Site- and Enantiocontrol in Intramolecular C-H Insertion Reactions of α-Diazo Carbonyl Compounds Catalyzed by Dirhodium(II) Carboxylates

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Abstract: The full potential of rhodium(II)-catalyzed intramolecular C-H insertion reactions of α-diazo carbonyl compounds as a powerful tool for the construction of both carbocycles and heterocycles has been developed by variation of the bridging ligands of the dirhodium(II) catalysts: (1) Dirhodium(II) tetrakis(triphenylacetate) featured by the steric bulk of the bridging ligands on the rhodium has been demonstrated to exhibit an exceptionally high order of selectivity for C-H insertion into methylene over methine on a cycloalkane ring as well as for aromatic substitution over aliphatic C-H insertion. (2) Dirhodium(II) complexes incorporating N-phthaloyl-(S)-amino acids as bridging ligands have proven to be the chiral catalysts of choice for allowing high levels of differentiation of enantiotopic methylene C-H bonds and enantiotopic benzene rings, affording optically active cyclopentanone, 2-azetidinone, and 2-indanone derivatives in up to 80%, 96%, and 98% ee, respectively.

1. Introduction

The development of catalytic asymmetric C-C bond forming reactions mediated by chiral metal complexes is one of the most important and challenging goals in organic synthesis (ref. 1). In this respect, dirhodium(II) tetraacetate, Rh₂(OAc)₄, may be regarded as one of the promising prototypical catalysts, because Rh₂(OAc)₄-catalyzed transformations of α-diazo carbonyl compounds include cyclopropanation, C-H insertion, rearrangement or cycloaddition via ylide generation, and aromatic cycloaddition to form a C-C bond with simultaneous creation of a stereogenic center (ref. 2). While a rhodium(II) carbene has not yet been detected by spectroscopic analyses, the accumulated experimental results afford sufficient evidence for this species as the reactive intermediate in rhodium(II)-mediated decomposition of α-diazo carbonyl compounds. Besides, the acetate ligands can be varied to other carboxylates, carboxamidates, sulfates, or phosphates by ligand exchange with the acidic reagents, of which dirhodium(II) complexes are thermally stable and air stable (ref. 3). Thus, the development of the enantioselective version of these reactions catalyzed by chiral dirhodium(II) complexes should be a significant addition to the field of asymmetric synthesis.

Dirhodium(II) complex-catalyzed intramolecular C-H insertion reaction of α-diazo carbonyl compounds, featured by C-C bond formation at an unactivated carbon atom, is currently emerging as a potentially powerful tool for the construction of both carbocycles, especially cyclopentanones, and heterocycles (ref. 4, 5). However, lack of site-selectivity, the Achilles heel of this reaction, not only appears to preclude its application to the synthesis of complex organic molecules but also has presented a serious obstacle to the development of the enantioselective version of this reaction, aside from the design of the chiral dirhodium(II) catalyst. In this account, we will describe the results of our efforts directed toward the site- and enantiocontrol by variation of the dirhodium(II) carboxylate ligands.

2. Site-Control in Intramolecular C-H Insertion Reaction

It is well documented that Rh₂(OAc)₄-catalyzed C-H insertion reaction of α-diazo carbonyl compounds leads to the preferential formation of five-membered rings in an acyclic, conformationally mobile system, where the order of reactivity of the target C-H site is methine > methylene >> methyl (ref. 6). However, there have recently been reported a number of examples of C-H insertions leading to...
four- and six-membered rings as well as facile insertion into a methyl C-H bond in a constrained rigid system (ref. 7) and even in an acyclic system (ref. 8-10). Apart from the order of reactivity of the target site governed by the electron density of the C-H bond, it has thus been disclosed that the site-selectivity is also governed by conformational factors as well as steric factors, depending on the type of α-diazo carbonyl compounds (ref. 5, 6, 10). Given that site-control based on modification of the substrate by fine-tuning the above factors is possible, the realization of the control based on the variation of the bridging ligands of the rhodium(II) catalysts should make this reaction of wider applicability.

