Selectivity in Rhodium(II) Catalyzed Reactions of Diazo Compounds: Effects of Catalyst Electrophilicity, Diazo Substitution, and Substrate Substitution. From Chemoselectivity to Enantioselectivity

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Received 9 December 2002; revised 22 April 2003

Abstract: Rhodium catalyzed reactions of diazo compounds form a powerful set of tools for synthetic organic chemists. Reactivity modes include cyclopropanation, C–H insertion, X–H insertion, and ylide formation. A myriad of factors influences the mode of reaction, selectivity, and yield for these reaction processes. This review examines the subtle electronic, steric and conformational effects that in turn have profound impacts on reaction paths and selectivity.

1 Introduction

α-Diazo carbonyl compounds are ideal substrates for generating carbenes,1 which in turn are powerful intermediates in organic synthesis. Free carbenes are accessed by thermal or photochemical means, while formation of carbenoids (carbene complexes) is possible via reaction of the diazo precursors with transition metal complexes.2 Although many transition metal complexes afford carbenoids, the development of dirhodium(II) carboxylate and carboxamidate catalysts, in particular, has resulted in highly chemo-, regio- and stereoselective reactions of α-diazoacarbonyl compounds via a variety of reactivity modes.3 This widely utilized methodology originated with the work of Hubert, Teyssie and co-workers. Pioneering studies determined the extent of catalysis with various substrates and an extensive library of successful transformations rapidly evolved, ranging from Rh(II) catalyzed O–H and X–H insertion to cyclopropanation of olefins6 and aromatic systems3 (Scheme 1).

The potential utility of this methodology was immediately realized by the synthetic community. For example, in 1980, Merck researchers incorporated a rhodium(II) acetate catalyzed N–H insertion reaction into the synthesis of the β-lactam antibiotic thienamycin (8) (Scheme 2).8 Nearly complete conversion to bicyclic β-lactam 10 was achieved under Rh2(OAc)4 catalysis, while only a 1:9 ratio of 10 to undesired imide byproduct 11 was obtained with photolysis. The applicability of this methodology continues to be elegantly demonstrated today in numerous syntheses of complex natural product targets (Figure 1).9
The evolution of Rh(II) catalysis commenced with rhodium(II) acetate, which continues to be widely used for achiral reactions. Synthesis of the air-stable green solid is readily achieved by reaction of rhodium trichloride trihydrate with sodium acetate and acetic acid. Ligand exchange with various substituted acetates or substituted acetamides provides access to an extensive collection of catalysts exhibiting varying degrees of reactivity (Figure 2).

**Figure 1** Natural products recently synthesized via rhodium carbeneoid methodology.

**Figure 2** Achiral rhodium(II) carboxylate and carboxamidate catalysts.

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**Biographical Sketches**

**Professor Craig A. Merlic** was born in San Jose, California. He received his B.S. degree in chemistry from the University of California, Davis in 1982 and then earned his PhD degree in Chemistry from the University of Wisconsin, Madison in 1988 under the guidance of Professor Barry M. Trost as a Hertz Foundation fellow. His doctoral research focused on molybdenum catalyzed reactions of sulfones, diastereoselective synthesis of sulfones, and asymmetric molybdenum catalyzed allylic alkylations. As a graduate student, he also had the distinct pleasure of working with Professor Teruaki Mukaiyama at the University of Tokyo for two summers. During 1988 and 1989, he was a National Institutes of Health Postdoctoral Fellow with Professor Martin Semmelhack at Princeton University and researched palladium catalyzed coupling reactions. In 1989 he joined the faculty at the University of California, Los Angeles and was promoted to Associate Professor in 1995. He was Vice Chair of the Department of Chemistry and Biochemistry from 1997 through 2000. Professor Merlic’s research focuses on development of new synthetic methods for organic synthesis and natural product synthesis with a particular focus on applications of transition metal organometallic chemistry. He also developed Internet based educational projects for course management and organic spectroscopy. He has received several honors for his work, including a National Science Foundation Young Investigator Award in 1992, a Camille Dreyfus Teacher-Scholar Award in 1994, and an Alfred P. Sloan Research Fellowship in 1995.

**Andrea L. Zechman** was born in Danville Pennsylvania. She received her B.S. degree in chemistry from Pennsylvania State University, University Park in 1996. She conducted undergraduate research with Professor Robert Minard on structure elucidation of ligands under the auspices of a TEAS Scholarship. She then moved to the University of California, Los Angeles and earned her PhD degree in 2002 under the direction of Professor Craig A. Merlic. Her doctoral research focused on the reactivity of \( \eta^6\)-arene}tri-carbonylrhodium complexes with rhodium carbeneoids. She received two Distinguished Teaching Assistant Awards and a Departmental Service Award from the UCLA Department of Chemistry and Biochemistry. During 2000-2001, she was a University Teaching Fellow.
Doyle’s widely accepted mechanism for dirhodium(II) catalyzed reactions of α-diazocarbonyl compounds is shown in Scheme 3.2,3,6 Solvent dissociation provides reactive catalyst $L_n M$ (I). Nucleophilic attack of the diazo species on the electrophilic catalyst affords intermediate ylide II, which upon extrusion of nitrogen generates rhodium carbenoid III. The carbenoid III maintains the core structure of the starting dirhodium tetraacetate with only slight elongation of the Rh–Rh bond.12 Product formation occurs, upon transfer of the carbene moiety to the appropriate reactive functionality, i.e. olefin, heteroatom–H bond, aromatic system, carbonyl, etc. Extensive studies in this field demonstrate that chemoselectivity, and hence, product yields are highly dependent on three factors: catalyst electrophilicity, carbenoid substitution, and substrate substitution. Further, research in the last ten years has found that these same factors have profound effects on enantioselectivity in reactions employing chiral catalysts. This review focuses on these issues, revealing that subtle electronic, steric, and/or conformational changes often have a monumental impact on the reaction path and enantioselectivity.

