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Rhodium-Catalyzed Cyclopropanation of Alkenes with Dimethyl Diazomalonate

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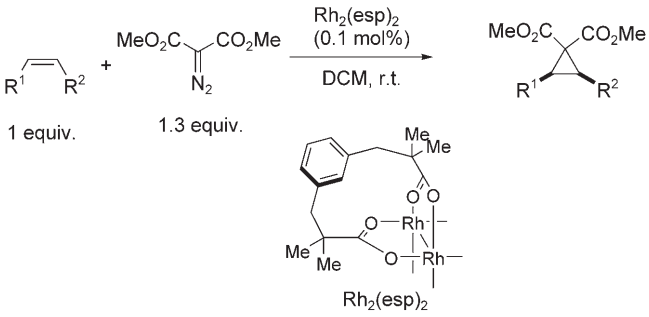
Abstract: The outstanding ability of dirhodium α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate [Rh_2(esp)$_2$; esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate] to catalyze the cyclopropanation of a wide range of alkenes with malonate-derived carbenoids under mild reaction conditions is reported in this communication. The experimental protocol is remarkably simple, uses readily accessible and stable dimethyl diazomalonate with very low catalyst loading. More importantly, the alkene is employed as a limiting reagent.

Keywords: alkenes; carbenoids; C–C bond formation; cyclopropanes; diazo compounds; rhodium

The cyclopropyl moiety is found in a variety of molecules of biological and pharmaceutical interest. The reactivity of cyclopropane derivatives also makes them versatile intermediates in the preparation of a range of natural and synthetic products. Cyclopropanation of olefins arguably represents the most straightforward and convergent approach to synthesize this important class of compounds. In this regard, catalysts that allow for the addition of various carbenoids to alkenes, including several chiral catalysts that enable enantioselective versions of these reactions, have been developed.[1] Despite significant achievements in the field,[2] the metal-catalyzed cyclopropanation reaction of alkenes with malonate-derived carbenoids remains a significant synthetic challenge. Although iodonium-ylides derived from malonates have been used successfully in cyclopropanation of olefins,[3] these processes result in the formation of one equivalent of iodobenzene as a by-product, and typically require high temperatures. Furthermore, the olefin is used in large excess, or even as a solvent, constituting an important limitation for the use of the methodology for more elaborate alkenes. The relative stability of diazomalonates has limited their use as carbenoid precursors,[1,4] thus, the scope of the reaction of alkenes with diazomalonates has yet to be reported.

While developing the synthesis of a drug candidate, we desired access to an intermediate 1,1-cyclopropyl diester. We initiated our work toward identifying a suitable catalytic system for the cyclopropanation of olefins with diazomalonates to overcome the limitations described above. Herein we present the first report of a simple catalytic system for the use of diazomalonates as carbenoid precursors, which is effective in the preparation of a wide range of malonate-derived cyclopropanes under remarkably mild conditions. There are additional advantages to this system which include: minimization of organic by-products; slow addition of the carbenoid is not required; the olefin is used as the limiting reagent; and very low catalyst loading is employed (Scheme 1) [esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate].[5]

We initially explored the reactivity of various commercially available achiral rhodium catalysts[6] with a challenging susbtrate, pentafluorostyrene. This elec-



Scheme 1.

tron-poor alkene should more readily distinguish the performance of the catalysts.

It was anticipated further that an effective catalytic system for this substrate would be suitable for a wide range of alkenes.[7] Our observations from the initial screen are summarized in Table 1.[8]

Both $Rh_2(esp)_2$ and $Rh_2(TPA)_4$ [TPA = triphenylacetate] led to higher conversions than other rhodium catalysts typically used for related transformations.[9] $Rh_2(esp)_2$ was chosen for further development on the basis of its significantly lower cost.[10]

We then examined the scope of the $Rh_2(esp)_2$-catalyzed cyclopropanation on an array of diversely substituted styrene-type derivatives. We were pleased to find that the optimized conditions (Scheme 1) could be applied successfully to a range of substrates of diverse steric and electronic attributes (Table 2).