Because of its electrophilic character, a rhodium(II) carbene is often regarded as a rhodium-bound carbocation stabilized by electron donation from rhodium with a low or negligible barrier to rotation (Figure 1) (ref. 2e, 11). Assuming that the electrophilicity of rhodium(II) carbenes is the principal determinant of the reaction selectivity as well as their reactivities, competitive carbene transformations might be controlled by changing the electron density at the rhodium center. In this context, two types of dirhodium(II) complexes with different electronic influences of their ligands on the rhodium(II) center relative to Rh2(OAc)4 have recently been developed and evaluated by Doyle and Padwa (ref. 3c, 9, 12).

One type includes dirhodium(II) tetrakis(trifluoroacetate), Rh2(tfa)4, and dirhodium(II) tetrakis(perfluorobutyrate), Rh2(pfb)4, featured by more electron-withdrawing ligands, and the other type is a dirhodium(II) carboxamidate complex such as dirhodium(II) tetraacetamidate, Rh2(acam)4, or dirhodium(II) tetraacaprolactamate, Rh2(cap)4, with decreased electron-withdrawing ligands. In a systematic study of competitive rhodium(II) carbene reactions, they have found that the highly electrophilic rhodium(II) carbenes generated with the former catalyst exhibit the highest selectivity for aromatic substitution, whereas the weakly electrophilic rhodium(II) carbenes generated with the latter catalyst exhibit the highest selectivity for cyclopropanation (ref. 12). While decreased electron withdrawal by the ligands (tfa, pfb > OAc > acam, cap) has been demonstrated to display a tendency to enhance the selectivity for insertion into the more electron-rich C-H bond (ref. 9), there is great room for improvement of site-control based on the catalyst in intramolecular C-H insertion reactions. From a different viewpoint, steric influences of the ligands on the rhodium(II) center may lead to a solution to this problem.

2.1. Emergence of Dirhodium(II) Tetrakis(triphenylacetate)

Our interest in intramolecular C-H insertion reactions has originated from the synthetic approach to isocarbacyclin [(+)-9(O)-methano-Δ9(9α)-prostaglandin 1] (1), in phase III clinical trials as an antithrombotic agent, in which one of the key steps was the construction of a bicyclo[3.3.0]octane skeleton via rhodium(II)-catalyzed C-H insertion process (ref. 13). For a related transformation, Cane already reported that the insertion reaction of α-diazo β-keto ester 2 catalyzed by Rh2(OAc)4 into the C-H bond on a cyclopentane ring led to the formation of the bicyclic compound 3 and the spirocyclic compound 4 in a ratio of 59:41 (ref. 7a). In spite of the disappointing precedent, we explored this key
C-H insertion reaction, since the feasibility was considered to rely on the judicious choice of reaction parameters. Indeed, we found that Rh$_2$(OAc)$_4$-catalyzed C-H insertion of the ethylene acetal 5a produced a mixture of the desired bicyclic compound 6a and the spirocyclic compound 7a in a ratio of 37:63, whereas the catalytic decomposition of the acetals 5b of (+)-2,3-butanediol led to the exclusive formation of 6b (ref. 13a). Considering that the methine C-H insertion to form the spirocyclic compounds is electronically more favored but sterically less favored than the methylene C-H insertion to form the bicyclic compounds, these results might be accounted for by the difference in steric repulsion between the acetal moieties and the wall constructed from the acetate ligands; the steric repulsion overrides the electronic effects in cyclization of 5b with a methyl substituent on the acetal moiety as shown in Figure 2. We then reasoned that, if this assumption was correct, similar site-control could be attained by employing bulky bridging ligands relative to the acetates projecting toward the rhodium(II) carbene center. To this end, we chose dirhodium(II) tetrakis(triphenylacetate), Rh$_2$(TPA)$_4$, featured by the steric bulk of the bridging ligand on the rhodium. Indeed, we were gratified to observe that Rh$_2$(TPA)$_4$-catalyzed cyclization of 5a led to the preferential formation of 6a via the methylene C-H insertion (ref. 14). Furthermore, Rh$_2$(TPA)$_4$-catalyzed C-H insertions of 5b,c led to the exclusive formation of the bicyclic β-keto esters 6b,c. In particular, the result with 5c makes our convergent synthesis of isocarbacyclin and its analogues more efficient and practical (ref. 15). It is also worthy of note that Rh$_2$(TPA)$_4$ exhibits the virtually complete selectivity for insertion into the methylene C-H bond even with Cane's substrate 2 (ref. 14).
2.2. Scope and Potential of Dirhodium(II) Tetrakis(triphenylacetate)

In order to further demonstrate the latent ability of Rh\(_2\)(TPA)\(_4\), several sets of competitive intramolecular C-H insertion reactions were performed with Rh\(_2\)(OAc)\(_4\), Rh\(_2\)(tfa)\(_4\), and Rh\(_2\)(acam)\(_4\) as well as with Rh\(_2\)(TPA)\(_4\). Some selected examples focusing on the scope and potential of Rh\(_2\)(TPA)\(_4\) are presented here.