2. Achiral Rhodium(II) Catalysts

2.1. Effect of Catalyst Electrophilicity on Selectivity

Rhodium(II) carbenoids generated in situ from α-diazocarbonyl compounds offer access to a diverse library of molecules relevant to natural product synthesis. This access can be achieved via cyclopropanation of olefins, Buchner reaction with aromatic substrates (arene cyclopropanation), aliphatic C–H insertion, aryl C–H insertion, heteroatom–H insertion, and ylide generation followed by either [2,3]-sigmatropic rearrangement or dipolar cycloaddition. The electronic nature of the dirhodium(II) catalyst, and hence the electrophilicity of the carbenoid, determines the mechanistic pathway observed. However, a complex mixture of products is often obtained when more than one reaction pathway is possible.

Intramolecular competition experiments are an excellent means of directly comparing the chemoselectivity of various catalysts. With the goal of determining which catalyst is most appropriate for a specific mode of reactivity, Padwa and co-workers13 explored the chemoselectivity of three electronically diverse catalysts: rhodium(II) caprolactam (19b), rhodium(II) acetate (17a), and rhodium(II) perfluorobutyrate (18b). The electrophilicity of the resulting carbenoid increases significantly in the order $\text{Rh}_2\text{cap}_4 < \text{Rh}_2\text{OAc}_4 < \text{Rh}_2\text{pfb}_4$. Thus, product distributions from intramolecular competition experiments were expected to vary considerably.

Competition between olefin cyclopropanation and aryl C–H insertion was investigated using diazoketone 20 (Scheme 4).13 A complete reversal in reactivity was seen between $\text{Rh}_2\text{pfb}_4$ and $\text{Rh}_2\text{cap}_4$. Highly electrophilic $\text{Rh}_2\text{pfb}_4$ promoted aryl C–H insertion exclusively, while the more electron rich $\text{Rh}_2\text{cap}_4$ provided only cyclopropanation product 22. $\text{Rh}_2\text{OAc}_4$, with its middle-of-the-road electronics, afforded a 1:1 mixture of the two products.

Scheme 4

Diazoketone 23 was then constructed, incorporating functionality to compare aliphatic C–H insertion and olefin cyclopropanation (Scheme 5).13 Methylene C–H insertion was the only reaction pathway observed upon treatment with $\text{Rh}_2\text{pfb}_4$ yielding 2-allyl-4,4-dimethylcyclopentanone. In contrast, the rhodium carbenoid generated from $\text{Rh}_2\text{cap}_4$ failed to undergo C–H insertion, giving only cyclopropanation product 25. Again, minimal chemoselectivity was achieved with $\text{Rh}_2\text{OAc}_4$.

Scheme 5

Diazoacetamide 26, derived from N-tert-butyl-N-phenylethylamine, showed dramatic propensity for intramolecular Buchner reaction over benzylic C–H insertion when catalyzed by $\text{Rh}_2\text{pfb}_4$.13 This preference was seen to a lesser extent for $\text{Rh}_2\text{OAc}_4$ and was entirely inverted with the use of $\text{Rh}_2\text{cap}_4$ (Scheme 6).
Interaction of an electrophilic rhodium carbeneoid carbon with a tethered carbonyl oxygen forms a cyclic ylide. The resulting 1,3-dipole reacts with dipolarophiles to afford structurally complex bicyclic cycloadducts. Substrate 29 incorporates an aryl group and a ketone to examine competition between carbonyl ylide formation and aryl C–H insertion. Catalysis with Rh\(_2\)(cap)\(_4\) provided exclusive ylide generation and intermolecular trapping with dimethyl acetylene dicarboxylate (DMAD) furnished cycloadduct 31 with no trace of indanone 32 (Scheme 7).\(^{13}\) Competing reaction with the α-aryl substituent became more apparent with Rh\(_2\)(OAc)\(_4\), as a bias of 3:1 ylide formation over aryl C–H insertion product 32 was seen. Changing catalyst electronics even further to the electrophilic Rh\(_2\)(pfb)\(_4\) catalyst completely shut down the carbonyl ylide pathway. Instead, aryl C–H insertion was the sole reaction pathway observed.

