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cis-Enhanced cyclopropanation catalysts: reaction chemistry of three isomers of $Rh_2[N(C_6H_5)COCH_3]_4$

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Abstract—The catalytic activities of three structural isomers of $Rh_2[N(C_6H_5)COCH_3]_4$ in cyclopropanation reactions were surveyed. These studies showed *cis* cyclopropanation selectivity with bulky alkenes for 2,2-*cis*- and 2,2-*trans*-$Rh_2[N(C_6H_5)COCH_3]_4$. © 2003 Elsevier Science Ltd. All rights reserved.

Rhodium carboxylates have been used as catalysts for carbenoid transformations, allowing the synthesis of the cyclopropyl unit of pyrethroid insecticides as well as a variety of other compounds, incorporating a C_1-unit into the C=C bond in an alkene.[1] However, in cases where diastereomeric products are formed, these catalysts typically give rise to unacceptably low diastereoselectivities. Electron deficient catalysts such as the rhodium perfluorocarboxylates show essentially no diastereoselectivity, yielding *cis–trans* ratios of unity. Increasing the electron density about the rhodium centers through the use of rhodium carboxamidates yields more selective catalysts. These catalysts, however, allow the steric interactions of the alkene and carbene to influence the direction of the reaction, giving rise to excess of *trans* cyclopropanes.[2]

Demonceau and co-workers, in screening a variety of rhodium carboxylates and benzoates, have shown that catalysts with substituents in proximity of the axial site, such as *ortho* substituted rhodium benzoates, have the potential of catalyzing cyclopropane production with excesses of *cis* isomers.[3] Even with the bulkiest carboxylates, however, the *cis–trans* ratios did not exceed 1.22. The bulky equatorial ligands of the catalyst force the substituents of the incipient cyclopropane into a *cis* orientation. Imogai et al., synthesized *cis*-cyclopropanes by cyclopropenation of alkynes, followed by catalytic hydrogenation.[4] However, the lesser availability of alkynes relative to alkenes and the additional synthetic step render this method less than optimal.

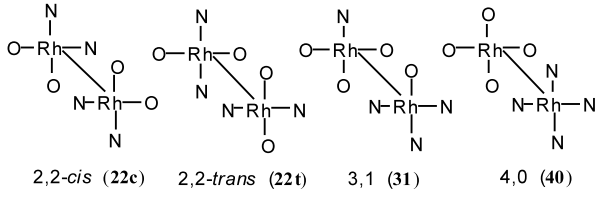

Figure 1. Four Isomers of rhodium tetrakisacetamidates.

In an effort to combine the greater selectivities of the carboxamidate derived catalysts with the *cis* directing effects of a sterically encumbered axial site, we have turned our attention to *N*-substituted dirhodium tetrakiscarboxamidates. Varying the substituents on the amide nitrogen provides a facile method for extensive modification of these catalysts.

We report herein the application of three isomeric *N*-substituted rhodium phenylacetamidates ($Rh_2[N(C_6H_5)C(O)CH_3]_4$) to diastereoselective control of cyclopropanation. Four isomers of $Rh_2[N(C_6H_5)C(O)CH_3]_4$ are possible, the 2,2-*trans* (**2,2-t**), 2,2-*cis* (**2,2-c**), 3,1 (**3,1**) and 4,0 (**4,0**), where the numbers indicate the number of nitrogen atoms bonded to each rhodium atom and the *cis–trans* designates the orientation of the nitrogen atoms around the rhodium (Fig. 1). We previously reported the synthesis and characterization of **2,2-t**;[5] Bear and Kadish[6] reported that of **2,2-c** and **3,1**; while no report of **4,0** has yet been made.[7] To date, no study has been made of the efficacy of these catalysts to control the diastereoselectivity of carbenoid reactions.

Keywords: cyclopropanation; rhodium catalysts; catalysis; rhodium carboxamides; carbene.

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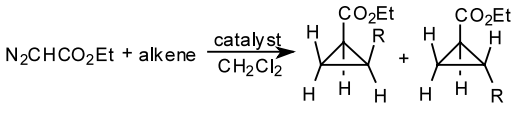
The catalysts were synthesized by refluxing rhodium acetate and an excess of *N*-phenyl acetamide in chlorobenzene. The three isomers were separated by flash column chromatography on silica gel using ethyl acetate/hexanes.[5] Cyclopropanations were conducted by slow addition (via syringe pump) of ethyl diazoacetate solution to a solution containing one mole percent catalyst and a ten fold excess of alkene. The products were examined by gas chromatography with a mass selective detector (see Table 1).

All three rhodium acetamidate isomers exhibit an increase in the *cis–trans* ratio as the bulk of the alkene R group ($CH_2=CHR$) increases. This trend is in contrast to the decrease in *cis–trans* ratio expected (vide infra) with increasing steric bulk. While the *cis–trans* ratios of the cyclopropanes produced with **3,1** never exceed unity, those produced by **2,2-c** and **2,2-t** did exceed unity, with **2,2-c** resulting in a *cis*/*trans* ratio of 1.78 with the bulkiest alkene.