The clear superiority of Rh\(_2\)(TPA)\(_4\) in insertion into the methylene C-H bond over any other type of dirhodium(II) catalyst was demonstrated by cyclization of our original substrate 5a (Table 1). While Rh\(_2\)(tfa)\(_4\) produced nearly equal amounts of products 6a and 7a, Rh\(_2\)(acam)\(_4\) was found to favor predominantly the C-H insertion into the methine over the methylene due to the electronically discriminating ability. Hence, Rh\(_2\)(TPA)\(_4\) and Rh\(_2\)(acam)\(_4\) can be complementary to each other for the site-selective C-H insertion reactions. The selectivities obtained by the use of dirhodium(II) tetrakis(diphenylacetate) and dirhodium(II) tetrakis(2,2-diphenylpropionate) with the electronic similarities were found to be modest, confirming that the exceptional bulk of the bridging triphenylacetate ligands on the rhodium is responsible for the remarkably high order of bicycloselectivity. The positive proof of this has recently been provided by the X-ray crystal structure of Rh\(_2\)(TPA)\(_4\), which demonstrates that the four phenyl groups from triphenylacetate ligands are oriented to an axial coordination site of each octahedral rhodium as shown in Figure 3. Accordingly, the four protruding phenyl groups are thought to give priority to the approach of the sterically less hindered methylene C-H bond over that of the methine C-H bond to the rhodium(II) carbene center.

In this regard, the following examples are particularly worthy of note. In cyclization of \(\alpha\)-diazo \(\beta\)-keto ester 10, Rh\(_2\)(TPA)\(_4\) showed the exceedingly high selectivity for the insertion into an electronically unfavorable methyl C-H bond, whereas Rh\(_2\)(OAc)\(_4\) favored the insertion into the benzylic methylene C-H bond in spite of the effect of steric bulk near the insertion site (ref. 16). The effectiveness of Rh\(_2\)(TPA)\(_4\) was further displayed by the competitive methylene C-H insertions with \(\alpha\)-diazo \(\beta\)-keto ester 13. Rh\(_2\)(TPA)\(_4\)-catalyzed cyclization of 13 led to the exclusive formation of 14, the key intermediate for the synthesis of benzene-annulated carbocyclic analogues of PGI\(_2\), via a preferential insertion into the C-H bond distal to the tert-butylidiphenylsilyloxyethyl group (ref. 17), whereas only modest selectivity was observed with Rh\(_2\)(OAc)\(_4\).

Site-control in the construction of 2-azetidinones via C-H insertion process has remained one of the challenging problems. It is well documented that site-selectivities in rhodium(II)-catalyzed C-H

<table>
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<tr>
<th>Rh(II) catalyst on site-selectivity</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>Rh(_2)(acam)(_4)</td>
<td>64:36</td>
</tr>
<tr>
<td>Rh(_2)(OCCMePh(_2))(_4)</td>
<td>82:18</td>
</tr>
<tr>
<td>Rh(_2)(TPA)(_4)</td>
<td>96:4</td>
</tr>
</tbody>
</table>

