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Rhodium-catalyzed enantioselective cyclopropanation of electron-deficient alkenes†

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The rhodium-catalyzed reaction of electron-deficient alkenes with substituted aryldiazoacetates and vinyldiazoacetates results in highly stereoselective cyclopropanations. With adamantylglycine derived catalyst Rh_2(*S*-TCPTAD)$_4$, high asymmetric induction (up to 98% ee) can be obtained with a range of substrates. Computational studies suggest that the reaction is facilitated by weak interaction between the carbenoid and the substrate carbonyl but subsequently proceeds *via* different pathways depending on the nature of the carbonyl. Acrylates and acrylamides result in the formation of cyclopropanation products while the use of unsaturated aldehydes and ketones results in the formation of epoxides.

Introduction

Cyclopropanes are a common subunit of natural products and bioactive compounds.[1] Additionally, they serve as building blocks in complex molecule synthesis, as the opening of the highly strained three-membered ring can lead to a number of synthetically useful intermediates.[2,3] One of the most effective strategies for the synthesis of cyclopropanes is the metal-catalyzed reaction of diazo compounds with alkenes.[4] The development of a wide variety of chiral catalysts has enabled cyclopropanation reactions to be highly enantioselective. Among them, chiral complexes of rhodium (*e.g.* Fig. 1) and copper are the most widely used catalysts, but their application in cyclopropanation reactions has been largely confined to electron-rich and electron-neutral alkenes.[4,5] The metal-catalyzed cyclopropanation of electron-deficient alkenes is considered to be much more challenging due to the electrophilic nature of metal-bound carbenes.[4,6,7] One approach has been to decompose diazo compounds in the presence of a dialkyl sulfide, which generates a sulfur-ylide capable of cyclopropanating electron-deficient olefins.[8] Recently, effective direct cyclopropanations of electron-deficient alkenes have been achieved using cobalt porphyrin, palladium acetate, and ruthenium salen as catalysts.[9] These reactions, however, are likely to be mechanistically distinct from the rhodium- and copper-catalyzed reactions. For example, the cobalt porphyrin-catalyzed reactions have been shown to proceed *via* radical intermediates[9a] and the palladium-catalyzed reaction has been proposed to be a [2 + 2] cycloaddition followed by a reductive elimination.[9d] On the other hand, cyclopropanation reactions of electron-deficient alkenes using rhodium-catalyzed decomposition of diazo compounds are scarce.[10] In this paper, we describe the first highly enantioselective cyclopropanation of acrylate derivatives with rhodium carbene intermediates derived from aryl and vinyldiazoacetates. The scope of this reaction is described and a computational analysis is presented to explain why highly electrophilic carbenoids are able to cyclopropanate electron-deficient alkenes.

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† Electronic supplementary information (ESI) available: (1) Experimental data for the reported reactions and a CIF file for the X-ray crystallographic data for **7l**, and **15**, (2) completed ref. 20, (3) Fig. SI-3 including calculated structures, important geometry parameters (in Å) and relative energies of the epoxidation of (a) acrylate, (b) acrylamide and methyl vinyl ketone, and (4) Cartesian coordinates all reported reactants, intermediates, transition states and products of the reaction of vinyldiazoacetate with methyl acrylate (R = OMe), *N*,*N*-dimethylacrylamide (R = NMe_2), and methyl vinyl ketone (R = Me). CCDC 908862 and 908861. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc50425e

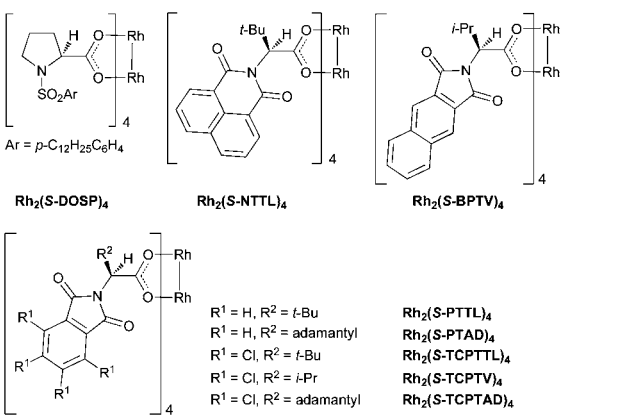


Fig. 1 Chiral rhodium catalysts.