Based on these extensive studies, reactivity trends for rhodium(II) carbeneoids derived from Rh\(_2\)(pfb)\(_4\) were established: aryl C–H insertion > tertiary aliphatic C–H insertion > olefin cyclopropanation ca. = Buchner reaction > secondary C–H insertion. This is in contrast to the substantially less electrophilic Rh\(_2\)(cap)\(_4\) catalyst, which provided the following reactivity trend: olefin cyclopropanation > aryl C–H insertion > tertiary C–H insertion > secondary C–H insertion > Buchner reaction. Chemoselectivity imparted by the catalyst was also explored in the comparison of ylide formation and aliphatic C–H insertion using diazoacetacetamide 36.\(^{15}\) In this particular study, Rh\(_2\)(cap)\(_4\) was replaced with the isoelectronic rhodium(II) acetamide catalyst 19a (Scheme 9). Performing the competition reaction with catalytic Rh\(_2\)(pfb)\(_4\) led to intramolecular trapping of the ester carbonyl as the major pathway, yielding predominantly 37. However, both Rh\(_2\)(OAc)\(_4\) and Rh\(_2\)(acam)\(_4\) underwent aliphatic C–H insertion to afford β-lactam 38 as the major product. γ-Lactam 38 was formed via C–H insertion into the preferred mode of reactivity over both aryl and aliphatic C–H insertions with Rh\(_2\)(cap)\(_4\). On the other hand, benzyllic C–H insertion dominated over the Buchner reaction. Additionally, ylide formation was highly favored, despite the presence of an aryl substituent. Rhodium(II) acetate displayed minimal chemoselectivity in comparison to its electronically diverse counterparts. Product ratios ranged from 1:1 in most cases to the modest selectivity of 3:1 in the case of ylide formation versus aryl C–H insertion.

In 1993, Padwa, Doyle and co-workers elaborated on their original findings to include competition between aliphatic C–H insertion and aryl C–H insertion.\(^{14}\) Rh\(_2\)(pfb)\(_4\) was found to be highly selective for aryl C–H insertion, in agreement with the aforementioned results, while the chemoselectivity achieved with both Rh\(_2\)(OAc)\(_4\) and Rh\(_2\)(cap)\(_4\) was limited. Experiments designed to compare olefin cyclopropanation with the Buchner reaction revealed that Rh\(_2\)(cap)\(_4\) was highly chemoselective for cyclopropanation, in contrast to the more electrophilic catalysts. In addition to catalyst selection, reaction temperature also played a substantial role in selectivity. For example, cycloheptatriene 34, obtained via intramolecular Buchner reaction of diazoacetamide 33, was formed almost exclusively over the benzylic C–H insertion product 35 at room temperature. In refluxing dichloromethane, however, no selectivity between the two pathways was observed (Scheme 8).
the deactivated C–H bonds as a minor product in all three cases.

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\text{Rh}_2(\text{tpa})_4, \quad \text{a dirhodium(II) catalyst derived from the sterically encumbering triphenylacetate ligand, was shown by}\n\]
Ikegami and co-workers to be extremely chemoselective for aryl C–H insertion with both \(\beta\)-diazo-\(\beta\)-ketesters and diazoketones.\(^{16}\) In fact, aliphatic C–H insertion at methylene or methine positions was not detected with intramolecular competition substrates. The most dramatic example involved a complete reactivity reversal by merely changing the ligand sterics from methyl in \(\text{Rh}_2(\text{OAc})_4\) to triphenylmethyl in \(\text{Rh}_2(\text{tpa})_4\) (Scheme 10). Additionally, aryl C–H insertion was also the exclusive pathway observed in competition with olefin cyclopropanation with \(\text{Rh}_2(\text{tpa})_4\) catalysis. This was in contrast to cyclopropanation being the preferred mode of reactivity for \(\text{Rh}_2(\text{OAc})_4\).

To determine the chemoselectivity consequences of an alcohol substituent in the \(\alpha\)-diazo carbonyl compounds, substrates 43a–c containing a variety of \(\pi\)-systems in addition to a hydroxyl group were submitted to various Rh(II) catalysts.\(^{17}\) O–H insertion was found to prevail over aryl C–H insertion, benzylic C–H insertion, intramolecular Buchner reaction, olefin cyclopropanation, and alkyn cyclopropanation with electronically diverse catalysts (Scheme 11). Although yields were low in several instances, clear evidence of other reaction pathways was not apparent by NMR studies for all catalysts employed. Thus, O–H insertion precedes all other modes of reactivity in previously reported reactivity trends.\(^{14}\)

Moody, Padwa, and co-workers also investigated competition between benzylic C–H insertion and aryl C–H insertion for diazoamide esters.\(^{18}\) Reaction yields, as well as selectivities, improved substantially on replacing \(\text{Rh}_2(\text{OAc})_4\) with rhodium(II) perfluorobutyramide, \(\text{Rh}_2(\text{NHCOC}_3\text{F}_7)_4\). In particular, aryl C–H insertion product 47, isolated as the siloxyindole, was formed exclusively (Scheme 12). Of special note is the absence of a Buchner reaction pathway.