The $Rh_2(esp)_2$ catalytic system we developed for styrenyl alkenes was also effectively applied without major modifications to a range of other olefins, including non-conjugated aliphatic alkenes (Table 3).[11]

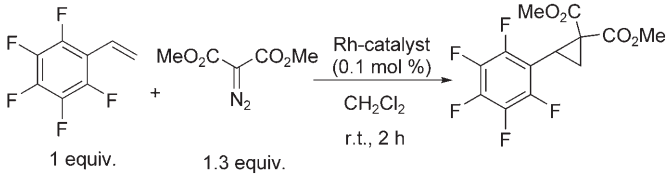
Terminal olefins (entries 1–5) afforded the corresponding cyclopropanes in good to excellent yields without any evidence of C-H insertion at the allylic or benzylic positions. Increasing the steric bulk in the allylic position of the terminal olefin did not negatively impact the outcome of the cyclopropanation reaction (entry 6). Cyclic alkenes reacted smoothly rendering cyclopropanation adducts in good yields (entries 7–9). Interestingly, the outcome of the reaction of β-methylstyrenes depended on the stereochemistry of the alkene. While the *cis*-isomer afforded exclusively the *cis*-cyclopropane product in high yield (entry 10), the *trans*-isomer led to a complex mixture of products from which the *trans*-cyclopropane was isolated in 28% yield (entry 11).[12] *cis*- and *trans*-internal olefins also showed markedly different reactivity (entries 12–14). Whereas the *cis*-isomers of 1,3-dichloro-1-propene (entry 12) and 4-octene (entry 13) produced predominantly the cyclopropanation adducts, albeit in lower yield than terminal olefins, *trans*-4-octene generated a mixture of products with the cyclopropane present only as a minor component (entry 14).[13]

The nitrile group is known to react with carbenoids in a [3+2] fashion, leading to the formation of oxazoles. Although reaction of substrates containing nitrile functionality did lead to competing oxazole side-products with the $Rh_2(esp)_2$ catalytic system,[14] these cyclopropanations are higher yielding than those previously described (Scheme 2).[15]

Another remarkable feature of the $Rh_2(esp)_2$ catalyst was observed upon reaction of 1-phenylpropyne. The corresponding cyclopropene was obtained as the major product (Scheme 3). To the best of our knowledge this is the first report of a rhodium-catalyzed cyclopropenation of an internal alkyne with a diazomalonate.[16,17]

In conclusion, we have demonstrated that cyclopropanation of an unprecedented array of alkenes with diazomalonates can be accomplished through the use of the $Rh_2(esp)_2$ catalyst. The experimental protocol is remarkably simple, uses readily accessible and stable diazomalonate, and, in sharp contrast with previously reported systems, uses only stoichiometric amounts of alkene substrates. We also believe that

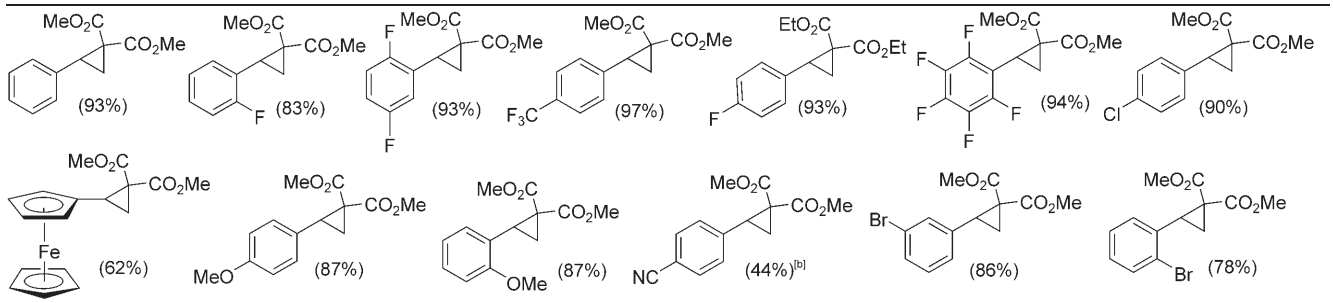
Table 1. Catalyst effect.



