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Rh-Catalyzed Intermolecular Reactions of Cyclic α-Diazocarbonyl Compounds with Selectivity over Tertiary C−H Bond Migration

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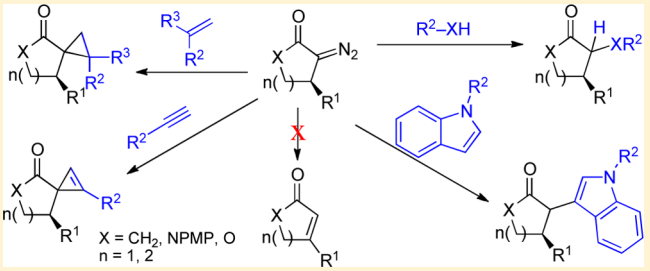
Supporting Information

ABSTRACT: Intermolecular Rh-catalyzed reactions of cyclic α-diazocarbonyl compounds with chemoselectivity over β-hydride elimination are described. These methods represent the first general intermolecular reactions of Rh-carbenoids that are selective over tertiary β-C−H bond migration. Successful transformations include cyclopropanation, cyclopropenation, and various X−H insertion reactions with a broad scope of substrates. We propose that the intermolecular approach of substrates to carbenes from acyclic diazo precursors may be relatively slow due to a steric interaction with the ester function, which is perpendicular to the π-system of the carbene. For carbenes derived from five- and six-membered cyclic α-diazocarbonyls, it is proposed that the carbene is constrained to be more conjugated with the carbonyl, thereby relieving the steric interaction for intermolecular reactions, and accelerating the rate of intermolecular reactivity relative to intramolecular β-hydride migration. However, attempts to use α-diazo-β-ethylcaprolactone in intermolecular cyclopropanation with styrene were unsuccessful. It is proposed that the conformational flexibility of the seven-membered ring allows the carbonyl to be oriented perpendicular to Rh-carbene. The significant intermolecular interaction between the carbonyl and approaching substrate is in agreement with the poor ability of α-diazo-β-ethylcaprolactone to participate in intermolecular cyclopropanation reactions. DFT calculations provide support for the mechanistic proposals that are described.

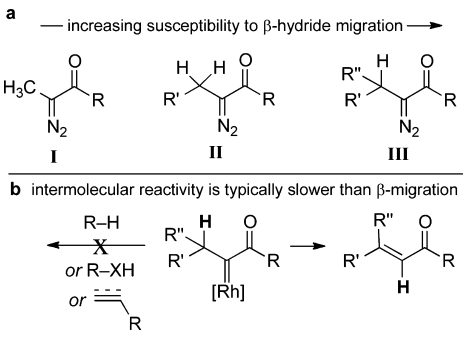


INTRODUCTION

α-Diazocarbonyl compounds engage in a myriad of useful reactivity, including cyclopropanation, cyclopropenation, C−H or heteroatom−H bond insertions, and ylide forming reactions.[1] α-Diazocarbonyl compounds with α-alkyl substitution (**I**–**III**) are readily available and attractive precursors to Rh-carbenoids. However, the reactivity of such diazo compounds can be relatively limited due to their propensity to undergo β-hydride migration to give alkene products.[2] The migratory aptitude of α-diazocarbonyl compounds (**I**–**III**) with β-C−H bonds follows the pattern displayed in Scheme 1a, with methine C−H bonds of **III** having the highest propensity for migration. Seminal studies on α-alkyl-α-diazocarbonyl compounds by Ganem[2a] and McKervey[3] first established that β-hydride migration could be avoided in favor of intramolecular benzoate migration[2a,4] and intermolecular S−H insertion.[3,5] Subsequently, Rh-catalyzed reactions of α-diazocarbonyl compounds with primary alkyl substitutents had been well demonstrated for a number of intramolecular processes.[6−12] In contrast, the intermolecular Rh-catalyzed reactions of α-diazocarbonyl compounds **II** were more limited and had until recently been limited to insertions into heteroatom−H bonds.[5,13−15] In these studies, key observations were made by Taber,[10a] Moody,[15a] and Hashimoto[10o] on the effects of ligands[10a,15a] and temperature[10o] on selectivity over β-hydride migration in Rh-catalyzed transformations.[16]

Our group has described several intermolecular Rh-catalyzed transformations of α-alkyl diazoesters that tolerate β-hydrogens, including cyclopropenation,[17] cyclopropanation,[17a,18] indole C−H functionalization,[17a,19] and carbonyl ylide-forming reactions that produce dihydrofuran, tetrahydrofuran, and dioxolane products.[20] Low reaction temperatures (−78 °C) and the use of sterically demanding carboxylate ligands were key to the success of these reactions and to the dramatic suppression of β-hydride migration. These include enantioselective methods for cyclopropanation[17a,18b] and indole C−H functionalization.[17a,19] Recently, Hashimoto has elegantly described methods for enantioselective cyclopropenation using α-alkyl-α-diazoesters[21]

Scheme 1



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and cyclopropanation and indole C−H functionalization using α-diazopropionates.[22] Collectively, these protocols are largely successful for α-methyl and α-methylene substituted α-diazocarbonyl compounds (**I** and **II**). However, substrates with α-methines (**III**) typically give rise solely to the products of β-hydride elimination, and general conditions for promoting intermolecular reactions with substrates of this type have not been realized.