Results and discussion

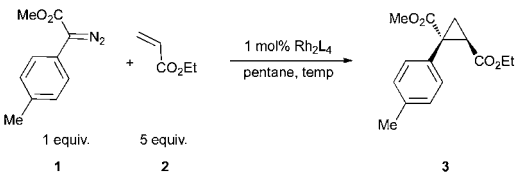
Previously, we had observed that additives such as methyl benzoate can have a beneficial effect on rhodium-catalyzed carbenoid transformations.[11] During studies to further explore the influence of ester additives, we happened to find that ethyl acrylate can react with rhodium carbene intermediates to form cyclopropane products. Further study showed that the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl *p*-tolyldiazoacetate **1** with ethyl acrylate **2** produced cyclopropane **3** in 59% yield with >97 : 3 dr and 77% ee (Table 1, entry 1). Intrigued by this result, we conducted a systematic study with a series of chiral dirhodium catalysts (Fig. 1). As shown in Table 1, the optimum catalyst was found to be Rh_2(*S*-TCPTAD)$_4$. Though Rh_2(PTAD)$_4$ (ref. 5*e–g*) has been used in cyclopropanation reactions, catalyst Rh_2(TCPTAD)$_4$, which we had previously developed for asymmetric C–H amination reactions,[12] has not been applied to carbenoid reactions. With this catalyst, in refluxing pentane, the cyclopropane **3** was formed in 71% yield as a single diastereomer and with 84% ee (entry 8). Generally, the dirhodium(II) tetrachlorophthalimido-protected amino acid catalysts provided markedly improved levels of enantio-induction over the phthalimido-protected analogs (see entries 2 *vs.* 8 and 3 *vs.* 6). For example, in the presence of Rh_2(*S*-PTTL)$_4$, the cyclopropane **3** was generated with only 27% ee. However, using Rh_2(*S*-TCPTTL)$_4$ the level of enantioselectivity increased to 74% ee.[13] The same trend was observed with the bulkier adamantylglycine-derived catalysts, where we obtained 35% ee with Rh_2(*S*-PTAD)$_4$, and 84% ee with Rh_2(*S*-TCPTAD)$_4$. In the presence of Rh_2(*S*-TCPTAD)$_4$, the amount of acrylate can be reduced to 1 equiv. with a slight drop of the reaction yield and enantioselectivity (entry 10).

The effect of diazo ester size on the enantioselectivity of the Rh_2(*S*-TCPTAD)$_4$-catalyzed reaction of ethyl acrylate was examined for phenyldiazoacetates **4a–d** (Table 2). The highest level of enantioselectivity was observed with *tert*-butyl phenyldiazoacetate **4d** (entry 4). Under these conditions, the cyclopropane **5d** was formed in 78% yield and with 91% ee.

The scope of this reaction was investigated with respect to both the aryldiazoacetates and alkenes (Table 3). Carbenoids with electron rich aryl groups performed well giving the cyclopropane products **7a–d** in good yields (61–91%) and with excellent levels of enantioselectivity (88–94% ee). Both naphthyl and halo-substituted aryl groups were tolerated giving the cyclopropanes **7e** and **7f** in excellent yields and levels of enantioselectivity. The reaction of aryldiazoacetate **6h**, containing a strong electron-withdrawing group, resulted in decreased yield of the cyclopropane product **7h** (22%) relative to the more electron-rich aryl groups, as well as decreased dr (92 : 8), though the product was isolated in 91% ee. A variety of acrylate esters, including the bulky *t*-Bu and Ph esters gave cyclopropanation products in good yields (74–91%) and with excellent levels of enantioselectivity (90–96% ee). Of particular note is that acrylamides are also efficiently cyclopropanated to give the products (**7n** and **7o**) with excellent levels of enantioselectivity (92–94% ee), albeit in slightly lower yields. Addition of a substituent at the α position of the acrylate caused a decrease in both diastereo- and enantioselectivity giving cyclopropane **7p** in 55% yield with 84 : 16 dr and 77% ee. The absolute configuration of product **7l** was determined by X-ray crystallography[14] and the structures of other products were assigned by analogy.[15]