Entry	Catalyst	Yield [%][a]
1	$Rh_2(TFA)_4$	11
2	$Rh_2(OAc)_4$	22
3	$Rh_2(TPA)_4$	89
4	$Rh_2(esp)_2$	97

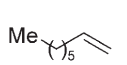
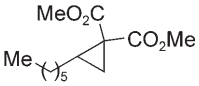
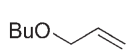
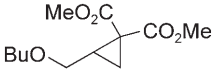
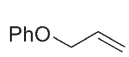
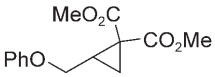
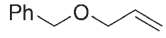
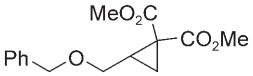
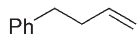
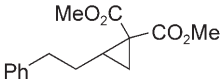
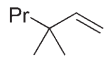
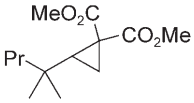
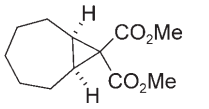
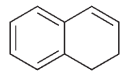
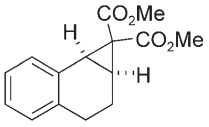
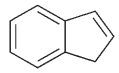
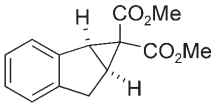
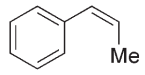
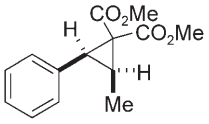
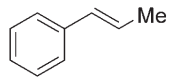
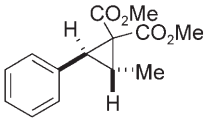
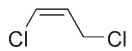
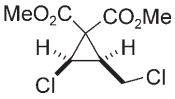
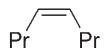
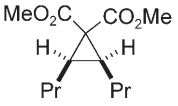
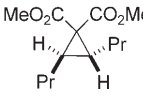
[a] Calibrated GC yield *vs.* an internal standard.

Table 2. Products from the $Rh_2(esp)_2$-catalyzed cyclopropanation of styrene-type alkenes.[a]



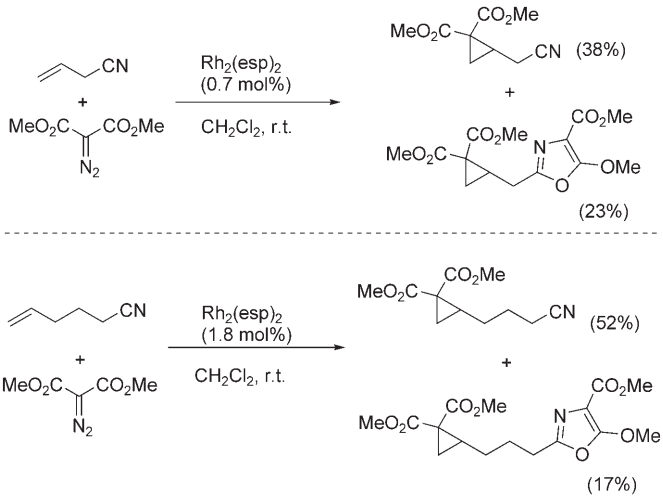
[a] Calibrated GC yield *vs.* an internal standard.[a] Isolated yields.
[b] 0.8 mol% of catalyst was used.

Table 3. $Rh_2(esp)_2$-catalyzed cyclopropanation of alkenes.