Chemoselective Rh-catalyzed reactions of α-diazocarbonyl compounds with β-tertiary C−H bonds are rare, and even intramolecular transformations have proven challenging.[10a] Taber has described Rh-catalyzed intramolecular C−H insertion reactions with selectivity over tertiary C−H bond migration[10e,23] for substrates containing tethered acetals, where the selectivity was attributed to the remote electron-withdrawing effect[24] of the ether oxygen atoms. Brown has demonstrated intramolecular C−H insertion reactions of α-diazobutyrolactones containing β-tertiary C−H bonds proceed with selectivity over β-hydride migration for insertions into α-heteroatom substituted C−H bonds.[25] Sha has described an intramolecular azirdination via N−H insertion of a substrate containing a tertiary C−H bond.[26] Tang has shown that with β-cyclopropyl-α-diazoesters, ring expansion (C−C bond migration) of the cyclopropanes to form cyclobutenes is the predominant pathway,[27] although cyclopropyl C−H bonds, being particularly strong, are resistant to migration. Padwa has demonstrated that intramolecular vinyl carbene formation from an α-diazo-β-substituted cyclohexanone can outcompete β-hydrogen migration.[28]

Reports of intermolecular reactions of α-diazocarbonyl compounds with β-substitution are rare and are described only in cases where the β-hydride migration product would be highly strained. Doyle and co-workers have demonstrated that α-diazonorbornan-2-one undergoes $Rh_2(OAc)_4$-catalyzed Si−H insertion with triethylsilane;[29] however, β-hydride elimination in this case would lead to an anti-Bredt olefin. Intermolecular cyclopropanation and X−H insertion reactions of fused bicyclic α-diazo-β-lactams have been reported,[30] although yields are modest (10−49%), and in these reactions, and β-hydride elimination would lead to strained unsaturated β-lactam derivatives.

As compared to the scope of reactivity that has been described for acyclic α-diazocarbonyl compounds, the use of cyclic α-diazocarbonyl compounds as carbene precursors has been the subject of relatively few studies.[31] Brown has elegantly demonstrated that α-diazobutyrolactones with β-substitution are useful substrates for intramolecular C−H insertion chemistry.[25] However, conditions for intermolecular reactivity of cyclic α-diazocarbonyl compounds with β-substitution had not been described. Moreover, there has not been an explicit correlation between the cyclic structure of α-diazocarbonyls and the ability to avoid β-hydride migration.

For Rh-carbenes derived from diazoesters (**IV**), it is calculated that the π-systems of the carbene and ester carbonyl are perpendicular.[32] The perpendicular orientation has been rationalized on the basis of conjugation of the carbonyl π* orbital with the Rh−C σ-bond, which is more favorable than conjugation of the carbonyl with the π system of the electron-deficient carbene.[32] As a consequence of this perpendicular orientation, the intermolecular approach of substrates to carbenes **IV** may be relatively slow due to a steric interaction with the ester function (e.g., **V**) as depicted in Figure 1a. For carbenes derived from cyclic α-diazocarbonyls (**VI**), we reasoned that the ring would constrain the carbonyl to be more conjugated

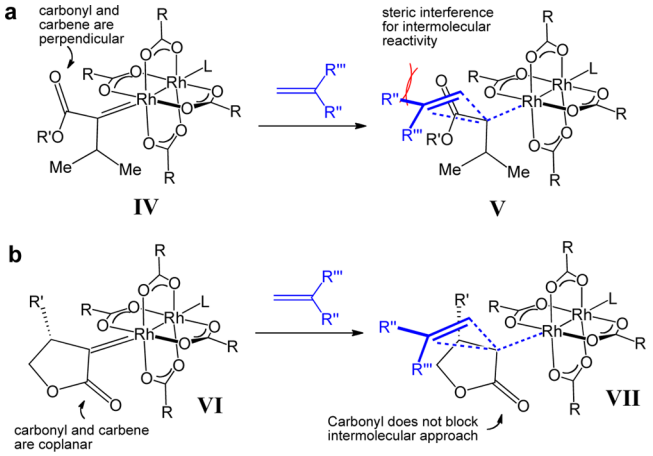


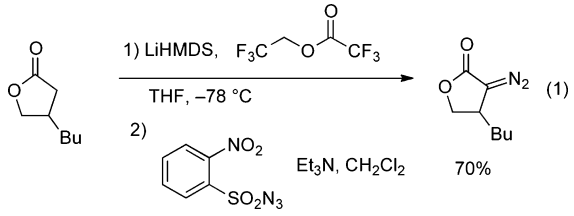
Figure 1. (a) For Rh-carbenes derived from α-diazoesters, calculations predict that the π-bonds of the carbonyl and carbene are nearly perpendicular. For intermolecular reactions, it is proposed that steric interference of the carbonyl slows the rate of intermolecular reactivity relative to intramolecular β-hydride migration. (b) For Rh-carbenes from cyclic α-diazoesters, it is proposed that the ring will constrain the dihedral angle between the carbonyl and the carbene, and relieve the steric interaction for intermolecular reactions.

with the carbene, thereby relieving the steric interaction for intermolecular reactions (e.g., **VII**), and accelerating the rate of intermolecular reactivity relative to intramolecular β-hydride migration (Figure 1b).

Herein, we describe the use of cyclic α-diazocarbonyl compounds containing β-tertiary C−H bonds in various intermolecular Rh-catalyzed reactions that proceed with high selectivity over β-hydride elimination. The use of sterically demanding carboxylate ligands and low reaction temperatures is key to this transformation.

EXPERIMENTAL RESULTS

The α-diazolactones and α-diazolactam used in this study were synthesized by a modification of the Danheiser method of deacylative diazo transfer,[33] as exemplified by the synthesis of 2-butyl-α-diazo-γ-butyrolactone (eq 1). Thus, sequential treatment of 2-*n*-butyl-γ-butyrolactone with LiHMDS and 2,2,2-trifluoroethyl trifluoroacetate gave 2-*n*-butyl-1-trifluoroacetyl-γ-butyrolactone. Similar procedures for the preparation of α-diazolactones had been described previously by Brown.[25] Diazo transfer was most effectively accomplished using *o*-nitrobenzenesulfonyl azide, a reagent that was used by Du Bois for in situ generation of α-diazolactones, α-diazolactams, and α-diazoesters.[31c] 2-Diazo-3-methylcyclohexanone was prepared by adapting the azide reduction protocol of Raines.[34] The compounds in this work were prepared in racemic form. However, enantioselective conjugate addition[35] and conjugate reduction[36] reactions are well-established methods for establishing β-stereocenters in lactones, lactams, and cyclic ketones.