Vinyldiazoacetates were also tested in the Rh_2(*S*-TCPTAD)$_4$-catalyzed cyclopropanation of acrylates (Table 4). The levels of enantioselectivity with vinyldiazoacetates were generally higher (91–98% ee) than those obtained with aryldiazoacetates. The aryl groups of styryldiazoacetates could be substituted with both electron rich and electron poor substituents, cyclopropanes being formed in excellent yields (75–89%) and with excellent levels of enantioselectivity (95–98% ee). A slight drop of

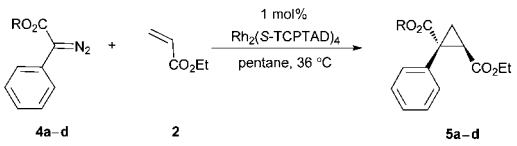
Table 1 Optimization of the chiral catalyst



Entry	Catalyst	Temperature (°C)	dr[a]	Yield[b] (%)	ee[c] (%)
1	Rh_2(*S*-DOSP)$_4$	36	>97 : 3	59	77
2	Rh_2(*S*-PTAD)$_4$	36	>97 : 3	70	35
3	Rh_2(*S*-PPTL)$_4$	36	>97 : 3	68	27
4	Rh_2(*S*-NTTL)$_4$	36	>97 : 3	69	24
5	Rh_2(*S*-BPTV)$_4$	36	>97 : 3	65	5
6	Rh_2(*S*-TCPTTL)$_4$	36	>97 : 3	71	74
7	Rh_2(*S*-TCPTV)$_4$	36	>97 : 3	62	65
8	**Rh_2(*S*-TCPTAD)$_4$**	**36**	**>97 : 3**	**71**	**84**
9	Rh_2(*S*-TCPTAD)$_4$	36	>97 : 3	65[d]	79
10	Rh_2(*S*-TCPTAD)$_4$	36	>97 : 3	60[e]	73
11	Rh_2(*S*-TCPTAD)$_4$	23	>97 : 3	22	82
12[f]	Rh_2(*S*-TCPTAD)$_4$	40	92 : 8	81	71

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 2.0 equiv. alkene used. [e] 1.0 equiv. alkene used. [f] Dichloromethane was used as solvent.

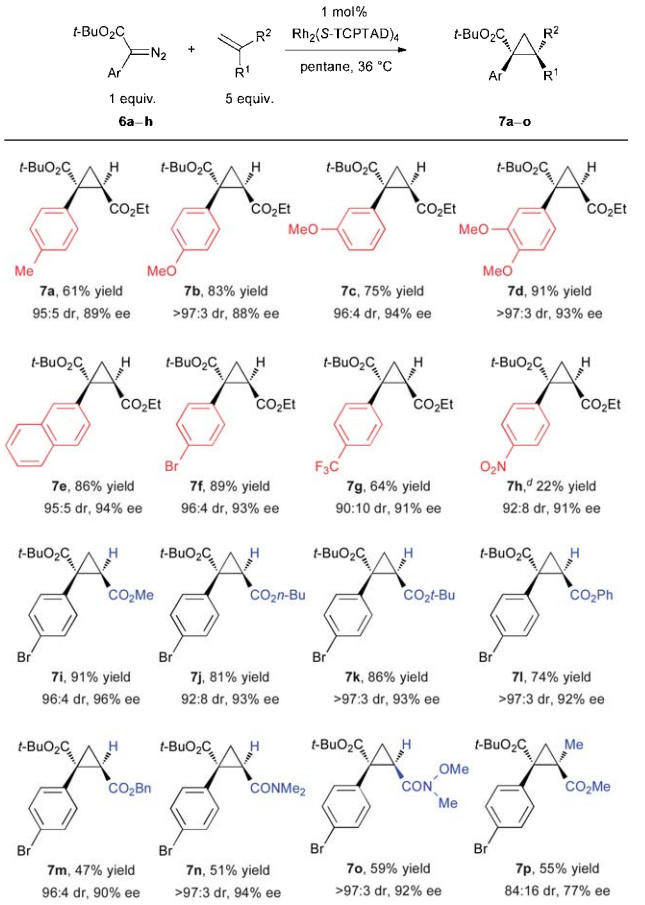
Table 2 Effect of ester group



Entry	R	Product	dr[a]	yield[b] (%)	ee[c] (%)
1	Me	**5a**	97 : 3	83	86
2	Et	**5b**	>97 : 3	78	85
3	*n*-Bu	**5c**	>97 : 3	84	81
4	*t*-Bu	**5d**	>97 : 3	78	91

