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Transition Metal-Catalyzed Cyclopropanation of Alkenes in Water: Catalyst Efficiency and in Situ Generation of the Diazo Reagent

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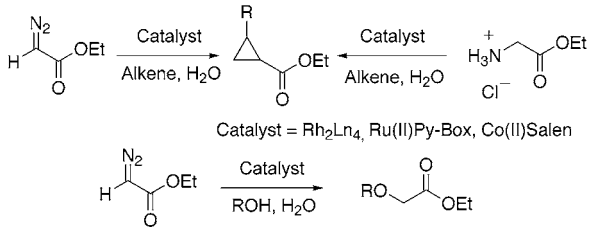
ABSTRACT



A cyclopropanation reaction involving ethyl diazoacetate and olefins proceeds with surprisingly high efficiency in aqueous media using Rh(II) carboxylates. Nishiyama's Ru(II) Py-box and Katsuki's Co(II) Salen complexes that allow for highly enantioselective cyclopropanations in organic solvents can also be applied to aqueous cyclopropanations with similar results. In situ generation of ethyl diazoacetate and cyclopropanation also proceeds efficiently. A chemoselective O–H insertion is also possible in water when hydrophobic catalysts and alcohols are used.

Over the years, our group has been interested in the preparation of cyclopropanes because of their applications in pharmaceuticals,[1] presence in naturally occurring products,[2] and use as synthetic intermediates.[3] Transition-metal-catalyzed cyclopropanation of alkenes with diazo compounds represents a direct approach for their preparation. Although diazo reagents have been sporadically used for the large-scale preparation of cyclopropanes, the potential hazardous nature of the sulfonyl azide precursor[4] has led researchers to find alternative methods for their manipulation.[5]

In an attempt to improve the viability of large-scale diazo-mediated cyclopropanation reactions and make their use more appealing, we turned to water as a reaction solvent due to its low toxicity and inertness.[6] Furthermore, we reasoned that the use of *hydrophobic* catalysts and non-water-soluble

(1) Biochemistry of the Cyclopropyl Group. In *The Chemistry of the Cyclopropyl Group*, Patai, S., Rappoport, Z., Eds.; Wiley: New York 1987; Chapter 16, p 959.

(2) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, p 1045.

(3) Carbocyclic Three- and Four-Membered Ring Compounds. In *Methods of Organic Chemistry (Houben-Weyl)*; de Meijere, A., Ed.; Verlag: New York, 1997; Vols. E17a,b. Small Ring Compounds in Organic Synthesis VI. In *Topics in Current Chemistry*; de Meijere, A., Ed.; Springer: New York, 2000; Vol. 207.

(4) For an excellent discussion on the hazardous properties of sulfonyl azide reagents, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998.

(5) (a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433. (c) For a recent report on the large scale generation of ethyl diazoacetate and its direct use in solution without isolation in neat form see: Scott, J. W. *Organ. Chem. (Abstr. Am. Chem. Soc. Div. Org. Chem.)* **2002**, *186*, 223.

(6) For recent reviews on carrying stereoselective transformations in water, see: (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Grieco, P. A., Ed. *Organic Synthesis in Water*; Blackie Academic & Professional: London, 1998. (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (d) Cornils, B.; Hermann, W. A. *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*; Wiley-VCH: New York, 1998.

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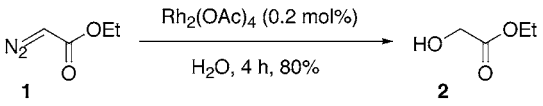
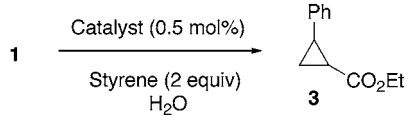
alkenes would lead to small alkene/catalyst beads or micelles in water. Since ethyl diazoacetate is quite soluble in water, its concentration in the alkene beads would be relatively low and the reagent should slowly diffuse into the alkene layer as the reaction proceeds. This approach contrasts those using catalysts bearing hydrophilic ligands to increase their water solubilities.[7] Generally, cyclopropanations employing diazo substrates are performed under anhydrous conditions due to the competing O−H insertion reaction affording **2** (eq 1).[8] However, we believed that this pathway should be suppressed if the reaction occurs in the alkene/catalyst beads.



1 2 (1)

To illustrate this idea, a number of Rh(II) carboxylate catalysts were screened for their cyclopropanation activity with styrene in water (see Table 1).

Table 1. Effect of Rh(II) Catalyst on Cyclopropanation Yields[a]



3

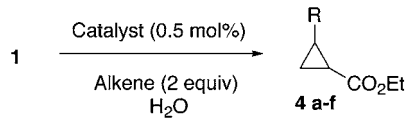
entry	catalyst	yield **3** (%)	ratio trans/cis
1	$[Rh(OAc)_2]_2$	26	1.6
2	$[Rh(CF_3CO_2)_2]_2$	11	1.0
3	$Rh(C_7H_{15}CO_2)_2]_2$	72	1.5
4	$Rh(C_7H_{15}CO_2)_2]_2$	47[b]	1.4
5	$[Rh(OPiv)_2]_2$	61	1.5
6	$[Rh(1\text{-adamantylCO}_2)_2]_2$	58	1.5

[a] Reaction conditions: a 0.18 M solution of **1** was added over 1 h to the catalyst and alkene and then stirred for an additional 2 h. [b] 1 equiv of styrene was used.

