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Rh-catalyzed Intermolecular Cyclopropanation with α -Alkyl- α -diazoesters: Catalyst Dependent Chemo- and Diastereoselectivity

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Abstract

cat. = Rh_2TPA_4 : dr 98:2

cat. = Rh_2Piv_4 : dr 42:58

A Rh-catalyzed procedure for the cyclopropanation of alkenes with α -alkyl- α -diazoesters is described. With dirhodium tetraoctanoate, the predominant pathway is β -hydride elimination. While a number of sterically demanding carboxylate ligands serve to avoid β -hydride elimination, it was found that triphenylacetate (TPA) also imparts high diastereoselectivity.

Rhodium carbenoids are reactive intermediates that effect a range of transformations, and both the nature of the carbenoid and the auxiliary ligands on rhodium have a dramatic impact on the selectivity of these reactions.¹ While α -alkyl- α -diazoesters (**1**) are readily available and attractive precursors to Rh-carbenoids, such carbenoids had only limited applicability in intermolecular reactions due to their propensity to undergo β -hydride elimination.² Recently, our group described several intermolecular Rhcatalyzed transformations of α -alkyl diazoesters that tolerate β -hydrogens, including reactions that produce cyclopropenes (**2**)³ and dioxolanes via putative carbonyl ylides of structure **3** (Scheme 1).⁴ Low reaction temperatures ($-78\text{ }^{\circ}\text{C}$)⁵ and the use of sterically demanding carboxylate ligands⁶ [e.g. dirhodium tetrapivalate (Rh_2Piv_4)] were key to the success of these reactions and to the dramatic suppression of β -hydride elimination. In prior studies on the effects of ligand structure⁶ and temperature⁵ on suppressing β -hydride elimination, only modest effects had been noted.

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The rhodium catalyzed cyclopropanation of alkenes has broad applicability in organic syntheses.^{1,7} However, examples of intermolecular cyclopropanation by diazoalkanes are rare.^{8–10} With Rh-catalysis, we are aware of only three reports that describe intermolecular cyclopropanation in preference to β -hydride elimination.⁸ These transformations involved a limited range of alkenes (diketene,^{8a} methylenespiropentane^{8b} or furans^{8c}) with ethyl α -diazopropionate. Rh-catalyzed cyclopropanation of α -alkyldiazo compounds with more reactive β -hydrogens had not been described previously.

Unlike the reactions displayed in Scheme 1, cyclopropanation reactions have the additional challenge of diastereocontrol. Diastereocontrol in cyclopropanation chemistry can be highly dependent on the structure of the carbenoid,¹ and it was unclear if the reactions of α -alkyl diazoesters would be selective. As shown in Table 1, a range of catalysts were surveyed for their effectiveness in the reaction of ethyl α -diazobutanoate with styrene. These reactions were screened using the diazoalkane as the limiting reagent, so that the relative amounts of cyclopropanation and β -hydride elimination could be measured.

Consistent with earlier observations on the reactions of alkynes with α -alkyl- α -diazoesters,³ dirhodium tetraoctanoate (Rh_2Oct_4) gave only small amounts of cyclopropane products: *cis*-ethyl crotonate **6** and azine **7**⁴ dominated. While dirhodium tetrapivalate (Rh_2Piv_4) is the most useful catalyst for cyclopropanation and dioxolane formation,^{3,4} this catalyst gave rise to cyclopropane products **4** and **5** only in modest yields and with poor diastereoselectivity (42:58), with a slight preference for **5**. The use of Rh_2esp_2 ¹¹ provided no significant advantage (Table 1, entry 9). However, increasingly higher selectivities were observed along a series of catalysts with increasingly larger carboxylate ligands. Thus, **4** and **5** were obtained in a 76:24 ratio with $\text{Rh}_2(\text{O}_2\text{CCMe}_2\text{Ph})_4$ (**8**), in a 89:11 ratio with $\text{Rh}_2(\text{O}_2\text{CCMePh}_2)_4$ (**9**), and in a 98:2 ratio with Rh_2TPA_4 . In line with previous observations, the use of low temperature was critical: β -hydride elimination predominated in experiments that were carried out at room temperature (Table 1, entries 2, 4 and 8).