Rh-complexes with varying steric and electronic properties were screened in the cyclopropanation reaction between 3-diazo-4-methyldihydrofuran-2-one and styrene (3 equiv), and the results are

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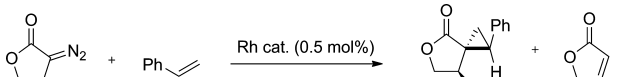
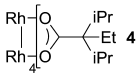
summarized in Table 1. In general, sterically demanding carboxylate ligands on rhodium served to avoid β-hydride elimination, and

Table 1. Optimization Study[a]



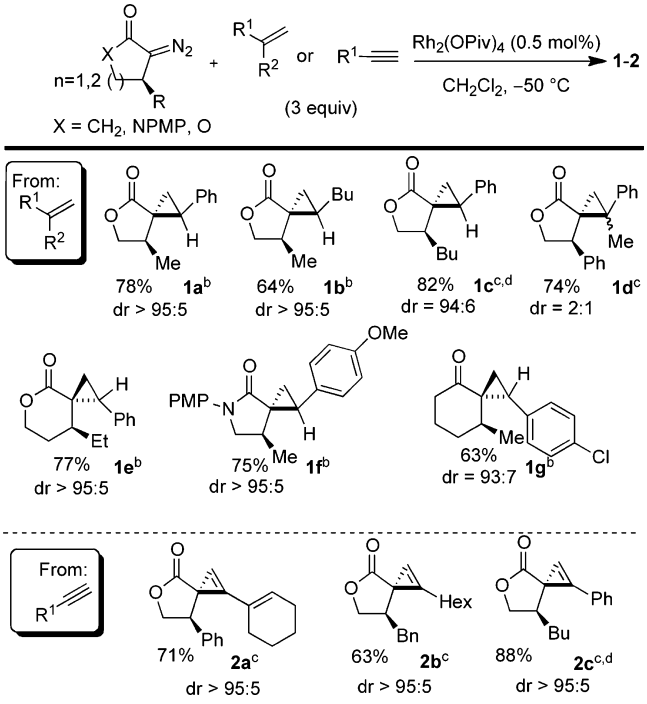
Entry	Rh cat.	Yield of **1a** (dr)[b]	Yield of **3a**[b]
1	Rh_2Oct_4 (R = C_7H_{15})	30% (93:7)	38%
2	Rh_2TPA_4 (R = CPh_3)	19% (3:2)	56%
3	**$Rh_2(OPiv)_4$** (R = CMe_3)	**85% (95:5)**	**9%**
4	$Rh_2(OPiv)_4$ (at rt)	30% (95:5)	43%
5	$Rh_2(TFA)_4$ (R = CF_3)	0%	78%
6	 **4**	75% (95:5)	6%
7	Rh_2(1-adamantoate)$_4$	68% (95:5)	13%
8	Rh_2esp_2	78% (94:6)	11%

[a]The optimized conditions are highlighted in bold. [b]Yields and diastereomer ratios were determined by crude ^{1}H NMR analysis using mesitylene as an internal standard. [c]Under conditions of entry 3, a lower yield (59%) was observed when 2 equiv of styrene was employed. Increasing to 4 equiv of styrene provided no significant advantage.

$Rh_2(OPiv)_4$ was found to be the optimal catalyst as cyclopropane **1a** was formed in 85% yield and 95:5 dr, and butenolide **3a**, the product of β-hydride elimination, was suppressed to 9%. Interestingly, dirhodium tetrakis(triphenylacetate), Rh_2TPA_4, a catalyst that gave high diastereoselectivity in cyclopropanation reactions with acyclic α-alkyl-α-diazoesters,[18a] gave **1a** in not only low yield (19%), but poor diastereoselectivity as well (dr = 3:2). The ligand effect on the suppression of β-hydride elimination is not as pronounced as in other transformations we have studied. For instance, dirhodium tetraoctanoate, Rh_2Oct_4, a complex that was ineffective for cyclopropanation reactions in the acyclic series,[18a] still formed **1a** in 30% yield and reasonable diastereoselectivity (dr = 93:7). However, the use of strongly electron-deficient dirhodium tetrakis(trifluoroacetate), Rh_2TFA_4,[2b] led to a precipitous loss of selectivity as butenolide **3a** was formed in 78% yield with no cyclopropane detected. Consistent with previous findings,[17−20] a low yield (30%) and increased proportion of β-hydride elimination (43%) was observed in the $Rh_2(OPiv)_4$-catalyzed reaction performed at room temperature. This finding once again demonstrated the importance of low temperature (−50 °C)[37] in maintaining selectivity over β-hydride elimination.

The optimized reaction conditions were applied to a variety of alkenes and alkynes, and the results are summarized in Scheme 2.[38] Reactions were successful with methyl, ethyl, *n*-butyl, phenyl, and benzyl β-substituents on the diazo compound. α-Diazolactones of ring sizes 5 and 6 (**1a**−**e**, −-**c**), as well as an α-diazo-γ-lactam (**1f**) and an α-diazocyclohexanone (**1g**) were tolerated, as were ether (**1f**) and halogen (**1g**) functional groups. Interestingly, the products of cyclopropanation with six-membered ring diazo compounds (**1e** and **1g**) are formed with a sense of diastereoselectivity different from those generated from five-membered ring diazo compounds (**1a**−**1d**, **1f**). Aromatic and aliphatic substituted alkenes and alkynes successfully reacted to form cyclopropanes and cyclopropenes in good yield. The use of simple aliphatic alkenes and alkynes is noteworthy, as we have previously shown that