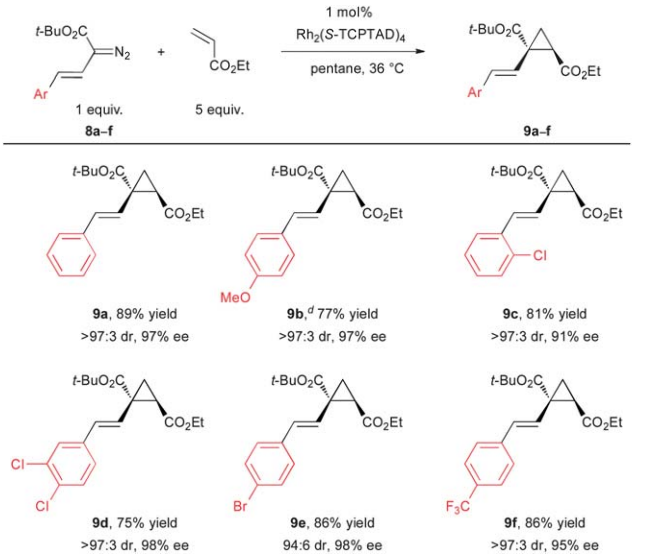
[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] Determined by chiral HPLC.

Table 3 Scope of aryldiazoacetates and alkenes[a,b,c]



[a] dr was determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] Yields are isolated yield. [c] ee was determined by chiral HPLC. [d] The diazo compound was dissolved in pentane–dichloromethane (v/v = 10/1).

Table 4 Scope of vinyldiazoacetates[a,b,c]



[a] dr was determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] Yields are isolated yield. [c] ee was determined by chiral HPLC. [d] Reaction was conducted with 0.2 mol% Rh_2(*S*-TCPTAD)$_4$.

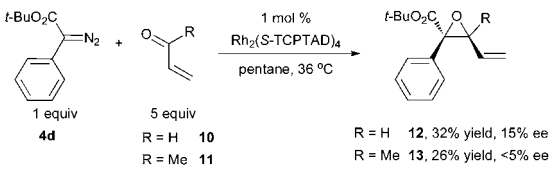
enantioselectivity (91% ee) was observed with *o*-substituted styryldiazoacetate **8c**. In the case of methoxy-substituted diazo **8b**, due to difficulties separating the cyclopropane product **9b** from the rhodium catalyst, the reaction was conducted at 0.2 mol% catalyst loading. Although we have not conducted a detailed study of the lower limit of catalyst needed for these reactions, this experiment shows that at least several hundred catalyst turnovers are feasible in these reactions.

A different outcome was observed when the reaction was extended to α,β-unsaturated aldehydes and ketones (Scheme 1). The reactions of acrolein **10** and methyl vinyl ketone **11** with diazo compound **4d** provided epoxides **12** and **13**, respectively. Under these conditions, the formation of cyclopropanes was not observed. As observed in previous studies of rhodium-catalyzed epoxidation with diazo compounds,[16] there was almost no asymmetric induction for the Rh_2(*S*-TCPTAD)$_4$-catalyzed epoxidation in either case.