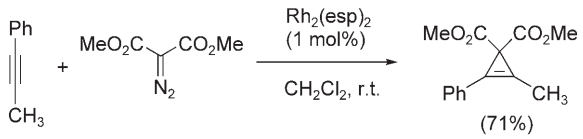
Entry	Alkene	Product	Yield [%][a]
1			91
2			87
3			72
4			83
5			95
6			91
7			72
8			82[b]
9			89
10			87[b]
11			28[c]
12			43
13			41
14			<5

[a] Isolated yields.
[b] 14 h; 0.5 mol% of catalyst was used.
[c] 1 mol% of catalyst was used.

the availability of chiral rhodium catalysts structurally related to the $Rh_2(esp)_2$ may lead to new and exciting opportunities for asymmetric cyclopropanation reactions.[18]



Scheme 2.



Scheme 3.

Experimental Section

General Protocol (Table 2, Table 3 and Scheme 2)

In the air, $Rh_2(esp)_2$ (2 mg, 2.5 5 μmol, 0.1 mol%) was placed in a 100-mL three-necked flask equipped with a stir bar. The flask was capped and purged with nitrogen (three vacuum/refilling cycles). CH_2Cl_2 (2.5 mL) was added by syringe leading to a pale green homogenous solution. The alkene (2.5 mmol, 1 equiv.) was added and the reaction mixture was then cooled in a water/ice bath. After 5 min, a solution of diazodimethylmalonate (514 mg, 3.25 mmol, 1.3 equiv.) in CH_2Cl_2 (2.5 mL) was added by syringe. The resulting solution was kept in the bath for 10 min and then stirred at room temperature. After 2 h, the reaction mixture was treated with a saturated solution of aqueous thiourea (50 mL) and diluted with 25 mL of CH_2Cl_2. The mixture was stirred for 30 min and then transferred into a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was then purified by column chromatography on silica gel with the solvent systems indicated (see Supporting Information for details).

Supporting Information

Complete experimental procedures and full characterization data for all the compounds reported are given in the Supporting Information.

Acknowledgements

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Sherbine and Dr. David R. Kronenthal for helpful discussions. Dr. Charles Pathirana and Dr. Baoning Su are acknowledged for 2D-NMR experiments.

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[2] Remarkable progress towards the development of related asymmetric reactions using malonate-derived carbenoids has been reported recently by different research groups. A detailed discussion of these results is beyond the scope of this communication. For leading references, see: a) A. Ghanem, F. Lacrampe, V. Schuring, *Helv. Chim. Acta* **2005**, *88*, 216–239; b) P. Müller, A. Ghanem, *Chirality* **2005**, *17*, 44–50; c) P. Müller, A. Ghanem, *Org. Lett.* **2004**, *6*, 4347–4350; d) P. Müller, Y. Allenbach, E. Robert, *Tetahedron: Asymmetry* **2003**, *14*, 779–785; e) M. P. Doyle, W. Hu, *Arkivoc* **2003**, 15–22; f) M. P. Doyle, S. B. Davies, W. Hu, *Org. Lett.* **2000**, *2*, 1145–1147; g) H. M. L. Davies, *Eur. J. Org. Chem.* **1999**, 2459–2469; h) H. M. L. Davies, P. R. Bruzinski, M. J. Fall, *Tetrahedron Lett.* **1996**, *37*, 4133–4136.

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[5] The $Rh_2(esp)_2$ catalyst was designed by Du Bois and co-workers and was originally used for C–H activation reactions; for leading references, see: a) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562–568; b) M. Kim, J. V. Mulcahy, C. G. Espino, J. Du Bois, *Org. Lett.* **2006**, *8*, 1073–1076; c) C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379; for a recent example of the use of this catalyst for the cyclopropanation of alkenes with nitromethane-derived iodonium ylides, see: d) H. T. Bonge, T. Hansen, *Synlett* **2007**, 55–59.

[6] Under these conditions several Cu-based catalysts gave no cyclopropanation products.