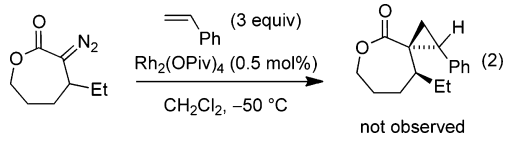
Scheme 2. Cyclopropanation/Cyclopropenation Reactions of Cyclic α-Diazocarbonyl Compounds[a]



[a](a) Yields represent isolated yields (average of two runs). (b) Stereochemical assignment was made on the basis of X-ray crystallography. (c) Stereochemical assignment was made on the basis of 1-D and 2-D NMR experiments (see the Supporting Information). (d) Reaction carried out in hexanes.

these substrates fail in reactions of acyclic α-alkyl-α-diazoesters, and only the products of β-hydride elimination are observed.[17,18] Generally, diastereocontrol was excellent (>93:7), and, in many cases, only one diastereomer was detected within the limits of ^{1}H NMR integration. Compound **1d**, which was generated from a 1,1-disubstituted alkene, was the exceptional case as it was obtained in 74% yield, but with only 2:1 diastereoselectivity. The formation of compounds **1c** and **2c** highlights the selectivity over intramolecular C−H insertion, as fused bicyclic lactone formation can be a competing reaction pathway (vide infra).

In an attempted reaction of α-diazo-β-ethylcaprolactone with styrene, a complex mixture was obtained but the product of intermolecular cyclopropanation was not observed (eq 2). The complexity of the crude reaction mixture made it difficult to quantify the amount β-elimination.



To broaden the scope of Rh-catalyzed transformations of cyclic diazocarbonyl compounds, we also explored various X−H bond insertion reactions. The results are summarized in Scheme 3. O−H insertion reactions of allyl- and ethyl alcohol (entries −-**5c**) proceed with good yield of the α-functionalized product; however, diastereoselectivity is modest. No products of olefin cyclopropanation were detected in the syntheses of **5a** and **5c** from allyl alcohol. S−H insertion reactions of ethane- and benzenethiol (entries **6a** and **6b**), as well as N−H insertion of aniline (entry **7**), also smoothly form the desired insertion products. The Si−H insertion reaction of triethylsilane with 3-diazo-4-phenyl-dihydrofuran-2-one gave **8** in both excellent yield (92%) and diastereoselectivity (>95:5). *N*-Methylindole was efficiently function-

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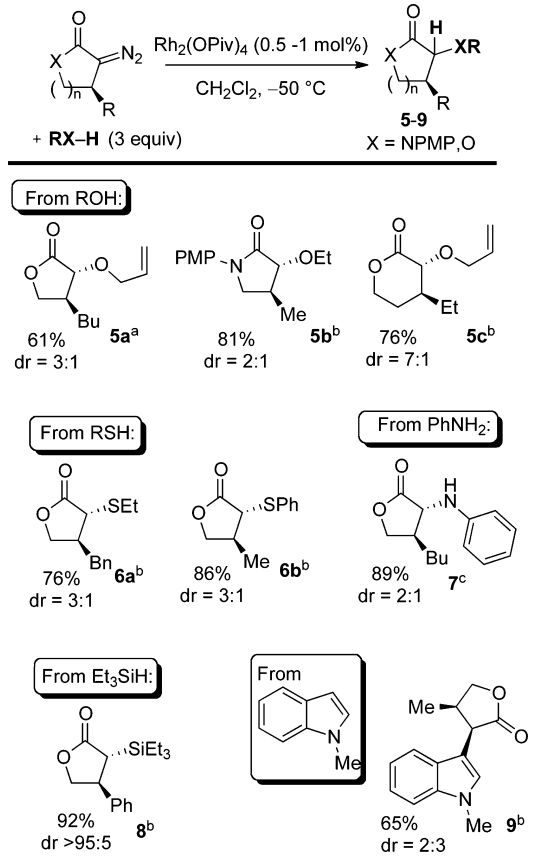
Scheme 3. X−H Insertion Reactions of Cyclic α-Diazocarbonyl Compounds[a]



[a](a) Diastereomer ratio was determined by ^{1}H NMR analysis following chromatography. (b) Diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. (c) Diastereomer ratio was determined gravimetrically following chromatography. (d) Yields represent isolated yields (average of two runs). (e) Stereochemical assignments were made on the basis of ^{1}H NMR analysis (see the Supporting Information).

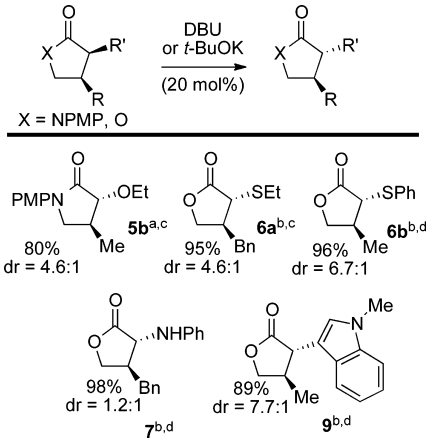
alized at C(3) to give **9** in 65% yield, but only 3:2 dr with slight preference for the *syn*-isomer.

Despite the modest diastereocontrol of a number of the insertion reactions, epimerization of the products could be performed to increase the ratio of the *anti* isomers (Scheme 4). The *syn* diastereomers of **6b** and **9**, which could be separated from their *anti* diastereomers following chromatography, were isomerized with good selectivity to their *anti*-isomers (6.7:1 for **6b** and 7.7:1 for **9**) upon treatment with DBU. The *syn* diastereomer of **7** could be equilibrated to a 1.1:1 mixture of isomers slightly favoring the *anti* product. With compounds **5b** and **6a**, which were isolated as inseparable mixtures of diastereomers, the *anti*:*syn* ratios could be enhanced to 4.6:1 in both cases upon treatment with base (*t*-BuOK for **5b**, and DBU for **6a**).

