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

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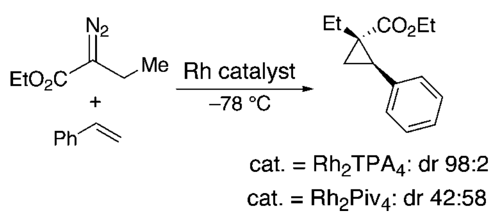
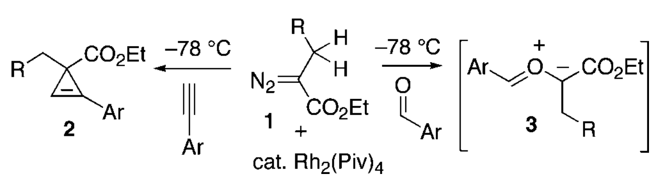
ABSTRACT



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 Rh-catalyzed 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 °C)[5] and the use of sterically demanding carboxylate ligands[6] [e.g., dirhodium tetrapivalate (Rh_2Piv_4)] were key to the success of these reactions and

Scheme 1. Intermolecular Reactions without *β*-Hydride Elimination



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to the dramatic suppression of β-hydride elimination. In prior studies on the effects of ligand structure[6] and temperature[5] on suppressing β-hydride elimination, only modest effects had been noted.

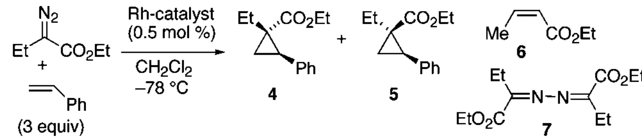
The rhodium-catalyzed cyclopropanation of alkenes has broad applicability in organic syntheses.[1,7] However, examples of intermolecular cyclopropanation by diazoalkanes are rare.[8–10] With Rh catalysis, we are aware of only three reports that describe intermolecular cyclopropanation in preference to 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 has not been described previously.

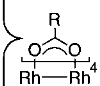
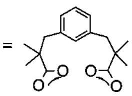
Unlike the reactions displayed in Scheme 1, cyclopropanation reactions have the additional challenge of diastereocontrol. Diastereocontrol in cyclopropanation chemistry can be highly dependent on the structure of the carbenoid,[1] and it was unclear if the reactions of α-alkyl diazoesters would be selective. 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 with use of 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 cyclopropenation 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 $Rh_2(O_2CCMe_2Ph)_4$ (**8**), in a 89:11 ratio with $Rh_2(O_2CCMePh_2)_4$ (**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 tranformations.[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*-

Table 1. The Effect of Ligand Choice on Rh-Catalyzed Cyclopropanation



entry	catalyst	cyclopropane yield[a] (4:5)	6[a]	7[a]
1	Rh_2Oct_4 (R = C_7H_{15})	5%[b]	25%	30%
2	Rh_2Oct_4 at rt	0%	75%	<5%
3	Rh_2Piv_4 (R = CMe_3)	29% (42:58[c])	33%	<5%
4	Rh_2Piv_4 at rt	0%	72%	<5%
5	R = CMe_2Ph (**8**) 	40% (76:24[c])	29%	<5%
6	R = $CMePh_2$ (**9**)	54% (89:11[c])	32%	<5%
7	Rh_2TPA_4 (R = CPh_3)	73%[d] (98:2[c])	10%	<5%
8	Rh_2TPA_4 at rt	0%	65%	10%
9	Rh_2esp_2 (esp = )	30% (2:1[e])	10%	45%

[a] Yields were determined by analyzing the crude ^1H NMR spectrum with mesitylene as a standard. "Cyclopropane yield" represents the combined yield of **4** and **5**. [b] Impurities in the ^1H NMR made it difficult to determine the ratio of **4**:**5**. [c] The dr was determined by GC analysis. [d] The yield of **4** as determined by ^1H NMR analysis (this table) was slightly higher than the isolated yield (Scheme 2). [e] The dr was determined by ^1H NMR.

(5) Lowering temperature had been shown to have an effect on selectivity over β-hydride elimination in Rh_2(*S*-PTTL)$_4$-catalyzed, intramolecular C−H insertions: 99:1 selectivity was observed at −78 °C vs 82:18 selectivity at 0 °C. Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483.