Substitution of the \(p\)-methoxyphenyl substituent in diazoacetate 45 with benzyl created a \(C_2\)-symmetric substrate for comparison of benzylic C–H insertion and the intramolecular Buchner reaction.\(^{18}\) Aryl C–H insertion was not a viable reaction pathway for diazoacetate 48 as a result of energetically unfavorable six-membered ring formation. In changing the catalyst from \(\text{Rh}_2(\text{OAc})_4\) to \(\text{Rh}_2(\text{NHCOC}_3\text{F}_7)_4\), the preferred reaction pathway was altered from 3:1 in favor of benzylic C–H insertion to 1:5.8 favoring Buchner reaction (Scheme 13).

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**Scheme 9**

**Scheme 10**

**Scheme 11**

**Scheme 12**

**Scheme 13**
α-Diazoimides substituted with a variety of electronically variable substituents were also subjected to Rh₃(OAc)₄ and Rh₂(NHCOOC₃F₇)₄ catalysis. Possible reaction pathways included carbonyl ylide generation and subsequent epoxide formation versus isomünchnone formation and ensuing dipolar cycloaddition. The product distribution was highly dependent on the catalyst chosen, as Rh₂(OAc)₄ afforded epoxides exclusively in 80–90% yields in all cases. In contrast, isomünchnone cycloadducts were obtained in high yields under Rh₂(NHCOOC₃F₇)₄ catalysis via intermolecular capture with N-phenyl maleimide (Scheme 14). Further, the chemoselectivity achieved for Rh₂(OAc)₄ catalyzed reactions was completely reversed by changing solvent polarity. For example, use of acetonitrile or nitromethane led to isomünchnone cycloadducts 53a–e exclusively, with no evidence of epoxide formation. However, nonpolar solvents such as pentane, benzene, and chloroform afforded only epoxides 55a–e.

Pirrung and Morehead made significant strides in describing the electronic effects of ligands in rhodium(II) carboxylate catalysts using infrared spectroscopy and linear free energy analyses. Their results emphasized the importance of backbonding in designing an appropriate catalyst. In particular, carbon monoxide complexes of rhodium carboxylates were formed as model systems of rhodium carbenoids. IR analysis suggested that backbonding was indeed significant in rhodium carbenoids, as evidenced by the increase in carbonyl stretching frequency with decreasing ligand polarizability (increasing ligand electronegativity). Thus, the electron withdrawing ability of trifluoroacetate ligands, for example, diminished the metal’s ability to backbond, creating a more electrophilic and thus more reactive carbenoid. This groundbreaking discovery has received much attention in the design of catalysts for enantiocontrol (vide infra).

2.2 Effect of Diazo Substitution on Selectivity

Varying the substitution pattern of α-diazocarbonyl compounds in rhodium(II) catalyzed reactions has a large impact on chemoselectivity, diastereoselectivity, and product yields. For example, Rh₂(OAc)₄ catalyzed reaction of ethyl diazoacetate and trans-cinnamyl methyl ether preferentially generated an allylic oxonium ylide, which subsequently underwent [2,3]-sigmatropic rearrangement in a 3:1 ratio over olefin cyclopropanation. The resulting major product was obtained as a 5:1 mixture of erythro and threo isomers (Scheme 15). Chemoselectivity increased significantly when using aryl diazoketones in place of diazoacetates. In particular, diazoacetophenone 57 afforded sigmatropic rearrangement products in a 16:1 chemoselectivity with a 10:1 diastereoselectivity in favor of the erythro isomer.

Rhodium(II) catalyzed cyclopropanation of 1,1-dialkoxydienes with vinyl diazoacetates affords cis-divinylcyclopropanes which readily undergo the Cope rearrangement. Hydrolysis and oxidation of the cycloheptadiene products allow for rapid entry into a variety of substituted tropones. In a study performed by Davies and co-workers, the consequence of vinyl diazoacetate substitutions at both the terminal vinyl position and the diazo carbon were explored. A high yield of cycloheptadiene was achieved with α-diazostyrylacetaest 61a and diene 60 (Scheme 16). However, replacing the diazoacetate with a diazoketone as in 61b completely impeded the tandem cyclopropanation/Cope rearrangement pathway. Reaction of vinyl diazoacetate 61c, derived from trans-diethylglutaconate, provided cycloheptadiene 62c in high yields. However, additional olefin substitution, i.e. 61d, shut down the desired reaction pathway.

In both failed instances, changing the reaction conditions from Rh₂(OAc)₄ in dichloromethane to Rh₂(OPiv)₄ in pentane allowed for relatively high yields of the previous-
ly inaccessible products. This dramatic change in reactivity is thought to be due to the suppression of a dipolar transition state in nonpolar solvents. In dichloromethane a dipolar transition state is favored, leading to alternative mechanistic pathways and minimal cycloheptadiene formation. Thus, although a large substituent effect is apparent for vinyldiazoacetates, this can be overcome with the use of nonpolar solvents.