The yields of the desired cyclopropane were highly dependent upon the nature of the carboxylate used. Low yields were observed with water-soluble catalysts (entries 1 and 2), while higher yields were obtained with hydrophobic catalysts (entries 3−6). The Rh(II) octanoate catalyst (Table 1, entry 3) was the most efficient with this substrate,[9] even affording a 47% yield of cyclopropane[3] when only 1 equiv of styrene was used (Table 1, entry 4).

To further examine the generality of this reaction, other substrates were also tested (Table 2) with the two most efficient catalysts. For comparison, the reactions were also performed in CH_2Cl_2 using the same alkene equivalents and catalyst loadings.

Table 2. Reaction Scope of Cyclopropanation[a]



4 a-f

entry	yield (%) (CH_2Cl_2)	ratio trans/cis (CH_2Cl_2)
styrene (**a**)	61 (72)	1.5 (1.5)
a	72 (84)[b]	1.5 (1.5)
4-Cl-styrene (**b**)	73 (77)	1.5 (1.3)
α-methylstyrene (**c**)	72 (75)	1.1 (1.2)
cyclohexa-1,4-diene (**d**)	53 (55)	2.2 (2.0)
2-vinylnaphthalene (**e**)	52 (57)[c]	1.5 (1.5)
e	49 (64)[b]	1.5 (1.5)
(*E*)-PhCH=CH_2CH=CH_2 (**f**)	59 (64)	1.5 (1.5)
f	56 (61)[b]	1.0 (1.1)

[a] Reaction conditions: a 0.18 M solution of **1** was added over 1 h to $[Rh(OPiv)_2]_2$ and alkene and then stirred for an additional 2 h. [b] In this case, $[Rh(C_7H_{15}CO_2)_2]_2$ was used as the catalyst. [c] The alkene was dissolved in 0.5 mL of toluene.

The results in Table 2 suggest that under the same addition times of the diazo substrate, the aqueous-based cyclopropanation proceeds with efficiency similar to that performed in anhydrous CH_2Cl_2 (yields and ratios shown in parentheses are for the reactions run in CH_2Cl_2). Additionally, the diastereoselectivities of the products are nearly identical. Solid substrates such as 2-vinylnaphthalene (**4e**) can also be submitted to this cyclopropanation by using a small amount of toluene, thereby creating a liquid organic phase.

The success of this cyclopropanation may possibly result from the biphasic nature of the reaction. Hydrophobic catalysts migrate into the alkene substrate leading to a high effective concentration of alkene. Upon diffusion of **1** into the organic phase, cyclopropanes are formed preferentially.

Jessop et al. have reported that the dielectric constant of the solvent can have a negative effect on the enantioselectivities of a cyclopropanation reaction with certain diazo substrates.[10] Thus, we became interested in determining whether asymmetric cyclopropanations in aqueous media were possible.[5,11] Unfortunately, few intermolecular cyclopropanations with Rh(II) type catalysts are known to cyclopropanate with **1** in high diastereoselectivities and enantioselectivities.[12] This prompted us to try other known cyclopropanation catalysts (Figure 1) for their compatibility with water (see Table 3).

Ruthenium(II)based catalyst **5** reported by Nishiyama et al. was also found to be effective in aqueous media, affording highly diastereoselective and enantioselective formation of cyclopropanes **4a**−**h**, nearly identical to the reaction per-

(7) For a water-soluble Ru(II) catalyst, see: Iwasa, S.; Takezawa, F.; Tuchiya, Y.; Nishiyama, H. *Chem. Commun.* **2001**, 59.

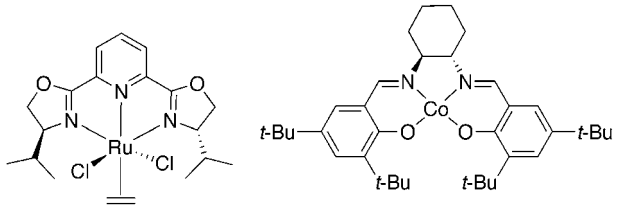
(8) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1973**, *14*, 2233.

(9) The Rh(II) hexanoate catalyst shows slightly improved yields compared to that of the pivalate when styrene is used as a substrate; see: Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem.* **1980**, *45*, 695.

(10) Wynne, D. C.; Olmstead, M. M.; Jessop, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7638.

(11) For Co(II) cat. cyclopropanations in 5% aqueous solvents, see: Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* **2001**, 406.

(12) (a) Doyle, M. P.; Davies, S. B.; Hu, W. *Chem. Commun.* **2000**, 867. (b) Barberis, M.; Lahuerta, P.; Pérez-Prieto, J.; Sanaú, M. *Chem. Commun.* **2001**, 439.