Table 1. Influence of Rh(II) catalyst on site-selectivity
insertion reaction of α-diazo amides are highly dependent on the α-substituents of the diazo carbon as well as N-substituents (ref. 5, 10). In this context, installation of bulky groups such as a tert-butyl or neopentyl group as the N-substituent in α-diazo amides, which are placed syn to the sterically less demanding amide carbonyl group, is essential for providing a conformational bias for the smooth cyclization onto the other N-alkyl substituents. Thus, we explored the feasibility of this process by catalyst variation with N-tert-butyl-N-propyl-α-diazoacetamide 16a and its analogues 16b and 16c bearing different α-substituents (ref. 18). While cyclization of α-diazoacetamide 16a with Rh₂(TPA)₄ produced 2-pyrrolidone 18a exclusively as was the case with the other catalysts used, catalyses of α-diazoacetoacetamide 16b resulted in the formation of an approximately equal mixture of 2-azetidinone 17b and 2-pyrrolidone 18b in all cases except for Rh₂(acam)₄ (17b:18b = 25:75). However, the superiority of Rh₂(TPA)₄ over any other catalyst was demonstrated by cyclization of α-methoxycarbonyl-α-diazoacetamide 16c to form 2-azetidinone 17c with 3,4-cis relationship as the sole product (vide infra).

Another interesting and synthetically useful feature of this catalyst was introduced by cyclization of α-diazo β-keto ester 19a,b, in which aromatic substitution and aliphatic C-H insertion were possible. Of a variety of dirhodium(II) catalysts screened, Rh₂(TPA)₄ proved to be the only catalyst for allowing an exceptionally high order of selectivity for aromatic substitution over aliphatic C-H insertion (ref. 19).

While the precise mechanism remains presently unclear, aromatic substitution is thought to proceed via an electrophilic addition of the rhodium(II) carbene carbon to the aromatic ring followed by a 1,2-hydride shift with a concurrent dissociation of the rhodium (II) catalyst and subsequent aromatization rather than via a direct C-H insertion mechanism (Figure 4) (ref. 12, 20). This mechanistic hypothesis explains why Rh₂(TPA)₄ retards the aliphatic C-H insertion to favor predominantly the aromatic C-H insertion, because aromatic substitution is presumed to be less sensitive to nonbonding interactions relative to aliphatic C-H insertion. In this regard, it is of particular interest to mention that Padwa and Doyle recently reported that aromatic substitution was the exclusive transformation in reaction of the corresponding α-diazo ketone 19c with Rh₂(pfb)₄ (ref. 12). Since cyclization of 19c with Rh₂(TPA)₄ was also found to produce 20c exclusively, the rationale for this apparent anomaly could be attributed to the steric bulk of the ligand with Rh₂(TPA)₄ as well as to electronic preference for aromatic substitution with Rh₂(pfb)₄.

Figure 4. Mechanistic hypothesis for rhodium(II)-catalyzed aromatic substitution reactions

![Mechanism Diagram](image-url)
3. Enantiocontrol in Intramolecular C-H Insertion Reaction

The above findings that the steric bulk of the bridging triphenylacetate ligands on the rhodium dramatically influenced site-selectivity in C-H insertion reaction provided a great incentive to the development of the enantioselective version of this reaction catalyzed by chiral dirhodium(II) carboxylates. One of the most crucial problems is the creation of an effective chiral environment around the rhodium(II) carbene center, because fixation of the chiral center α to the carbene center is impossible, and the chiral center is far away from the carbene center. Recently, Doyle resolved this problem by devising a special class of chiral dirhodium(II) carboxamidates such as dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(S)-carboxylate], Rh₂(5S-MEPM)₄, and dirhodium(II) tetrakis[methyl 2-oxazolidinone-4(S)-carboxylate], Rh₂(4S-MEOX)₄, which provide a position of the chiral center in close proximity to the rhodium(II) carbene center, thereby exhibiting an exceptionally high order of enantioselection in cyclopropanations (ref. 21). However, their salient ability in C-H insertions has been limited to the enantioselective construction of heterocycles, inter alia, γ-lactones and 2-azetidinones, thus leaving the enantioselective construction of carbocycles unsettled.

3.1. Emergence of Dirhodium(II) Tetrakis[ N-phthaloyl-(S)-phenylalaninate] and Enantioselective Construction of 3-Substituted Cyclopentanones