Studying the effect of carbene substitution in the intermolecular aliphatic C–H insertion with cyclohexane, Davies and co-workers found that rhodium(II) catalyzed reactions of cis- and trans-vinyl diazoacetate isomers led to entirely different products. For example, the rhodium carbenoid of cis-phenyl vinyl diazoacetate 63c, generated with catalytic \( \text{Rh}_2\text{(OPiv)}_4 \), failed to undergo intermolecular C–H insertion with cyclohexane. Instead, intramolecular aryl C–H insertion was observed, providing indene 64 in 86% yield (Scheme 17). Reaction of the trans-isomer gave a mixture of products 65 arising from intermolecular C–H insertion, and 66, via cis–trans isomerization of the carbenoid followed by aryl C–H insertion and subsequent intermolecular cyclopropanation of the resulting indene. These results substantiate the large impact of vinyl diazo structure on reaction pathway, not only through substituent steric and electronic effects, but also through the implications of olefin geometry.

Müller and Tohill synthesized six structurally and electronically varied diazo compounds to determine the favored mode of reactivity for each: olefin cyclopropanation or aliphatic C–H insertion. The ultimate goal was to obtain high stereoselectivity in intermolecular insertion reactions at the allylic position utilizing a chiral catalyst. However, initial investigations centered on chemoselectivity issues using the diazo substrates shown in Figure 3. \( \text{Rh}_2\text{(OAc)}_4 \) catalyzed reactions in dichloromethane with ten equivalents of cyclohexene were examined first. The highest level of chemoselectivity was obtained with ethyl diazoacetate 1 favoring cyclopropanation over insertion. However, this preference was reversed in the case of methyl 2-diazophenylacetate 70 (Scheme 18).

More promising chemoselectivities were achieved with 1,4-cyclohexadiene (Scheme 19). While ethyl diazoacetate again afforded predominantly cyclopropanation products, both methyl 2-diazopropionate 68 and methyl 2-diazophenylacetate 70 provided 98:2 ratios of insertion over cyclopropanation products. Thus, incorporating both an electron-withdrawing substituent and an electron-donating substituent on the diazo carbon promotes C–H insertion at the allylic position.

In an effort to achieve \( \text{Rh}_2\text{(OAc)}_4 \) catalyzed N–H insertion of hexamethyldisilazane using dimethyl diazomalonate in benzene, Livant co-workers unexpectedly obtained bis-cyclopropanation product 81 in 58% yield via a double Buchner reaction on the solvent (Scheme 20). The more traditional cycloheptatriene product from a single Buchner reaction was also formed in 19% yield. Under similar reaction conditions, the sole product obtained with both methyl and ethyl diazoacetate was a cycloheptatriene derivative. Since the rhodium carbenoid of dimethyl diazomalonate is less reactive than that derived from diazoacetates, the initial norcaradiene formed in the reaction is argued to be about 550 times more reactive than benzene for a second cyclopropanation. This chemistry al-
lows for facile synthesis of otherwise difficult to construct tricyclic ring systems. Aryl bis-addition products have been previously reported in the thermal reaction of naphthalene and dimethyl diazomalonate, albeit in extremely low yields.\(^{26}\)

![Scheme 20](image)

**Scheme 20**

Wee and co-workers synthesized eleven ester substituted diazoanilides with varying \(N\)-substituents to explore aryl versus alky C–H insertion.\(^{27}\) In all cases, no evidence of aryl C–H insertion was found. Instead, aliphatic C–H insertion was the preferred mode of reactivity, generating \(\beta\)-lactams in reasonable yields, while substrates bearing longer \(N\)-alkyl chains produced predominantly \(\gamma\)-lactams (Scheme 21). Surprisingly, aryl C–H insertion was still not observed with the more electron-rich \(p\)-methoxyphenyl nitrogen substituent. The alternate mode of reactivity, however, was seen exclusively by altering the diazo portion of the substrate from an \(\alpha\)-ester to a ketone or phenylsulfone.

![Scheme 21](image)

**Scheme 21**

In addition to substituent electronic effects, neighboring group participation in the rhodium carbenoid intermediate has been shown to greatly influence product yields. For example, \(\text{Rh}_2(\text{OAc})_4\) catalyzed cyclopropanation/Cope rearrangement of \(N\)-Boc pyrrole with methyl vinyldiazoacetate afforded tropane \(89a\) in moderate yield (Scheme 22).\(^{28}\) Davies and co-workers found this reaction pathway to be highly dependent on the electronic nature of the aromatic component.\(^{29}\) For example, benzene, toluene, and \(\delta\)-butylbenzene allowed access to bicyclo[3.2.2]nonatriene \(96\), although in low yields due to product instability. Anisole, 1,2-dimethoxybenzene and 1,2,3-trimethoxybenzene, however, afforded alkylation products of the structure \(97\), presumably due to greater stabilization of transition state \(94\) (Scheme 23).

![Scheme 22](image)

**Scheme 22**

As was seen for catalyst structure, diazo substitution also controls reaction pathways to an enormous extent. For example, subtle changes from diazoacetates to diazoketones can dramatically alter reaction selectivity. For diazoacetates in particular, the presence of an \(\alpha\)-electron-withdrawing or -donating group greatly influences reactivity and, hence, product distribution. Even subtle differences between electron withdrawing groups can alter reaction selectivity.

