981**, *46*, 5094-5102.

(71) Becke, A. D. A new mixing of Hartree–Fock and local density-functional theories. *J. Chem. Phys.* **1993**, *98*, 1372-1377.

(72) Hay, P. J.; Wadt, W. R. Ab initio effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals. *J. Chem. Phys.* **1985**, *82*, 299-310

(73) Wadt, W. R.; Hay, P. J. Ab initio effective core potentials for molecular calculations. Potentials for main group elements Na to Bi. *J. Chem. Phys.* **1985**, *82*, 284-298.

(74) Grimme, S.; Hansen, A.; Brandenburg, J. G.; Bannwarth, C. Dispersion-corrected mean-field electronic structure methods. *Chem. Rev.* **2016**, *116*, 5105-5154

(75) Cancès, E.; Mennucci, B.; Tomasi, J. A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics. J. *Chem. Phys.* **1997**, *107*, 3032-3041.

(76) Ye, Q.-S.; Li, X.-N.; Jin, Y.; Yu, J.; Chang, Q.-W.; Jiang, J.; Yan, C.-X.; Li, J.; Liu, W.-P. Synthesis, crystal structures and catalytic activity of tetrakis(acetato)dirhodium(II) complexes with axial picoline ligands. *Inorg. Chim. Acta.* **2015**, *434*, 113-120.

(77) Anderson, B. G.; Cressy, D.; Patel, J. J.; Harris, C. F.; Yap, G. P. A.; Berry, J. F.; Darko, A. Synthesis and catalytic properties of dirhodium paddlewheel complexes with tethered, axially coordinating thioether ligands. *Inorg. Chem.* **2019**, *58*, 1728-1732.

(78) Sheffield, W.; Abshire, A.; Darko, A. Effect of Tethered, Axial Thioether coordination on rhodium(II)-catalyzed silyl-hydrogen insertion. *Eur. J. Org. Chem.* **2019**, *2019*, 6347-6351.

(79) Cressy, D.; Zavala, C.; Abshire, A.; Sheffield, W.; Darko, A. Tuning Rh(II)-catalysed cyclopropanation with tethered thioether ligands. *Dalton Trans.* **2020**, *49*, 15779-15787.

(80) Wu, R., Lu, J., Cao, T., Ma, J., Chen, K. and Zhu, S. Enantioselective Rh (II)-Catalyzed Desymmetric Cycloisomerization of Diynes: Constructing Furan-Fused Dihydropiperidines with an Alkyne-Substituted Aza-Quaternary Stereocenter. *J. Am. Chem. Soc.* **2021**, *143*, 14916-14925.

SYNOPSIS TOC