When the optimized reaction conditions were applied to the intramolecular C−H insertion reaction of 4-*n*-butyl-3-diazodihydrofuan-2-one (Scheme 5), the desired fused bicyclic lactone **10** was obtained in 73% yield, but as a 59:41 mixture of diastereomers favoring **10b**. However, with the use catalyst **4**, a more sterically hindered analogue of $Rh_2(OPiv)_4$, not only was a higher yield (84%) and higher stereoselectivity obsereved, but the stereoselectivity was reversed (89:11 favoring **10a**) as compared to the $Rh_2(OPiv)_4$-catalyzed reaction.

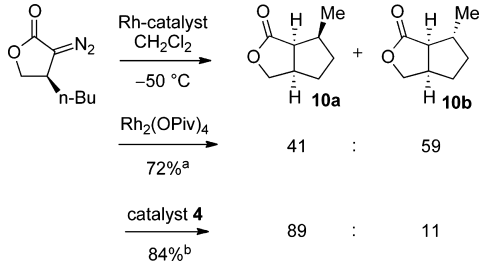
To demonstrate that the selectivity over β-hydride elimination was not simply due to the remote electron-withdrawing effect of the heteroatom or carbonyl on the diazo compound, diazo compound **11** was synthesized, an acyclic analogue of an α-diazovalerolactone that has electronic properties similar to those of the analgous cyclic compounds,

Scheme 4. Epimerization Studies[a]



[a](a) Epimerized with *t*-BuOK. (b) Epimerized with DBU. (c) Epimerization of an inseparable mixture of diastereomers. (d) Epimerization of the chromotographically separated *syn*-isomer.

Scheme 5. Catalyst Influence on Intramolecular C−H Insertion[a]

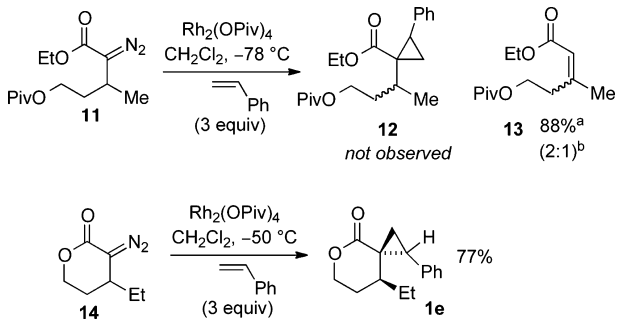


[a](a) Determined by crude ^{1}H NMR analysis using mesitylene as an internal standard. (b) Isolated yield.

but has no stereoelectronic constraints. Compound **11** was then subjected to cyclopropanation reaction conditions with a 3-fold excess of styrene catalyzed by $Rh_2(OPiv)_4$: the β-hydride elimination pathway predominated, and alkene **13** was formed in 88% yield as a 2:1 mixture of geometrical isomers; cyclopropane **12** was not detected (Scheme 6). The results of this experiment imply that the inductive deactivation of the C−H bond for migration is minimal.

Stereochemical assignments were made on the basis of X-ray crystal structures for compounds **1a**, **1e**, **1f**, and **1g**, 1-D NOE and chemical shift anisotropy for **1d**, NOESY experiments for **1b**, **1c**, **2a**, **2b**, **2c**, and

Scheme 6. Attempted Cyclopropanation of Styrene with 11, an Acyclic Analogue of an α-Diazovalerolactone 14[a]



[a](a) Determined by crude ^{1}H NMR analysis using mesitylene as an internal standard. (b) Alkene geometry not determined.

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10a, and 1-D NOE experiments for **6b**. Compounds **5a−c**, **6a**, and **7−9** were assigned by analogy to **6b**.

COMPUTATIONAL STUDIES ON CARBENE GROUND STATES

To better understand the effect of ring size on selectivity over β-hydrogen migration, computational studies were conducted. Studied were four model carbenes that would result from reaction of $Rh_2(OAc)_4$ with α-diazobutryolactone, α-diazovalerolactone, α-diazocaprolactone, and α-diazobutyric acid. With the B3LYP method and two basis sets [lanl2dz for Rh and 6-311+G(d,p) for other atoms], computations were carried out for the carbenes from α-diazobutryolactone (**16**), α-diazovalerolactone (not displayed), α-diazocaprolactone (**17**), and α-diazobutyric acid (**15**). For each carbene, conformations were considered in which the Rh−O bonds are both eclipsed and staggered relative to the Rh−C bond. The staggered conformation was lowest in energy for all of the carbenes except for **17**, where the staggered and eclipsed conformations are isoenergetic.[39]

As has been discussed previously, computations on Rh-carbenes from α-diazoesters show the ester carbonyl to be deconjugated with the electrophilic carbene.[32] Thus, the Rh−C−C−O dihedral angle is 93.9° for carbene **15** (Figure 2a). As expected, the analogous dihedral angle for butryolactone-derived carbene **17** is much smaller (>Rh−C−C═O 6.4°) due to the ring constraints of the five-membered ring (Figure 2b). However, Rh-carbenes from larger lactones distort to avoid conjugation with the lactone carbonyl. For the more flexible caprolactone **17**, the Rh−C−C═O dihedral angle (>Rh−C−C═O 78.3°) approaches that of acyclic **15**. Between these extremes is the six-membered valerolactone analogue (not displayed, see the Supporting Information), which has a Rh−C−C═O dihedral angle of 56.8°. The Rh−C bond length also increases with ring size. Thus, the five-membered lactone **16** has a short (1.941 Å) Rh═C bond, whereas the seven-membered lactone **17** has a 1.980 Å Rh═C bond, which is similar to the acyclic carbene **15**. To summarize, these computations suggest that ring constraints cause carbenes from five- and six-membered lactone to differ from the parent carbene **15** in terms of steric environment and bonding properties. However, the structure and bonding properties of the conformationally flexible caprolactone **17** are similar to those of the parent carbene **15**.