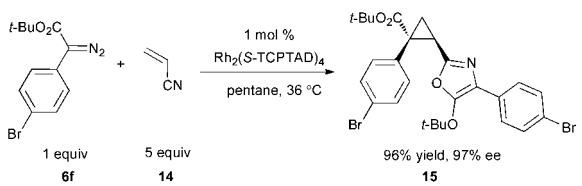
Under the standard reaction conditions, the reaction of acrylonitrile **14** with diazo compound **6f** generated an interesting oxazole-substituted cyclopropane **15** in 96% yield and with 97% ee (Scheme 2). The formation of **15** is postulated to begin by reaction of **6f** with the nitrile group of **14** to form an electron-rich oxazole-substituted alkene, which then preferentially reacts with another molecule of **6f** to give the observed cyclopropane product. The absolute configuration of cyclopropane **15** was assigned by X-ray crystallography.[14]

Computational analysis

As rhodium bound carbenes are considered to be highly electrophilic, it was intriguing that the Rh_2(TCPTAD)$_4$ catalyzed cyclopropanation of electron-deficient olefins worked so efficiently. Palladium- and ruthenium-catalyzed cyclopropanations have been proposed to occur *via* a [2 + 2] cycloaddition, and cobalt-catalyzed cyclopropanations have been demonstrated to



Scheme 1 Reactions of unsaturated aldehydes and ketones.

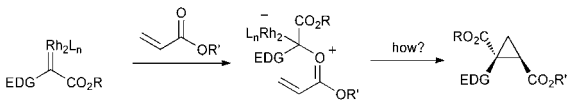


Scheme 2 Reaction of acrylonitrile.

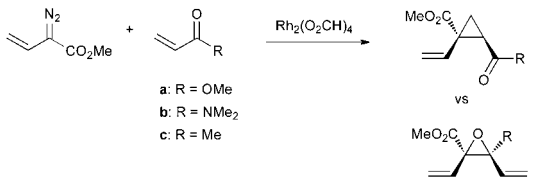
proceed through a radical addition–substitution pathway.[9,17] Cyclopropanation by rhodium carbene intermediates, however, has been proposed to be a direct cyclopropanation of the alkene in a concerted asynchronous manner.[18] For the rhodium-catalyzed reactions of acrylate derivatives, the highly electron-deficient rhodium carbene intermediates would be expected to react preferentially with the more nucleophilic oxygen of an unsaturated carbonyl system to form a rhodium bound carbonyl ylide (Scheme 3).[19] Therefore, it became of interest to determine how and why a system that would be expected to form a carbonyl ylide actually resulted in a highly enantioselective cyclopropanation.

For this reason we conducted detailed DFT studies[20] on three model systems: (a) vinyldiazoacetate with methyl acrylate, (b) vinyldiazoacetate with *N*,*N*-dimethylacrylamide and (c) vinyldiazoacetate with methyl vinyl ketone (Scheme 4).

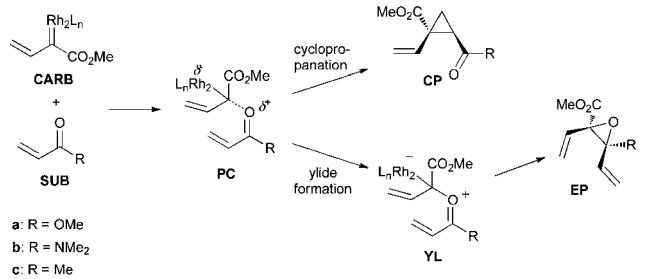
For each of these systems we investigated the mechanisms of cyclopropane (CP) formation, ylide (YL) formation and epoxide (EP) formation of these reactions by using dirhodium tetraformate as a model catalyst (Scheme 5). The studies showed that the reaction of carbenoid **CARB** with **SUB** is initiated by weak interaction between the carbenoid and the substrate carbonyl (resulting in a weakly-bound pre-reaction complex **PC**, which is more stable for the *N*,*N*-dimethylacrylamide than methyl acrylate or methyl vinyl ketone), but proceeds *via* different pathways from this point depending on the nature of the unsaturated carbonyl compound.



Scheme 3 Mechanistic question associated with the cyclopropanation.



Scheme 4 Model reactions for computational analysis.



Scheme 5 Schematic presentation of the cyclopropanation, ylide formation and epoxidation pathways of the reaction of rhodium carbene intermediates with (a) methyl acrylate, (b) *N*,*N*-dimethylacrylamide and (c) methyl vinyl ketone.