[7] We have observed similar catalytic reactivity for other substrates.

[8] Experimental results were very similar in different chlorinated solvents (CH_2Cl_2, 1,2-dichloroethane or PhCl). Toluene and benzonitrile led to lower yields of cyclopropane. No reaction was observed in DMF.

[9] $Rh_2(TPA)_4$ has been recently shown to be an efficient catalyst for N–C bond formation through C–H activation processes, showing similar reactivity to $Rh_2(esp)_2$, see: H. Lebel, K. Huard, *Org. Lett.* **2007**, *9*, 639–642.

[10] 1 mmol of $Rh_2(esp)_2$ = US $198 (Aldrich catalog, based on the price for a 500 mg sample). 1 mmol of $Rh_2(TPA)_4$ = US $1886 (TCI catalog, based on the price for a 100 mg sample).

[11] A trisubstituted olefin, (2-methylprop-1-enyl)benzene, produced only trace amounts of cyclopropane. Allyl phenyl sulfide and allyl phenyl sulfone yielded essentially no cyclopropane (<10%). Electron-rich olefins such as 2,3-dihydropyran and benzofuran produced mixtures of products under these conditions. Attempts to isolate the cyclopropanes by column chromatography on silica gel were unsuccessful. No attempts to optimize the reaction for each particular substrate have been carried out.

[12] The relative stereochemistry of the cyclopropanes has been unequivocally established by 2D NMR experiments.

[13] a) No attempts to optimize each individual substrate have been conducted. In the reaction of *trans*-4-octene, the C–H insertion product at the allylic position was isolated as the major product. See Supporting Information for more details. A similar observation has been previously reported: see ref.[3b]; b) During the preparation of this manuscript Davies and co-workers reported a systematic study on the balance between allylic C–H insertion and cyclopropanation: H. M. L. Davies, M. G. Coleman, D. L. Ventura, *Org. Lett.* **2007**, *9*, 4971–4974.

[14] In the cyclopropanation reaction of 4-cyanostyrene (Table 2) the corresponding oxazole side-product was isolated in 24% yield. See Supporting Information.

[15] $Rh_2(OAc)_4$-catalyzed cyclopropanation of buten-3-nitrile under similar experimental conditions has been reported to proceed in 21% yield, see: R. D. Connel, M. Tebbe, A. R. Gangloff, P. Helquist, B. Åkermark, *Tetrahedron* **1993**, *49*, 5445–5449. Our system gave a 61% combined yield of cyclopropanated adducts.

[16] a) There is scant data available for the metal-catalyzed cyclopropenation of internal alkynes using malonate-derived carbenoids; for an isolated copper-catalyzed example, see: R. Breslow, R. Winter, M. Battiste, *J. Org. Chem.* **1959**, *24*, 415–416; b) the cyclopropene was obtained in 52% yield when 0.1 mol% of $Rh_2(esp)_2$ was used; c) the reaction was performed using 25 mmol of olefin. 4.3 grams of cyclopropene were isolated.

[17] For leading references on rhodium-catalyzed cyclopropenation of terminal alkynes: a) Y. Lou, T. P. Remarchuk, E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 14223–14230; b) Y. Lou, M. Horikawa, R. A. Kloster, N. A. Hawryluk, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 8916–8918; c) H. M. L. Davies; G. L. Lee, *Org. Lett.* **2004**, *6*, 1233–1236; for some selected applications of cyclopropenes, see: d) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117–3179; e) M. Rubin, M. Rubina, V. Gevorgyan, *Synthesis* **2006**, 1221–1245; f) F. Zhang, J. M. Fox, *Org. Lett.* **2006**, *8*, 2965–2968; g) S. Chuprakov, M. Rubin, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 3714–3715.

[18] Du Bois and co-workers have already reported chiral rhodium catalysts structurally related to $Rh_2(esp)_2$. See reference ref.[5a]