2.3. Effect of Substrate Substitution on Selectivity

In addition to the substantial impact that variations in diazo substitution impart on rhodium carbenoid reactivity, steric and electronic modifications in the substrates also play colossal roles in chemoselectivity. Several studies in the literature exemplify this reactivity dependence. For example, formal [3 + 2] annulation products \(96\) are generated from reaction of vinyldiazoacetates with benzene derivatives via cyclopropanation and subsequent Cope rearrangement. Davies and co-workers found this reaction pathway to be highly dependent on the electronic nature of the aromatic component.\(^{29}\) For example, benzene, toluene, and \(\delta\)-butylbenzene allowed access to bicyclo[3.2.2]nonatriene \(96\), although in low yields due to product instability. Anisole, 1,2-dimethoxybenzene and 1,2,3-trimethoxybenzene, however, afforded alkylation products of the structure \(97\), presumably due to greater stabilization of transition state \(94\) (Scheme 23).

![Scheme 23](image)

**Scheme 23**

The significance of electronic variations in substrate structure was addressed by Padwa co-workers for the intramolecular Buchner reaction.\(^{14}\) Diazooacetamide \(26\) yielded a 2:1 ratio of cycloheptatriene \(27\) to benzylic C–H insertion \(28\) (vide supra Scheme 6). This ratio improved to...
3:1 upon use of more electron rich ring system. In contrast, the electron deficient p-NO2Ph substituent in shut down the Buchner reaction pathway, instead leading to a mixture of C–H insertion products (Scheme 24). Thus, chemoselectivity is highly dependent upon the electronic nature of the aryl substituents.

Under certain circumstances, steric and conformational factors take precedence over electronic effects in determining chemoselectivity and product distribution. For example, four reaction pathways were possible in the Rh2(OAc)4 catalyzed reactions of diazoacetamides: methylene C–H insertion at the benzylic position, imine formation, intramolecular Buchner reaction, and methine C–H insertion at the bisbenzylic position (Scheme 25).30 When Ar = Ph (106a) or Ar = 4-chlorophenyl (106b), mixtures of the four products were obtained. Use of a more sterically encumbering aryl group such as 2-tolyl, however, prevented reaction at the bisbenzylic position, affording only cycloheptatriene. Why this steric effect would also inhibit benzylic reaction leading to is not obvious. Tethering the aryl substituents as fluorene provided C–H insertion product 112 in 66% yield, with a minor amount of imine formation (Scheme 26). Finally, eliminating the methine benzylic position and replacing it with a p-NO2 phenyl substituent promoted aryl C–H insertion exclusively to yield hydroxyindole 113. This surprising result arose from the highly unusual reactivity of an electrophilic carbenoid with an electron deficient ring system.

Olefin substitution on vinyldiazoacetates plays a crucial role in product distribution. Similar effects are noteworthy for remote olefins in substrates. Collomb and coworkers demonstrated that regiocomplimentary naphthols for remote olefins in substrates. Collomb and co-workers found that regiocomplimentary naphthols and Doyle who found that electron withdrawing substituents inhibited aryl C–H insertion, indicating that ketene formation is not favored for electron-poor olefins.

Recently, the effects of complexing arenes with a chromium tricarbonyl moiety were examined in the context of rhodium catalyzed aryl C–H insertion, benzylic C–H insertion and ary1 cyclopropanation (Buchner reaction).32 Complexation of arenes was found to protect them completely from the Buchner reaction in inter- and intramolecular experiments (Scheme 28). Considering the strong electron withdrawing nature of the chromium tricarbonyl moiety, these results are in line with the results of Padwa and Doyle who found that electron withdrawing substituents inhibited arene cyclopropanation (Scheme 24).
insertion into benzylic C–H bonds in complexed arenes does occur, and since the chromium imparts an element of chirality which makes the benzylic protons in diazoacetate an attractive substrate for asymmetric transformation. In 1990, Ikegami and co-workers introduced chiral rhodium(II) carboxylates derived from phthaloyl protected amino acids and co-workers introduced chiral rhodium(II) carboxylates derived from phthaloyl protected amino acids (Scheme 32).33 In this particular study, enantiomerically enriched cyclopentanones were constructed via aliphatic diazoacetate carboxylation. The most promising results were obtained for benzylic C–H insertion with rhodium(II) carboxylates 129a and 129b, which gave high yields and moderate enantioselectivity for cyclopentanone 133. In addition to the promising enantioselectivities obtained, a second encouraging feature of this methodology was isolation and reuse of the catalysts multiple times with minimal decrease in selectivity or turn-over numbers. Significantly improved enantioselectivity was achieved by merely substituting a bulky ester for the methyl ester in diazoacetate 133a.34 Thus, use of diisopropylmethyl ester 131b afforded cyclopentanone 133 in 81% yield and 76% ee. Increasing the ester steric bulk did not have a strong impact when catalysts derived from (S)-valine (129c) and (S)-tert-leucine (129d) were used, although moderate enantioselectivity for cyclopentanone