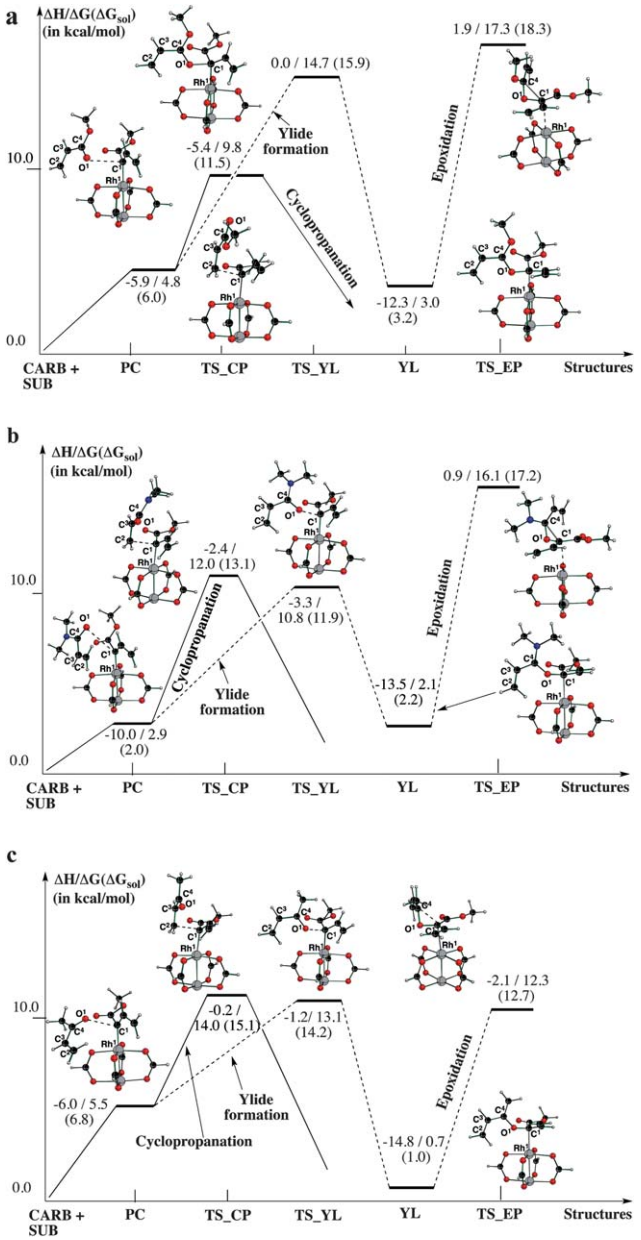


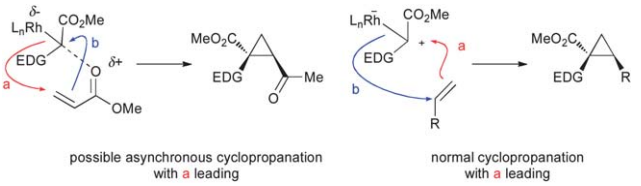
Fig. 2 Potential energy surfaces (scaled to Δ*G* values) of the cyclopropanation, ylide formation and epoxidation pathways for the reaction of (a) vinyldiazoacetate and methyl acrylate, (b) vinyldiazoacetate with *N*,*N*-dimethylacrylamide, (c) vinyldiazoacetate with methyl vinyl ketone.

Potential energy surfaces (PES) of the cyclopropanation, ylide formation and epoxidation pathways for the reaction of vinyldiazoacetate with (a) methyl acrylate, (b) *N*,*N*-dimethylacrylamide and (c) methyl vinyl ketone are shown in Fig. 2a–c, respectively.[21] For the methyl acrylate case, complex **PC** or reactants, *i.e.* **CARB** + **SUB**, does not proceed to form the ylide because the kinetically and thermodynamically preferred pathway involves direct reaction of the alkene to form the cyclopropane. As seen in Fig. 2a, the calculated energy barrier for the cyclopropane formation is $\Delta H = 5.4/\Delta G = 4.9$ ($\Delta G_{sol} = 4.4$) kcal mol^{-1} smaller than that for the ylide formation. Epoxidation requires even higher energy barrier and is not feasible.