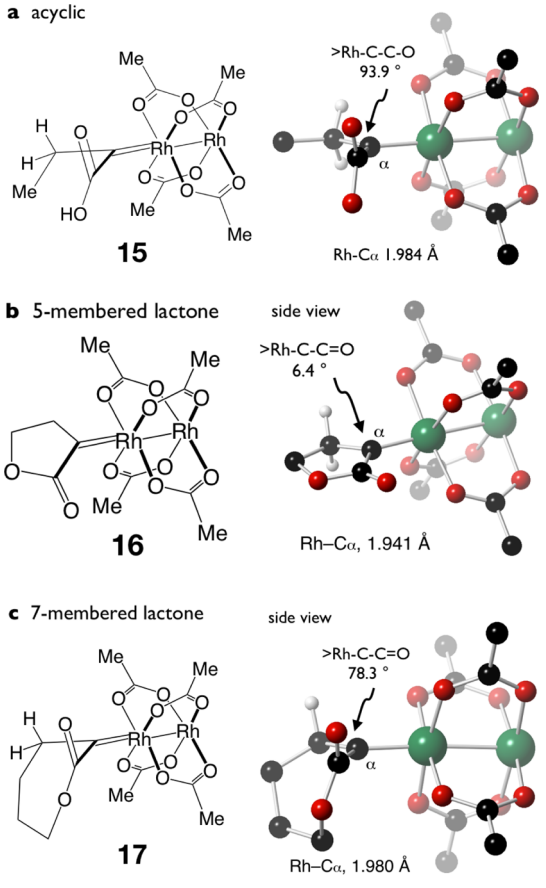

Figure 2. Computed structures of Rh-carbenes derived from $Rh_2(OAc)_4$ and (a) α-diazobutyric acid, (b) α-diazobutryolactone, and (c) α-diazocaprolactone. Also computed, but not displayed, was the analogous carbene from α-diazovalerolactone. Properties of the six-membered lactone: >Rh−C−C═O = 56.8°, Rh−Cα 1.946 Å.

TRANSITION STATE COMPUTATIONS

For each carbene described above, transition state calculations were carried out for β-hydride migration and for intermolecular cyclopropanation with ethylene. The transition state for β-hydride migration from five-membered carbene **16** is shown in Figure 3. The migration of the hydrogen from Cβ to Cα is

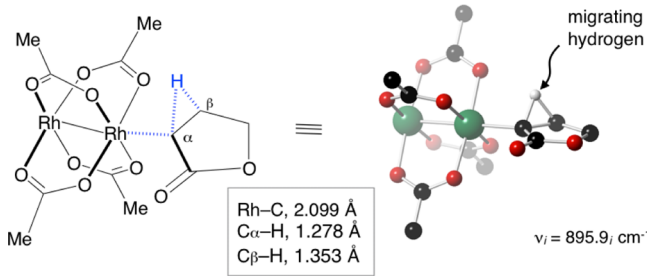

Figure 3. Transition structures for β-hydride migration from carbene **16**.

concerted but nonsynchronous with breakage of the Rh−Cα bond. Similarly, transition states for β-hydride migration were located for the acyclic carbene and the carbenes of the six- and seven-membered lactones (see the Supporting Information). For each calculation, an innocent ethylene (not shown) was included, so that energies could be compared to cyclopropanation of ethylene (Figure 4). The transition states for cyclopropanation are displayed in Figure 4. As for β-elimination, the transition state energies for cyclopropanation were calculated relative to a prereaction complex between ethylene and the carbene. Our analyses were focused on the difference between transition state energies of cyclopropanation and β-elimination from identical carbenes. Given the complexity of these systems and the different torsional considerations for differing ring sizes, quantitative comparisons of activation energies were not made between reactions of carbenes with different ring sizes.

For the carbene of the five-membered lactone (Figure 4a), the transition state barrier for cyclopropanation was lower than that for β-elimination ($\Delta\Delta E^{\ddagger}$ (ZPE) = 8.0 kcal/mol; $\Delta\Delta G^{\ddagger}$ = 4.4 kcal/mol). Similarly, for the six-membered lactone, the cyclopropanation barrier was lower than the β-elimination barrier ($\Delta\Delta E^{\ddagger}$ (ZPE) = 7.7 kcal/mol; $\Delta\Delta G^{\ddagger}$ = 4.5 kcal/mol). By contrast, for the seven-membered lactone, the activation enthalpy for cyclopropanation was only slightly lower than that for β-elimination ($\Delta\Delta E^{\ddagger}$ (ZPE) = 1.2 kcal/mol), and the free energy of activation for cyclopropanation (298 K) was higher than that for β-elimination ($\Delta\Delta G^{\ddagger}$ = 2.9 kcal/mol). The acyclic carbene (Figure 4d) was very similar to the seven-membered lactone. Thus, the activation enthalpy for cyclopropanation was only slightly lower than that for β-hydride migration ($\Delta\Delta E^{\ddagger}$ (ZPE) = 0.7 kcal/mol), and the free energy of activation for cyclopropanation (298 K) was higher than that for β-elimination ($\Delta\Delta G^{\ddagger}$ = 2.0 kcal/mol). Another similarity between the