3 Chiral Rhodium(II) Catalysts

3.1 Carboxylate Ligands

With the synthetic relevance of rhodium(II) catalyzed reactions of α-diazocarbonyl compounds established, several researchers initiated studies with chiral ligands in order to achieve asymmetric transformations. In 1990, Ikegami and co-workers introduced chiral rhodium(II) carboxylates derived from phthaloyl protected amino acids (Scheme 32).33 In this particular study, enantiomerically enriched cyclopentanones were constructed via aliphatic C–H insertion of α-diazo-β-ketoesters and subsequent decarboxylation. The most promising results were obtained for benzylic C–H insertion with rhodium(II) carboxylates 129a and 129b, which gave high yields and moderate enantioselectivity for cyclopentanone 133. In addition to the promising enantioselectivities obtained, a second encouraging feature of this methodology was isolation and reuse of the catalysts multiple times with minimal decrease in selectivity or turn-over numbers. Significantly improved enantioselectivity was achieved by merely substituting a bulky ester for the methyl ester in diazoacetate 133a.34 Thus, use of diisopropylmethyl ester 131b afforded cyclopentanone 133 in 81% yield and 76% ee. Increasing the ester steric bulk did not have a strong impact when catalysts derived from (S)-valine (129c) and (S)-tert-leucine (129d) were used, although moderate enantioselectivity for cyclopentanone
tivities were still achieved. Low enantioselectivities were obtained in all cases with catalyst 130, derived from (S)-benzoxoxyphenylacetic acid.

Although benzylic C–H insertion results were not as favorable with catalysts other than Rh2(S-PTPA)4, in the case of a double intramolecular C–H insertion at the benzylic position, Rh2(S-PTTL)4 was found to be the catalyst of choice.35 Hence, a one pot synthesis of 1,1'-spirobi[indan-3,3'-dione] was achieved in 78% yield and 80% ee (Scheme 33). With optically pure dione 137 available after one recrystallization, this methodology allowed facile access to potentially promising C2-symmetric chiral ligands for asymmetric catalysis.

In contrast to the success with ketone-derived ylide formation and trapping, the enantioselectivity observed with ester-derived ylides was disappointing.37 For example, diazo substrate 141 provided an extremely low yield and enantiomeric excess of bicyclo[3.2.1] product 142 (Scheme 35). Additionally, no cycloadduct was obtained with methyl ester 143. However, substituting the flexible aliphatic tether to a more rigid aryl tether dramatically improved yields and selectivity. The combination of a naphthyl tether and catalytic Rh2(S-PTTL)4 produced 146 in 71% yield and 93% ee.

Ylides generated from chiral catalysts can also undergo enantioselective [2,3]-sigmatropic rearrangements. If the diazo carbon bears two substituents, sigmatropic rearrangement results in facile enantioselective formation of a quaternary center. Hashimoto and co-workers found this methodology highly dependent not only on catalyst ligands, but also on solvent and reaction temperatures.38 In particular, Rh2(S-PTPA)4 catalyzed reaction of 147 in dichloromethane at room temperature resulted in low enantiocontrol for benzofuranone 149. However, enantioselectivities on the order of 74% were achieved with Rh2(S-PTTL)4 at 0 °C in toluene (Scheme 36). These results further substantiate the pro-
posal of a rhodium-bound ylide 148 participating in the reaction.

Independently, McKervey and co-workers also disclosed their findings on chiral rhodium(II) carboxylate catalysts derived from amino acids in 1990. However, unlike the acyclic amino acids used in Ikegami’s work, l-proline was the amino acid chosen for McKervey’s studies. Intramolecular Buchner reactions and aliphatic C–H insertions were the primary focus of McKervey’s preliminary report. In particular, N-naphthalenesulfonyl catalyst 150b provided cycloheptatriene 152 in 80% yield and 33% ee (Scheme 37). Low enantioselectivities were obtained in the case of aliphatic C–H insertion. Although selectivities in both reactions were modest, McKervey’s methodology paved the way for highly stereoselective transformations via rhodium(II) proline catalysis (vide infra).

Several derivatives of McKervey’s catalysts have been developed by Davies and co-workers. Initial reports compared enantioselectivities of McKervey’s catalysts to rhodium(II) N-((p-t-butylsulfonyl)proline 155 [Rh₂(S-TBSP)_4] for cyclopropanation of styrene with vinyl diazoacetates. In general, cyclopropanations with unsubstituted or alkyl substituted diazoacetates such as ethyl diazoacetates. In general, cyclopropanations with unsubstituted or alkyl substituted diazoacetates such as ethyl diazoacetate exhibited minimal diastereoselectivity (E/Z 1:2:1) and minimal enantioselectivity (≤30% ee). Conversely, use of vinyldiazoacetates afforded the E-cyclopropane isomer exclusively. Furthermore, vinyldiazoacetate 151 underwent cyclopropanation with McKervey’s catalyst in 87% ee, while Rh₂(S-TBSP)_4 provided the desired product in even higher enantioselectivity (Scheme 38).