At the outset, we screened a range of chiral dirhodium(II) carboxylates for asymmetric induction through cyclization of α-diazo β-keto methyl ester 22a bearing a phenyl group adjacent to the target C-H bond. The sense and extent of the enantiotopic selection at the insertion site were determined by transformation of the cyclic β-keto ester 23a to the known 3-phenylcyclopentanone (24). As might be expected, chiral dirhodium(II) carboxylates prepared from Rh₂(OAc)₄ by ligand exchange with a variety of chiral α-alkyl or α-hydroxy carboxylic acids showed enantioselectivities of less than 15%, which were comparable to those reported by McKervey (ref. 22a), Brunner and Doyle (ref. 23) for a related transformation with the use of dirhodium(II) tetrakis[N-benzenesulfonyl-(S)-prolinate], McKervey's catalyst (ref. 22), and dirhodium(II) tetrakis[4(S)-benzyl-2-oxazolidinone], Rh₂(4S-BNOX)₄, respectively. To our surprise, however, dirhodium(II) carboxylates derived from chiral N-phthaloyl amino acids were found to exhibit much better enantioselectivities (40-46% ee), little variation being observed with several kinds of amino acids such as alanine, valine, phenylalanine, and tert-leucine (ref. 24, 25).

Of these catalysts, we chose the most readily prepared dirhodium(II) tetrakis[N-phthaloyl-(S)-phenylalaninate], Rh₂(S-PTPA)₄, as a chiral catalyst, and explored the factors of this cyclization that influence the enantioselectivity (ref. 26). The enantioselectivities were found to diminish with the corresponding α-diazo ketone and α-diazo β-keto sulfone, and cyclization of the α-diazo α-acetyl ketone gave a complex mixture of products. While the ester moiety such as methyl, ethyl, isopropyl, or tert-butyl esters showed little influence on the enantioselectivity (38-46% ee) (Table 2), we were surprised to
find that cyclization of \( \alpha \)-diazo \( \beta \)-keto esters 22e-g of neopentyl alcohol, cyclohexanol, and 3-pentanol, less hindered alcohols than \( \text{tert} \)-butyl alcohol, exhibited higher enantioselectivities (56-62% ee). After further evaluation of the alkoxy group of the ester moiety, the enantioselectivities were found to be greatly enhanced up to 76% ee by successive substitution of 3-pentanol with methyl groups, which demonstrated that the steric shielding at both positions \( \beta \) and \( \beta' \) to the alkoxy oxygen atom was crucial to the high enantioselectivity. We assessed the 2,4-dimethyl-3-pentyl ester as the ester of choice from the standpoint of cyclization yield and practicality, and further explored the effects of the substituents adjacent to the target C-H bond on the enantioselectivity. Phenyl or vinyl groups at the insertion site were found to exhibit much higher selectivities than methyl or penty1 groups (76% and 53% ee vs. 32% and 35% ee). It is documented that phenyl and vinyl groups are inductively electron-drawing and so decrease the electron density of the adjacent C-H bond, rendering it resistant to attack by the electrophilic rhodium(II)-carbene species (ref. 6, 9). Thus, we reasoned that if a decreased rate at the C-H insertion step might be associated with an enhancement of the selectivity, much higher enantioselectivity could be achieved by appending the electron-drawing substituents to these groups. Cyclization of \( \alpha \)-diazo \( \beta \)-keto 2,4-dimethyl-3-pentyl esters 25 possessing substituted phenyl or vinyl groups at the insertion site showed that the substituent effects on enhancement of the enantioselectivity were even more pronounced with the vinyl group than with the phenyl group, though 80% ee could be achieved with both of the (E)-conjugated ester and \( p \)-trifluoromethanesulfonyloxyphenyl groups (ref. 27).

Table 2. Effect of ester moieties on enantioselectivity

<table>
<thead>
<tr>
<th>Substrate R</th>
<th>Yield (^a ) of 23 (^b ) ee of 24 (^a )</th>
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<tbody>
<tr>
<td>22a Me</td>
<td>96</td>
</tr>
<tr>
<td>22b Et</td>
<td>87</td>
</tr>
<tr>
<td>22c Pr (^f )</td>
<td>69</td>
</tr>
<tr>
<td>22d Bu (^f )</td>
<td>60</td>
</tr>
<tr>
<td>22e CH(_2)Bu (^f )</td>
<td>71</td>
</tr>
<tr>
<td>22f ( \alpha )C(_6)H(_4)</td>
<td>91</td>
</tr>
<tr>
<td>22g CH(_2)Et (_2)</td>
<td>86</td>
</tr>
<tr>
<td>22h CH(_2)Pr (_2) (_f )</td>
<td>86</td>
</tr>
<tr>
<td>22i CMePr (_2) (_f )</td>
<td>57</td>
</tr>
<tr>
<td>22j CHBu (_2) (_f )</td>
<td>68</td>
</tr>
</tbody>
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\(^a \) The values in per cent.