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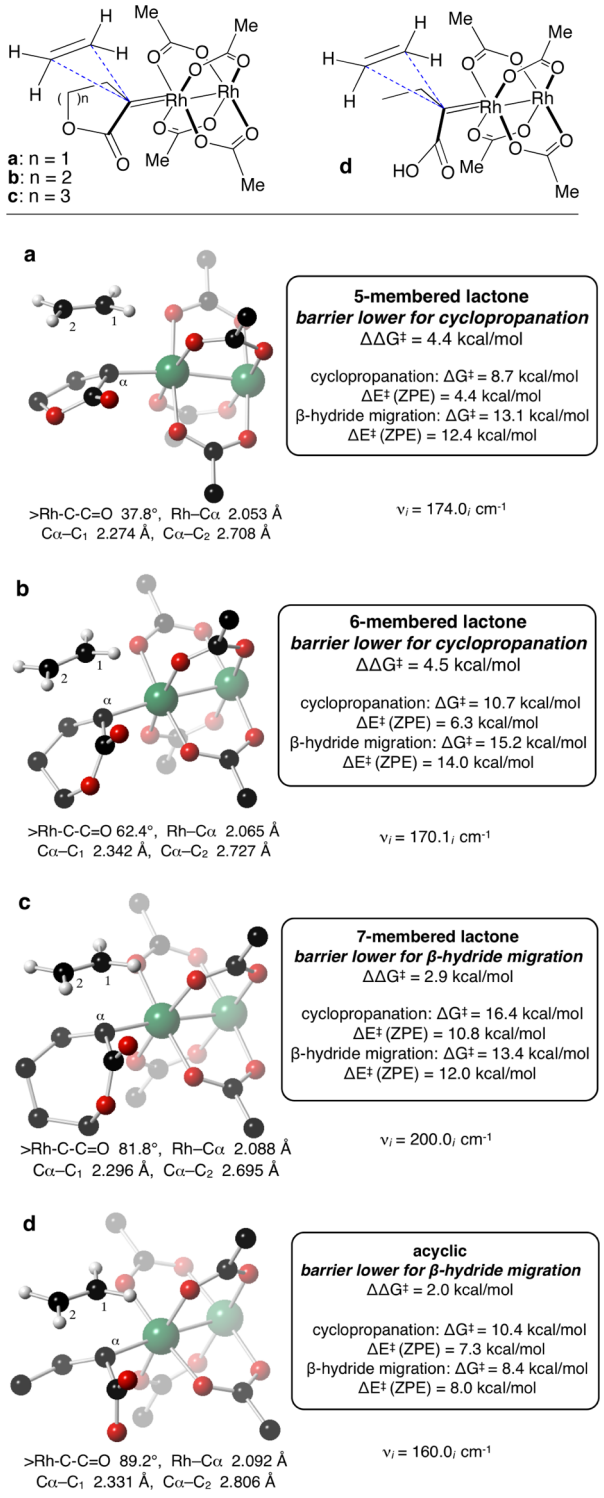

Figure 4. Transition structures for cyclopropanation by ethylene with carbenes derived from $Rh_2(OAc)_4$ and (a) α-diazobutryolactone, (b) α-diazovalerolactone, (c) α-diazocaprolactone, and (d) α-diazobutyric acid.

transition states for the seven-membered lactone (Figure 4c) and the acyclic carbene (Figure 3d) lies in their large Rh−C−C═O dihedral angles of 81.8° and 89.2°, respectively. By contrast, the analogous dihedral angles for the five- and six-membered lactones are considerably smaller (37.8° and 62.4°, respectively). Thus, we believe that these computations agree with the model set forth in Figure 1, which predicted that a repulsive interaction between the carbonyl and alkene would be significant for carbenes from α-diazoesters, but ameliorated for carbenes from α-diazobutyrolactones or α-diazovalerolactones. As for the acyclic carbenes, the computations demonstrate that the conformational flexibility of the seven-membered ring allows the carbonyl to be oriented perpendicular to Rh-carbene. The significant intermolecular interaction between the carbonyl and approaching substrate is in agreement with the poor ability of α-diazo-β-ethylcaprolactone to participate in intermolecular cyclopropanation reactions (eq 2).

MODEL FOR DIASTEREOSELECTIVITY

Interestingly, the cyclopropanation reactions of monosubstituted alkenes with α-diazobutyrolactones and α-diazovalerolactones lead to cyclopropanes with opposing senses of diastereoselectivity. With α-diazobutyrolactones, products are formed in which the carbonyl and cyclopropane substituents are *syn*, whereas α-diazovalerolactones lead to *anti*-products. We propose that the difference in the sense of diastereoselectivity in cyclopropanation reactions of five- versus six-membered ring diazo compounds is related to ring constraints. It has been proposed that the high *syn*-selectivity in cyclopropanation reactions with acyclic α-diazocarbonyl compounds is partially a result of steric hindrance of the ester group,[32] which adopts an orthogonal orientation with respect to the carbene, thus disfavoring alkene approach over the ester. In carbenoids derived from five-membered ring diazo compounds, ring constraints prevent the carbonyl from achieving an orthogonal orientation, leaving approach of the alkene over the carbonyl relatively unhindered and resulting in formation of the *syn*-diastereomer (Figure 5a). However, with

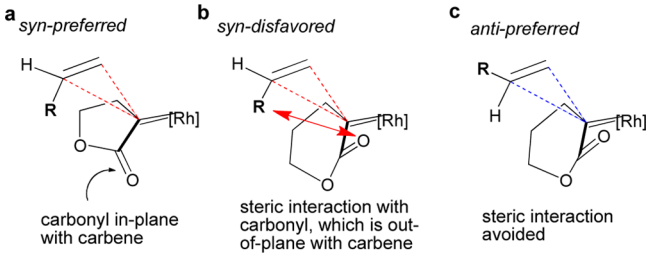

Figure 5. Model for diastereoselectivity with carbenes derived from (a) α-diazobutyrolactones and (b,c) α-diazovalerolactones.

carbenoids derived from six-membered ring diazo compounds, the larger ring size can allow the carbonyl to be oriented further out of coplanarity with the carbene, and the steric influence of the carbonyl likely becomes significant (Figure 5b). Thus, the preferred approach of a substituted alkene in reactions of six-membered ring carbenoids is *anti* to the carbonyl (Figure 5c), and on the face of the carbenoid opposite the bulky β-substituent.