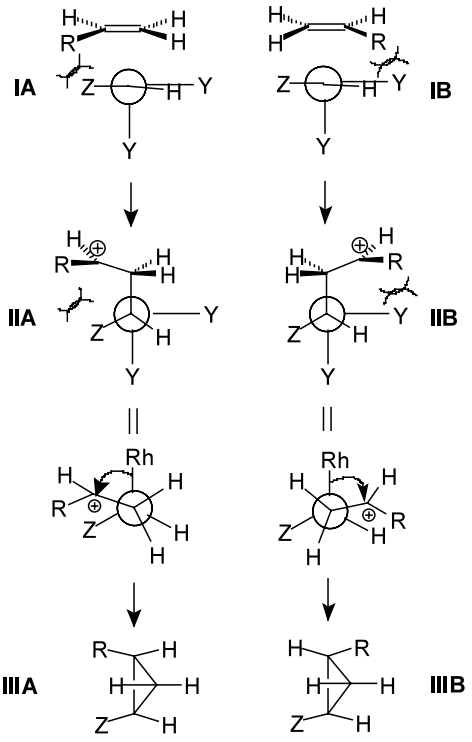
The alkene can approach the rhodium bound carbene with one of two possible orientations. This is shown in Scheme 1, following a mechanistic path similar to one put forth by Davies and co-workers.[8] Our mechanism is a modification of that of Davies and co-workers in that the carbenoid eclipses a pair of the carboxamidate ligands on the rhodium center. This eclipsing conformation is consistent with recent DFT calculations[9] and X-ray crystallographic structures of[10] and Fenske–Hall calculations[11] on rhodium carbenoid analogs. The alkene could approach with the R group oriented toward the Z group of the carbene, as depicted by **IA**. This approach, however, results in steric repulsion between the R and Z groups. Alternatively, the alkene could approach with the R group oriented away from the carbene Z group (toward the pendent arm Y) as depicted by **IB**. For unsubstituted amides (Y = H), orientation **IB** effectively eliminates the steric repulsion. The former approach leads to *cis*-cyclopropanes, while the latter leads to *trans*-cyclopropanes. Consequently, the '**B**' route is favored over the '**A**' route for catalysts in which the pendent arm is the diminutive hydrogen atom. Thus as the size of R or Z increases, the domination of route '**B**' would also increase, resulting in ever greater percentages of *trans* cyclopropanes. Indeed,

Table 1. Catalyst diastereoselectivities[a]



Alkene	3,1	2,2-t	2,2-c
Cyclohexene	0.2	0.3	0.3
Ethyl vinyl ether	0.7	0.6	1.0
Styrene	0.8	1.2	1.1
Trimethyl styrene	1.0	1.2	1.8

[a] Diastereoselectivities are reported as *cis*/*trans* ratios as determined by GC.



Scheme 1. Proposed mechanism for the reaction between the rhodium stabilized carbene and an alkene.

Doyle has demonstrated this quite clearly employing bulky diazoesters (thus, bulky Z groups rather than our bulky R groups) to produce cyclopropanes with *trans* selectivities well in excess of 90%.[12]

Rhodium catalysts based on *N*-substituted carboxamidates introduce another factor to the diastereoselectivity of the cyclopropanation reactions. As shown with **IB**, the steric repulsion between R and Y (the amide substituent) now competes with that between R and Z in directing the course of the reaction. In cyclopropanations catalyzed by 2,2-*cis*-$[Rh_2(N\{C_6H_5\}COCH_3)_4]$, the R–Y repulsion becomes the dominant factor as the size of the R group increases. Cyclohexene is essentially a 1,2-*cis*-disubstituted alkene, having two ethyl groups, with the caveat that these ethyl groups are 'pinned' together, thus minimizing the steric repulsion between R and Y. Consequently, the *cis*/*trans* ratio of these cyclopropanes is quite small (0.3, see Table 1). Indeed, **3,1** and **2,2-t** show similarly small ratios. As the size of the monosubstituted alkenes increases from cyclohexene to 2,4,6-trimethyl styrene, the *cis*/*trans* ratio increases steadily to approximately 1.8. Indeed, the same trend is seen with the **3,1** and **2,2-t** isomers, though to a lesser degree.

Cyclopropanations catalyzed with **3,1** almost certainly occur at the least congested site, that with only one pendant phenyl group. Even this one pendant Y group appears to be sufficient to induce some *cis*-cyclopropanation. As the size of the R group increases from ethoxy to trimethylphenyl, the *cis–trans* ratio increases from 0.7 to 1.0, the opposite of the decrease one expects with increasing alkene bulk (vide supra). Clearly, even

this single pendant Y group of the acetamidate ligand is exerting sufficient influence to effectively compete with the R–Z repulsion.

Similarly, **2,2-t** shows an increase in the *cis–trans* ratio with increasing size of R, from 0.61 for ethoxy, to 1.2 for trimethylphenyl. Again the results suggest a competition between the steric repulsion of R–Z on the one hand, and R–Y on the other.

In summary, we have demonstrated that rhodium carboxamidate catalysts modified with pendant arms can successfully influence the diastereoselectivity of carbenoid mediated cyclopropanations. We have produced the largest excesses of *cis*-cyclopropanes seen to date with this class of catalyst. While the diastereomeric excesses are modest, this class of catalysts is readily amenable to a wide variety of modifications. Such modifications can enable one to selectively tune the size and shape of the catalytic center, and thus control the selectivity of the catalyst.

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