The fact that the enantioselectivity in Rh\(_2\)(S-PTPA)\(_4\)-catalyzed intramolecular C-H insertion reactions can be improved up to 80% ee, though evaluation of both steric and electronic factors imparted on the substrate is crucial, suggests that a rigid chiral environment around the rhodium(II) carbene center may be created. After great difficulty in making a single-crystal of this catalyst, its structure was established as the bis(4-tert-butylpyridine) adduct by X-ray structural analysis (Figure 5). The notable feature is that two phthalimido groups in a pair of adjoining ligands are oriented to an axial coordination site of each octahedral rhodium. Construction of the two phthalimido walls protruding toward the

Figure 5. Crystal structure of bis(4-tert-butylpyridine) adduct of Rh\(_2\)(S-PTPA)\(_4\)
rhodium(II) carbene center not only explains the significance of N-phthaloyl protection but also provides a clue to answer why the enantioselectivity of up to 80% could be attained without any fixation of the chiral center α to the carboxylate.

Little is known about the mechanism of rhodium(II)-catalyzed C-H insertion reactions. Two different working models have been proposed originally by Taber (ref. 6) and later by Doyle (ref. 9). The former involves a cleavage of bridging of two ligands as well as the Rh-Rh bond to generate the rhodium(I)-carbene species, to which the oxidative addition of the target C-H bond is assumed to occur. The latter is featured by a three-centered transition state via overlap of the empty carbon p-orbital of the rhodium(II)-carbene with the σ-orbital of the target C-H bond, in which C-C and C-H bond formation proceeds as the ligated metal dissociates. Doyle’s model seems more persuasive to explain the high degree of enantioselectivity, in that the integrity of the ligands on the dirhodium framework remains intact during the insertion process. While we have briefly touched on the importance of the orientation of the target C-H bond in parallel with the rhodium(II)-carbene bond (ref. 28), Taber has quite recently proposed a computational model patterned after Doyle’s model, which additionally requires that the rhodium(II)-carbene bond is aligned with the target C-H bond in a transition state formed via rapid and reversible complexation of a three-centered, two-electron bond (Figure 6) (ref. 29). It is of interest to note that this model not only explains the retention of configuration at the target C-H bond but also predicts the relative configuration of the product.

Based on the Doyle-Taber model, we may explain the stereochemical outcome in the present reaction, provided that the solid state structure of Rh₂(S-PTPA)₄ is available in solution. Looking down into the Rh-Rh axis, the chiral environment around the rhodium(II) center can be divided into four quadrants, of which two are occupied by the protruding phthalimido walls (Figure 5). In consequence, two putative rhodium(II) carbene intermediates 27 and 28 can be presented (Figure 7), in which both the ester group and the carbon chain undergoing C-H insertion are accommodated in a less crowded space. In both of the intermediates, the reacting C-H bond is oriented toward the rhodium center and in parallel with the rhodium(II) carbene bond, in which the substituent at the insertion site is extended outward to avoid its intrusion into the face of the rhodium(II) carbene complex. Upon cyclization, the reactive intermediate 27 is favored over the reactive intermediate 28 owing to the steric repulsion between the tethered methylene-chain and the phthalimido group in 28, leading to the predominant formation of the 2,3-trans-cyclopentanone in accord with the observed enantioselection via enolization of the initially formed cis-isomer. Enhancement of the enantioselectivity with an increase in the steric bulk of the ester alkyl group suggests that the fourth quadrant provides sufficient space for the bulky ester group relative to the first quadrant, thus the intermediate 27 being preferred over 28. With respect to the substituent effects, we suppose that electron withdrawal from the target C-H by the substituents may lead to a later transition state and greater selectivity, whereas electron donation by alkyl groups may lead to an earlier transition state and lower selectivity.