CONCLUSIONS

In summary, we have developed various intermolecular reactions of cyclic α-diazocarbonyl compounds that display chemoselectivity over β-hydride migration. Intermolecular cyclopropanation, cyclopropenation, indole C−H functionalization, O−H−, N−H−, S−H−, and Si−H insertion reactions, as well intramolecular C−H insertion reactions are broadly successful. Previously, reports of intermolecular reactions of α-diazocarbonyl compounds with β-substitution were rare and described only in cases where the β-hydride migration product would be highly strained. On the basis of computational models, we

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proposed that the orientation of the carbonyl relative to the carbene influences the rate of intermolecular reactivity relative to intramolecular β-hydride migration. For Rh-carbenes derived from acyclic diazoesters, it is calculated that the π-systems of the carbene and ester carbonyl are perpendicular, and we proposed that the intermolecular approach of substrates to carbenes from acyclic diazo precursors is relatively slow due to a steric interaction with the ester function. For carbenes derived from five- and six-membered cyclic α-diazocarbonyls, computations suggest the carbene is constrained to be more conjugated with the carbonyl, thereby relieving the steric interaction for intermolecular reactions. As for the acyclic carbenes, the computations demonstrate that the conformational flexibility of the seven-membered ring allows the carbonyl to be oriented perpendicular to Rh-carbene. The significant intermolecular interaction between the carbonyl and approaching substrate is in agreement with the poor ability of α-diazo-β-ethylcaprolactone to participate in intermolecular cyclopropanation reactions.

EXPERIMENTAL SECTION

Representative Procedure for Cyclopropanation: Synthesis of 3α-(2α-Phenylcyclopropyl)-4α-methyldihydrofuran-2-one (1a). A flame-dried round-bottomed flask was charged with 1.5 mg (0.003 mmol) of $Rh_2(OPiv)_4$, and the flask was evacuated and filled with nitrogen. Anhydrous CH_2Cl_2 (3.5 mL) was added followed by 0.17 mL (1.5 mmol) of styrene, and the flask was cooled in a −50 °C bath. 3-Diazo-4-methyl-dihydrofuran-2-one 62 mg (0.49 mmol) was dissolved in 1.5 mL of anhydrous CH_2Cl_2 and added to the reaction mixture via a syringe pump over 1 h. Following addition, the reaction mixture was allowed to warm to room temperature, and 1 equiv of mesitylene (NMR standard) was added and a crude ^{1}H NMR spectrum was taken to estimate the yield and dr. The solvent was subsequently removed, and the residue was chromatographed on silica gel to give 78 mg (0.39 mmol, 80%) of the title compound as a white solid, mp 73−75 °C. The purity was measured to be >95% by ^{1}H NMR. The diastereomer ratio was measured to be 95:5 by integration of the methyl resonances in the crude ^{1}H NMR spectrum. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.33−7.25 (m, 2H), 7.25−7.19 (m, 3H), 4.54 (dd, J = 7.8 Hz, 8.8 Hz, 1H), 3.89 (app t, J = 9.2 Hz, 1H), 2.82−2.67 (m, 2H), 1.95 (dd, J = 7.8 Hz, 5.3 Hz, 1H), 1.38 (dd, J = 9.2 Hz, 5.2 Hz, 1H), 1.10 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 176.1 (u), 135.2 (u), 129.1 (dn), 128.1 (dn), 127.0 (dn), 72.5 (u), 34.6 (dn), 32.4 (u), 28.6 (dn), 15.6 (u), 14.4 (dn). IR ($CHCl_3$, cm^{-1}): 3028, 2968, 1770, 1458, 1389, 1343, 1246, 1103, 1014, 726, 697. HRMS-CI (NH_3) m/z: [M + H], calcd for $C_{13}H_{15}O_2$, 203.1072; found, 203.1072.

ASSOCIATED CONTENT

Supporting Information

Full experimental and computational details, ^{1}H and ^{13}C NMR spectra, stereochemical assignments, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(37) The diazo compounds used in this study did not react at −78 °C with the dirhodium catalysts that were screened.

(38) There are known limitations to the methods described herein. Reactions of α-diazo-β-isopropylbutyrolactone, α-diazo-β-ethylcaprolactone, and α-diazo-β-ethyl-*N*-(paramethoxyphenyl)-valerolactam with styrene did not give cyclopropanes and led to β-hydride elimination and a complex reaction mixture. Attempted intermolecular C−H insertion reactions with 1,4-cyclohexadiene, 1,3-dioxolane, or triethyl orthoformate led only to β-hydride elimination. An attempted N−H insertion with allyl amine gave no reaction at −50 °C or at room temperature. The reaction with α-diazo-β-phenylbutyrolactone and trimethylsilyl acetylene gave the cyclopropene in only 15% yield, and the product of β-hydride elimination in 61% yield. An attempt was made to bias the diastereoselectivity of the cyclopropanation reaction between styrene and enantioenriched 4-butyl-3-diazodihydrofuran-2-one (prepared in 90% ee) with both Rh_2(*S*-PTTL)$_4$ and Rh_2(*R*-PTTL)$_4$. However, in both cases, yield and diastereoselectivity cyclopropane **1c** were modest (34% yield with 68:32 dr for Rh_2(*S*-PTTL)$_4$ and 14% with 76:24 dr for Rh_2(*R*-PTTL)$_4$), while intramolecular C−H insertion predominated.

(39) For **15**, the staggered (bisected) conformation was more stable than the eclipsed conformation by 0.7 kcal/mol. For **16** and the carbene from α-diazocaprolactone, only the staggered conformation was found as a minimum. For **17**, the eclipsed and staggered conformations are isoenergetic.