Computation predicts a significantly different mechanism for the reaction of *N*,*N*-dimethylacrylamide compared to that of methyl acrylate. As seen in Fig. 2b, *replacement of the OMe group in methyl acrylate by the NMe_2 amido group facilitates ylide formation* by stabilizing the ylide complex (as well as the pre-reaction complex) and making the energy barrier required for the ylide formation 0.9/1.2 (1.2) kcal mol^{-1} smaller than that for the cyclopropanation. Indeed, as seen in Fig. 2a and b, the calculated energy of the reaction **CARB** + **SUB** → **YL** is −12.3/3.0 (3.2) and −13.5/2.1 (2.2) kcal mol^{-1} for methyl acrylate and *N*,*N*-dimethylacrylamide, respectively. This trend in the energy is consistent with the calculated C^1–O^1 bond distances, 1.479 and 1.456 Å, in the corresponding ylide complexes. In the case of *N*,*N*-dimethylacrylamide, the slight endothermicity of the ylide formation and the larger energy barrier required for the forward reaction (*i.e.* epoxide formation), make the ylide formation a reversible process. Since the energy barrier for cyclopropanation is only a few kcal mol^{-1} more than ylide formation, and since both transformations start from the same reactants (pre-reaction complex), the reaction of vinyldiazoacetate with *N*,*N*-dimethylacrylamide ultimately undergoes cyclopropanation.

In the case of the methyl vinyl ketone, the pre-reaction and ylide complexes are generated in an analogous fashion to *N*,*N*-dimethylacrylamide (Fig. 2c). However, in this case the *ylide undergoes a favorable cyclization to the epoxide*. As seen in Fig. 2c, the calculated energy barrier for epoxide formation from the ylide complex is 0.9/0.8 (1.5) kcal mol^{-1} smaller than the barrier for the reverse reaction. The ylide formation is therefore not reversible as it was for *N*,*N*-dimethylacrylamide. *Thus, donor/acceptor carbenoids do not undergo cyclopropanation of methyl vinyl ketone mainly due to facile ylide formation followed by epoxidation*. One should mention that the calculated C^1–O^1 bond distance, 1.421 Å, in the ylide complex of methyl vinyl ketone is 0.058 and 0.035 Å shorter than those found in ylide complexes of methyl acrylate and *N*,*N*-dimethylacrylamide, respectively.

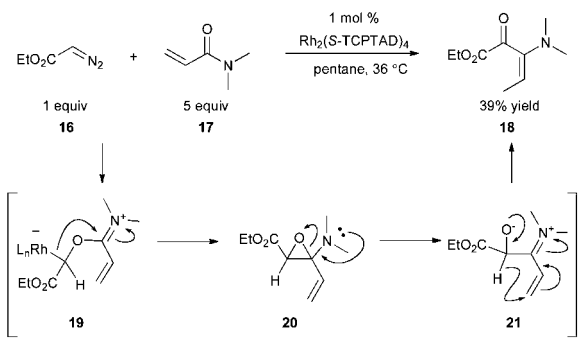
As shown in Fig. 2, as well as data presented in the ESI,† the cyclopropanation transition state **TS_CP** for all studied substrates reveals a concerted-asynchronous process. Natural bond analyses show that the interaction of the carbonyl of methyl acrylate with the carbenoid (*i.e.* formation of pre-reaction complex **PC**) makes the alkene even more electron deficient. The pre-reaction complex would therefore have to make the carbenoid more susceptible for reacting with electron deficient alkenes. Indeed, the calculated natural charges of the C^1 atom are +0.04 and +0.06 e in **CARB** and **PC**, respectively, which would suggest that metal back-bonding is less significant in the pre-reaction complex compared to the free carbene. Since the cyclopropanation of methyl acrylate by vinyldiazoacetate is found to be a facile process, this suggests that the $\{Rh_2\}$–C^1 sigma bond may be involved in a concerted non-synchronous cyclopropanation by nucleophilic attack on the alkene (Scheme 6). This is opposite to the normal cyclopropanation of electron rich alkenes, in which it is believed the reaction is initiated by an electrophilic attack by the carbenoid on the alkene.[18] More extensive computational studies will be necessary to understand fully this unconventional reactivity of Rh–carbene intermediates.