**Figure 6.** Doyle-Taber model for rhodium(II)-catalyzed C-H insertion mechanism

**Figure 7.** Putative rhodium(II) carbene intermediates leading to 3-substituted cyclopentanones
3.2. Enantioselective Construction of 2-Azetidinones

To further evaluate the chiral environment around the rhodium(II) center, we next explored Rh$_2$(S-PTPA)$_4$-catalyzed cyclization of N-alkyl-N-tert-butyl-$\alpha$-methoxycarbonyl-$\alpha$-diazoacetamides 29, which proved to be the substrate of choice for site- and diastereoselective construction of 3,4-cis-2-azetidinones when Rh$_2$(TPA)$_4$ was used as an achiral catalyst (vide supra). Rh$_2$(S-PTPA)$_4$ was found to cyclize 29 to afford the 2-azetidinones 30 with 3,4-cis relationship in enantioselectivities (56-84% ee) comparable with the highest values known to date for a related transformation (ref. 28). Virtually complete site-selectivities observed here suggest that Rh$_2$(S-PTPA)$_4$ is fairly similar to Rh$_2$(TPA)$_4$ in terms of electronic and steric demands. We can now explain the 3,4-cis diastereoselectivity based on the Doyle-Taber model, in which the conformer 31 leading to the 3,4-cis stereoisomer is favored over the conformer 32 to give the 3,4-trans stereoisomer because of the severe steric repulsion between the carbon chain undergoing C-H insertion and N-tert-butyl group in 32. The fact that only the cyclization of 29a bearing a sterically less demanding methyl group produced a trace amount of the trans isomer supports this hypothesis. Thus, the stereochemical outcome of the present cyclization may also be explained by the operational model proposed above, in which two putative rhodium(II) carbene intermediates 33 and 34 are presented. In both of the intermediates, the larger N-tert-butyl substituent placed syn to the amide carbonyl group is extended outward, and the reacting C-H bond is oriented toward the rhodium(II) center and in parallel with the rhodium(II) carbene bond. The reactive intermediate 33 is preferred over the reactive intermediate 34 because of the severe steric repulsion between the tert-butyl group and the phthalimido group in 34, directing cyclization toward C-H$_R$ bond in accord with the observed enantioselection.

![Diagram](image)

Considering that the tert-butyl group as N-substituent proved to be crucial to the present process but could not be removed, our interest was then centered on the utilization of 35 as a substrate, on the prospect that the N,O-acetal moiety could function as its substitute. Indeed, cyclization of 35 was mediated by Rh$_2$(S-PTPA)$_4$ and its analogues to give the 3,4-trans-2-azetidinone derivatives 36 with consistent sense of enantioselection at the insertion site in more than 88% ee in all cases, in which the catalysis of 35 with Rh$_2$(S-PTA)$_4$ derived from N-phthaloyl-(S)-alanine provided 96% ee (ref. 18). In a comparative experiment with 35, the enantioselectivities observed with Rh$_2$(5S-MEPY)$_4$ and

<table>
<thead>
<tr>
<th>Rh(II) catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>Rh$_2$(S-PTA)$_4$</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>Rh$_2$(S-PTV)$_4$</td>
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<td>Rh$_2$(S-PTPA)$_4$</td>
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<tr>
<td>Rh$_2$(S-PTTL)$_4$</td>
<td>85</td>
<td>93</td>
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McKervey's catalyst were 26% and 28% ee, respectively. The stereochemical outcome may again be understood based on our operational model, provided that 3,4-trans isomer is a product of kinetic control because a chair-like conformer 37 is preferred over a boat-like conformer 38. The 2-azetidinone 36 was transformed to the key synthetic intermediate for carbapenems such as thienamycin and PS-5. Further extension of the present protocol to 39 bearing an exocyclic olefin enabled the synthesis of the pivotal intermediate for 13-methylcarbapenems in up to 88% ee (ref. 18). Thus, the present protocol provides an efficient and general method for the catalytic asymmetric synthesis of carbapenems.

3.3. Asymmetric Creation of Quaternary Carbon Centers by Enantiotopically Selective Aromatic Substitution

As yet another interesting feature of our dirhodium(II) catalysts, we have recently found that these catalysts-mediated aromatic substitution of α-diazo ketones 41 exhibits a high order of differentiation between enantiotopic benzene rings, providing (S)-1-alkyl-1-phenyl-2-indanones 42 featured by a chiral quaternary carbon atom (Table 3) (ref. 30). It is of interest to note that the enantioselectivities sharply diminished with the corresponding α-diazo β-keto 2,4-dimethyl-3-pentyl esters, whereas the methyl esters provided fairly similar selectivities. While the secondary effects of the C-3 substituents of α-diazo ketones 41 and alkyl substituents of chiral bridging ligands have yet to be elucidated, Rh2(S-PTTL)4 derived from N-phthaloyl-(S)-tert-leucine, has proven to be the catalyst of choice for allowing high enantioselectivities ranging from 88 to 98% ee in this process (ref. 31).