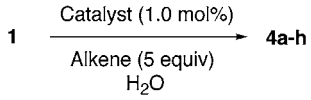


5 **6**

Figure 1. Catalysts for asymmetric cyclopropanation.

formed in CH_2Cl_2 (yields in parentheses).[13] In the case of the Co(II)-type catalysts **6** popularized by Katsuki,[14] an improvement in reaction yields was often observed in aqueous media, although the reaction had to be performed in argon-purged water.

Table 3. Asymmetric Aqueous Cyclopropanations[a]

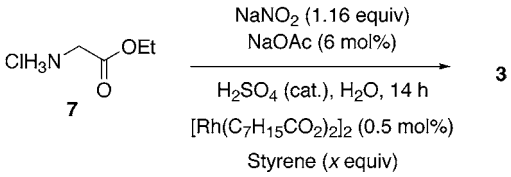


alkene	cat.	yield (%) of **4** (in CH_2Cl_2)	ratio trans/cis (in CH_2Cl_2)	ee (trans) (in CH_2Cl_2)
a	**5**	46 (48)	19:1 (24:1)	90 (86)
b	**5**	31 (40)	24:1 (24:1)	83 (89)
g[b]	**5**	42 (77)	19:1 (19:1)	87 (85)
h[c]	**5**	44 (74)		86 (83)
a	**6**[d]	61 (20)[f]	2.0:1 (nd)	22 (nd)
a	**6**[d,e]	80 (62)[f]	1.5:1 (1.5:1)	47 (56)
b	**6**[d,e]	60 (76)[f]	1.8:1 (1.3:1)	47 (46)

[a] A 0.18 M solution of **1** was added over 2 h to a mixture of **5** and the alkene, and the reaction mixture was stirred for an additional 4 h, or a 0.18 M solution of **1** was added in one portion to a mixture of **6** and the alkene. The mixture was stirred under argon for 24 h. [b] **g**: 4-methoxystyrene. [c] **h**: 1,1-diphenylethene. [d] 5 mol % of catalyst was used in argon-purged H_2O. [e] 10% *N*-methylimidazole was used as an additive. [f] The yield in parentheses is for the reaction in THF.

To address the explosive nature of the **1**, we believed in situ diazo generation followed by cyclopropanation[15] would eliminate the necessity of handling the reagent. Treatment of **7** with sodium nitrite affords **1**[16] and is rapidly consumed upon formation yielding the cyclopropane **3** (Table 4).

Table 4. In Situ Generation of Ethyl Diazoacetate[a]

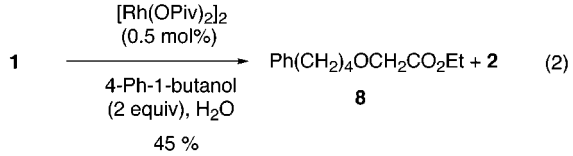


entry	styrene (equiv)	yield of **3**[b] (%)	ratio trans/cis
1	3	70	1.5:1
2	2	66	1.3:1
3	2[c]	54	1.1:1
4	1	45	1.2:1

[a] Reaction conditions: a 0.7 M solution of **7** and a 0.8 M solution of $NaNO_2$ were added to the catalyst and styrene at 0 °C. [b] Isolated yield of chromatographically pure cyclopropane. [c] Reaction time: 5 h.

The reaction yields compare nicely with those reported in Table 1, although slightly longer reaction times are required for higher yields. The reaction has been successfully performed on a 3 g scale and this method represents a cost efficient source of ethyl diazoacetate without the disadvantages of its handling and purification.

Finally, a selective O−H insertion of a primary alcohol in water can also be achieved if the combination of hydrophobic catalyst and hydrophobic substrate is used (eq 2).



(2)

Although the yield of **8** was a modest 45% based on **1**, when the corresponding reaction was performed with 2 equiv of EtOH as a substrate (a more hydrophilic alcohol), only trace amounts of the corresponding ethanol O−H insertion product resulted.

In conclusion, we have shown that water is a suitable solvent to use for the cyclopropanation of alkenes with α-diazoester reagents. This novel procedure also allows the in situ generation and reaction of the diazo compound without the need to isolate the sensitive reagent.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) and SFC traces for enantioselective cyclopropanations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park. S.-B.; Itoh, K. *J. Am. Chem. Soc*. **1994**, *116*, 2223.

(14) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647.

(15) Compound **7** was treated with $NaNO_2$ in 10:1 CH_2Cl_2/H_2O, 10 equiv of alkene, 0.5% TPPRhI, 4 days; see: Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem*. **2001**, *66*, 8260. It was also claimed that $Rh_2(OAc)_4$ was not an effective catalyst under these conditions.

(16) Nomack, E. B.; Nelson, A. B. *Org. Synth*. **1964**, *C. V. 3*, 392.

(17) A preferable method for generation of **1** involves using $Na_2B_4O_7 \cdot 10H_2O$ as a buffer and a 2% H_3PO_4 solution as the catalyst (see ref 5c). The cyclopropanation proceeds with equal or better yields than those reported in Table 4. See the Supporting Information for details.