Scheme 6 Possible alternative cyclopropanation mechanism.

We have previously demonstrated that donor/acceptor carbenoids are much more stabilized than the conventional acceptor carbenoid derived from ethyl diazoacetate.[18] The increased donating capability of donor/acceptor carbenes creates a stronger carbene–transition metal interaction, thus strengthening the rhodium carbene bond. Since, upon ylide formation, the nascent carbonyl-carbene bond competes with the Rh–carbene bond, we may expect more favorable ylide formation for the conventional acceptor carbenoids than for donor/acceptor carbenoids. Consequently, we might also expect complementary reactivity in these systems. To demonstrate this, we studied the reaction of ethyl diazoacetate **16** with *N*,*N*-dimethylacrylamide **17** (Scheme 7). In this case, no cyclopropanation was observed, and instead ketoester **18** was unexpectedly formed in 39% isolated yield. The most likely mechanism for the formation of **18** is initial formation of the ylide **19** and then cyclization to the epoxide **20**. Amine induced ring opening of the epoxide would generate a new ylide **21**, which then undergoes a hydride transfer to form **18**. Such a mechanism would suggest that the initial ylide is continuing through to product and the lack of cyclopropane formation is suggestive that the initial ylide formation step is not reversible, unlike the reaction of vinyldiazoacetate with *N*,*N*-dimethylacrylamide. Together with the computational results, this experiment provides strong evidence for the presence of ylide intermediates in these cyclopropanation reactions.

Thus, the above-presented computational studies illustrate the subtle difference in the reactions of donor/acceptor carbenoids with methyl acrylate, *N*,*N*-dimethylacrylamide, and methyl vinyl ketone. In each case a weakly bound pre-reaction complex is formed in which the carbonyl interacts with the carbenoid (which is thermodynamically stable relative to reactants only at the Δ*H* level). However, beyond **PC** formation, the reactions diverge (either from this weakly bound pre-reaction complex or from the reactants themselves). For the acrylate case,



Scheme 7 Reaction of ethyl diazoacetate with *N*,*N*-dimethylacrylamide.

cyclopropanation is preferred over ylide formation. With the acrylamide, the ylide is preferentially formed but the formation of this intermediate is reversible, and so, a cyclopropane is ultimately formed. However, with methyl vinyl ketone, ylide formation is not reversible due to the rapid epoxide formation.

The computational studies not only help to rationalize the rhodium-catalyzed reactions of donor/acceptor carbenoids with electron-deficient alkenes, but also give novel insights into carbenoid chemistry in general. Methyl benzoate has been shown to have a dramatic influence on the turnover capacity of dirhodium tetracarboxylates.[11] From these computational studies, it would be a reasonable hypothesis that this is due to interaction between the carbenoid and the ester carbonyl, which could protect the rhodium carbene intermediates from self-destruction. Donor/acceptor carbenoids are capable of a vast array of intermolecular C–H functionalizations by means of C–H insertion and this can be conducted in the presence of a range of heteroatoms and carbonyl functionality.[6] The observation that amide ylide formation is reversible is suggestive that the range of functional group tolerance may be due to the reversible nature of carbenoid/ylide formation. A further interesting possibility is that the ester carbonyl interaction may present the opportunity to use esters as directing groups in carbenoid C–H functionalization.

Conclusion

In summary, these studies demonstrate that aryldiazoacetates and vinyldiazoacetates are capable of undergoing highly enantioselective cyclopropanations with electron-deficient alkenes. The reaction involves initial formation of a weakly bound pre-reaction complex between the carbene intermediates and the carbonyl group of the substrate, but the subsequent reaction is dependent on the nature of the carbonyl group. Acrylates and acrylamides result in the formation of cyclopropanation products while the use of unsaturated aldehydes and ketones results in the formation of epoxides. The optimal catalyst for high asymmetric induction is shown to be Rh_2(*S*-TCPTAD)$_4$, a catalyst which had been used previously only for C–H amination. Further studies are in progress to more thoroughly understand the role of the pre-reaction complex with carbonyls and to determine whether this interaction can be used to enhance the selectivity of other types of rhodium-catalyzed carbenoid reactions.

Acknowledgements

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