According to the mechanistic hypothesis for aromatic substitution (vide supra), the stereochemical outcome may roughly be rationalized by evaluating two putative rhodium (II) carbene intermediates 43 and 44 (Figure 8), in which the benzene ring undergoing substitution is accommodated in a less crowded quadrant and placed perpendicularly to the plane of the other one extending outward for steric reasons. The reactive intermediate 43 is favored over the reactive intermediate 44 due to the severe steric repulsion between the substituent and the phthalimido group in 44, leading to the predominant formation of (S)-2-indanones 42 in accord with the observed enantioselection.

<table>
<thead>
<tr>
<th>Substrate R</th>
<th>Rh2(S-PTA)4</th>
<th>Rh2(S-PTV)4</th>
<th>Rh2(S-PTPA)4</th>
<th>Rh2(S-PTTL)4</th>
</tr>
</thead>
<tbody>
<tr>
<td>41a CH3</td>
<td>69</td>
<td>65</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>41b CH2CH3</td>
<td>92</td>
<td>74</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>41c CH3CH2CH2</td>
<td>53</td>
<td>41</td>
<td>33</td>
<td>88</td>
</tr>
<tr>
<td>41d CH2=CHCH2</td>
<td>60</td>
<td>48</td>
<td>55</td>
<td>88</td>
</tr>
</tbody>
</table>

Table 3. Differentiation of enantiotopic benzene rings
4. Conclusion

The emergence of Rh$_2$(TPA)$_4$ has made possible a virtually complete site-control in several sets of intramolecular C-H insertion reactions, where competitive C-H insertions take place with the use of a typical class of dirhodium(II) catalysts such as Rh$_2$(OAc)$_4$, Rh$_2$(tfa)$_4$, and Rh$_2$(acam)$_4$. In particular, Rh$_2$(TPA)$_4$ exhibits an exceptionally high order of selectivity for C-H insertion into methylene over methine on a cycloalkane ring as well as for aromatic substitution over aliphatic C-H insertion. The effectiveness of Rh$_2$(TPA)$_4$ as the sterically discriminating catalyst can be rationalized by its crystal structure, whereby the four phenyl groups from triphenylacetate ligands strongly influence the approach of the possible reaction sites to the rhodium(II) carbene center. It should be noted that not all competitive C-H insertion reactions can be controlled by catalyst variation. With certain substrates such as α-diazo amides, the matched combination of effects of the dirhodium(II) ligands and electronic/conformational effects imparted on the substrates is crucial to excellent site-selectivity.

Dirhodium(II) carboxylates incorporating N-phthaloyl-(S)-amino acids as bridging ligands, Rh$_2$(S-PTPA)$_4$, Rh$_2$(S-PTA)$_4$, and Rh$_2$(S-PTTL)$_4$, have proven to be the chiral catalysts of choice for allowing high levels of differentiation of enantiotopic methylene C-H bonds and enantiotopic benzene rings, affording optically active cyclopentanone, 2-azetidinone, and 2-indanone derivatives in up to 80%, 96%, and 98% ee, respectively. The efficacy of these catalysts can be rationalized by evaluating the chiral environment around the rhodium(II) carbene center featured by the two protruding phthalimido walls. As might be expected from the great difference in the electronic and steric influences of the ligands on the rhodium, our catalysts exhibit high enantioselectivities with α-diazo β-keto esters and α-methoxycarbonyl-α-diazoacetamides as substrates, whereas Doyle's catalysts work excellently with α-diazoacetates and α-diazoacetamides. It is of particular interest to note that the phthalimido group of our ligands functions effectively as a steric element, whereas the ester group of Doyle's ligands plays its role as a dipole element (ref. 21). The rational design and synthesis of a new class of chiral catalysts amenable to a broad spectrum of rhodium(II) carbene transformations is currently in progress (ref. 32).

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2725.

5109.


1491.


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