Rh_2TPA_4 had previously been shown to be uniquely effective in a number of catalytic transformations.^{12,13} With the discovery that Rh_2TPA_4 is also an effective catalyst for diastereoselective cyclopropanation, the substrate scope of the reaction was determined (Scheme 2).¹⁴ Successful cyclopropanations were observed with α -methyl and α -*n*-alkyldiazoesters. Successful alkene substrates include substituted styrenes, α -vinyl naphthalene α -methylstyrene, 1,1-diphenylethylene, butyl vinyl ether, and 3,4-dihydro-2*H*-pyran. The highest yields for cyclopropanation were obtained when the alkene was the limiting reagent; the diazo compound was typically used in three-fold excess. Under these conditions, all of the products in Scheme 2 were obtained in 80–100% yield with the exception of **2g**, which was obtained in 54% yield. Good yields were also obtained when the stoichiometry of the reactions in Table 1 was inverted, and the diazo compound was used as the limiting reagent with a three-fold excess of the alkene (Scheme 2). In an experiment with 1:1 stoichiometry of alkene and diazo compound, **4a** was obtained in 48% yield.

Recently, Davies and coworkers provided evidence that the high diastereoselectivity in cyclopropanations of styrene derivatives with α -aryl or α -styryl diazo compounds is partly due to an attracting π -interaction between the substituents on the carbenoid and the alkene¹⁵ in a mechanism involving a concerted, non-synchronous transition state.¹⁶ Our observations are consistent with Davies' hypothesis, as the Rh_2Piv_4 catalyzed reaction of styrene with ethyl α -diazopropionate proceeds with low diastereoselectivity relative to the analogous reactions of styrene with α -aryl or α -styryl diazoesters.¹³

In conclusion, a chemoselective and diastereoselective Rh-catalyzed protocol for cyclopropanation of alkenes with α -alkyl- α -diazoesters has been described. While a number

of sterically demanding carboxylate ligands serve to avoid β -hydride elimination, it was found that triphenylacetate (TPA) is uniquely effective in terms of diastereoselectivity. It is likely that the high diastereoselectivity observed in cyclopropanation reactions with Rh_2TPA_4 is a consequence of the very high steric demands of the TPA ligand. Ongoing experiments and calculations in our laboratories aim to understand the catalyst effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Intermolecular reactions without β -hydride elimination

Scheme 2.**Rh₂TPA₄ catalyzed cyclopropanation**

All yields refer to the average isolated yield from two experiments. Hexane was the solvent for the preparation of **9a–9c**; other compounds were prepared in CH₂Cl₂. ^a The alkene was the limiting reagent, and the diazo compound was used in three-fold excess. ^b The diazo compound was the limiting reagent, and the alkene was used in three-fold excess. ^c The alkene was the limiting reagent, and the diazo compound was used in four-fold excess.

Table 1

The Effect of Ligand Choice on Rh-catalyzed cyclopropanation

entry	catalyst	cyclopropane yield ^a (4:5)	6 ^a	7 ^a
1	Rh ₂ Oct ₄ (R = C ₇ H ₁₅)	5% ^b	25%	30%
2	Rh ₂ Oct ₄ at rt	0%	75%	<5%
3	Rh ₂ Piv ₄ (R = CMe ₃)	29% (42:58 ^c)	33%	<5%
4	Rh ₂ Piv ₄ at rt	0%	72%	<5%
5	R = CMe ₂ Ph (8)	40% (76:24 ^c)	29%	<5%
6	R = CMePh ₂ (9)	54% (89:11 ^c)	32%	<5%
7	Rh ₂ TPA ₄ (R = CPh ₃)	73% ^d (98:2 ^c)	10%	<5%
8	Rh ₂ TPA ₄ at rt	0%	65%	10%
9	Rh ₂ esp ₂ (esp =)	30% (2:1 ^e)	10%	45%

^aYields were determined by analyzing the crude ¹H NMR spectrum using mesitylene as a standard. "Cyclopropane yield" represents the combined yield of **4** and **5**.

^bImpurities in the ¹H NMR made it difficult to determine the ratio of **4**:**5**.

^cThe dr was determined by GC analysis.

^dThe yield of **4** as determined by ¹H NMR analysis (this table) was slightly higher than the isolated yield (Scheme 2).

^eThe dr was determined by ¹H NMR.