(6) Modest improvements in selectivity over β-hydride elimination had been previously observed in intermolecular O−H insertions and intramolecular C−H insertions when sterically demanding ligands were used in room temperature. For an intermolecular O−H insertion reaction, 88:12 selectivity was observed with Rh_2(1-adamantoate)$_4$ vs 82:18 selectivity with $Rh_2(OAc)_4$: (a) Cox, G. G.; Haigh, D.; Hindley, R. M.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett.* **1994**, *35*, 3139. For an intramolecular C−H insertion reaction, 85:15 selectivity was observed with $Rh_2(Piv)_4$ vs 78:22 selectivity with $Rh_2(OAc)_4$: (b) Taber, D. F.; Joshi, P. V. *J. Org. Chem.* **2004**, *69*, 4276. (c) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436.

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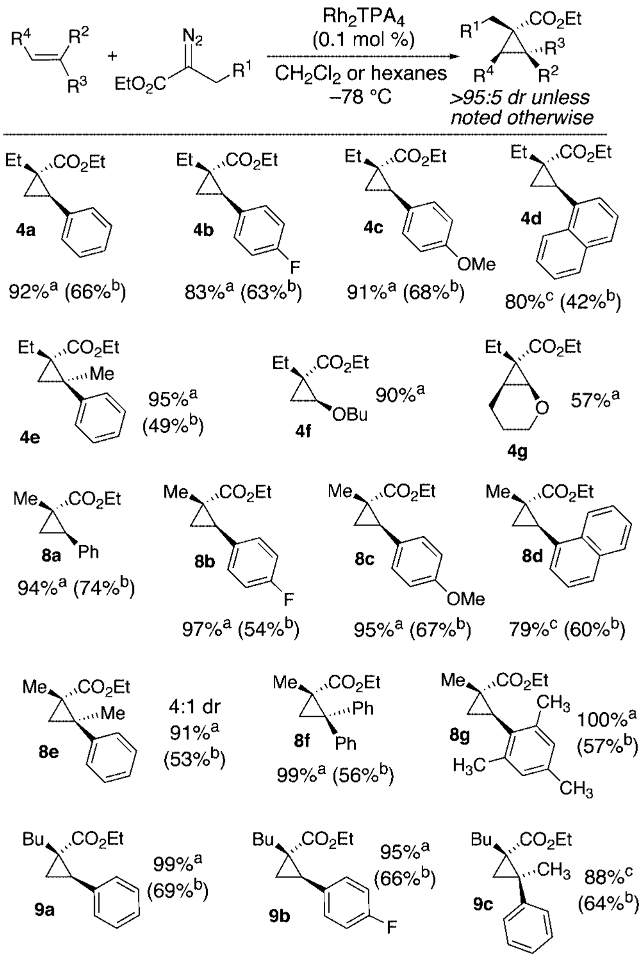
Scheme 2. Rh_2TPA_4-Catalyzed Cyclopropanation[d]



[a]The alkene was the limiting reagent, and the diazo compound was used in 3-fold excess. [b]The diazo compound was the limiting reagent, and the alkene was used in 3-fold excess. [c]The alkene was the limiting reagent, and the diazo compound was used in 4-fold excess. [d]All yields refer to the average isolated yield from two experiments. Hexane was the solvent for the preparation of **9a**−**c**; other compounds were prepared in CH_2Cl_2.

alkyldiazoesters. Successful alkene substrates include substituted styrenes, α-vinylnapthalene 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 3-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 3-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 co-workers 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 alkene[15] in a mechanism involving a concerted, nonsynchronous 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.

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Supporting Information Available: Experimental details, stereochemical assignments, and ^1H, ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We know of several limitations of the Rh_2TPA_4-catalyzed cyclopropanation reaction. Unlike the analogous reactions of ethyl α-diazopropionate to give **8f** and **8g**, the reactions of ethyl α-diazobutanoate (1 equiv) with either 1,1-diphenylethylene (3 equiv) or 1-vinylmesitylene (3 equiv) were both unsuccessful, and led predominantly to β-hydride elimination. Cyclopropane products were not observed in the reactions of ethyl α-diazobutanoate with 1-vinylcyclohexane, *trans-β*-methylstyrene, *cis*-diphenylethylene, or 1-octene. The reaction of ethyl α-diazohydrocinnamate (3 equiv) with styrene proceeded with poor efficiency: in hexane, the cyclopropanation product was formed in 28% yield (NMR analysis) along with uncharacterized products and unreacted styrene.

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