One benefit of Davies’ catalyst was its greater solubility in nonpolar solvents such as pentane, allowing for higher stereoselectivity. Other variables affecting enantioselectivity included ester size in the diazo substrate and olefin substituents. Methyl esters were determined to be superior to bulkier esters in cyclopropanations while reactions with electron-deficient olefins gave cyclopropanation products with substantially lower stereocontrol. From this thorough investigation, N-alkylsulfonyl substituents were determined to be inferior to their aryl counterparts. In addition, stericly demanding ortho substituted arylsulfonyl substituents lowered the enantioselectivity. Although azetidine and picolinate derived catalysts provided relatively high enantiocontrol, the most promising results were obtained with Rh₂(S-TBSP)_4 and Rh₂(S-DOSP)_4. Both catalysts displayed enhanced solubility in pentane compared to McKervey’s catalysts, presumably due to the lyophobic 4-alkyl substituents. Furthermore, the enantioselectivities were outstanding. In particular, the Rh₂(S-DOSP)_4 catalyzed reaction of vinyldiazoacetate 151a with styrene at −78 °C in pentane afforded a 68% yield of cyclopropane 157 in 98% ee.

In this report, Davies provided an excellent model for the stereoccontrol observed with rhodium(II) proline catalysts. Based on steric arguments, the aryl sulfonyle stilbuen ts are proposed to exist in an alternating up, down, up, down conformation (Figure 5). This D₂ symmetry allows for a side-on approach of the olefin substrate over the carbeneid ester. A side-on approach is in compliance with the fact that trans-alkenes are unreactive with these catalysts. Additionally, the steric bulk of the aryl sulfonates

Scheme 38 Application of Davies’ proline catalyst.

In 1996, Davies and co-workers synthesized eleven chiral dirhodium(II) carboxylate catalysts in a quest to determine the stereochemical consequences of various N-aryl sulfonyle prolinates (Figure 4). In addition, the requirement for a five-membered heterocycle was tested by synthesizing and comparing several acyclic, azetidinone, and picolinate derived catalysts. The mode of reactivity chosen was again cyclopropanation of styrene with vinyldiazoacetates. With the exception of catalysts 158e.f and acyclic catalysts 159a,b, enantioselectivities were ≥74%. Additionally, diastereoselectivities in all cases were ≥40:1 in favor of the E-isomer.

Figure 4 Chiral carboxylate catalysts.

From this thorough investigation, N-alkylsulfonyl substituents were determined to be inferior to their aryl counterparts. In addition, stericly demanding ortho substituted arylsulfonyl substituents lowered the enantioselectivity. Although azetidine and picolinate derived catalysts provided relatively high enantiocontrol, the most promising results were obtained with Rh₂(S-TBSP)_4 and Rh₂(S-DOSP)_4. Both catalysts displayed enhanced solubility in pentane compared to McKervey’s catalysts, presumably due to the lyophobic 4-alkyl substituents. Furthermore, the enantioselectivities were outstanding. In particular, the Rh₂(S-DOSP)_4 catalyzed reaction of vinyldiazoacetate 151a with styrene at −78 °C in pentane afforded a 68% yield of cyclopropane 157 in 98% ee.

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prohibits other orientations for alkene approach. Due to the D_2 symmetry of the catalyst, the same stereochemical outcome would arise from reaction at either end face of the catalyst.

The proposal that conformationally constrained D_2 symmetric catalysts allowed for excellent enantiocontrol led Davies co-workers to synthesize a ‘dimeric’ t-butylylnylsulfonyl prolinate catalyst 162 (Figure 6). In this design, TBSP ligands were joined at the 2 position of the prolinate through an m-xylene tether, thus locking the catalyst into an alternating up, down, up, down conformation. However, when compared to Rh_2(S-TBSP)_4, the enantiocontrol imparted by 162 is lower. In addition, the opposite cyclopropane enantiomer was obtained.

To determine if the origin of enantiomeric reversal was due to C-2 substitution, methyl derivative 163 was examined. Enantioselectivity was drastically reduced in comparison with the parent catalyst, although the absolute configuration was the same. To more closely mimic the steric demands of the tether, benzyl derivative 164 was also created. Extremely low enantiocontrol was obtained in this case and, indeed, the opposite absolute configuration was slightly favored.

Because additional proline C-2 substitution was detrimental to stereocntrol, a second class of bidentate ligands tethered at the C-5 position was developed. In contrast to previous reports where monodentate Rh(II) N-(2,4,6-triisopropylphenylsulfonyl) prolinate catalyst 158e induced less enantiocontrol than both Rh_2(S-TBSP)_4 and Rh_2(S-DOSP)_4, this was the N-substitution of choice in the bidentate derivative (Figure 7). In fact, cyclopropanation of styrene led to 98% ee of cyclopropane 157 in dichloromethane at –50 °C, while Rh_2(S-DOSP)_4 catalyzed cyclopropanation proceeded in 89% ee, albeit producing the opposite enantiomer. Thus, rhodium(II)-tethered prolinate 165 is superior to monodentate Rh_2(S-DOSP)_4 in more polar solvents, allowing for a broader range of reactivity with chiral rhodium(II) prolinate catalysts.

Ishitani and Achiwa prepared several substituted N-benzoyl prolinate catalysts to compare with the highly enantioselective N-arylsulfonyl catalysts. Catalysts 166a-e were utilized for ylide generation from diazo substrate 168 and subsequent trapping with dihydrofuran. Although the catalysts afforded fused tricycle 169 in ≥ 93% ee, product yields were largely dependent on the electronic nature of the N-benzoyl substituent. In general, electron rich N-substituents significantly lowered the yield of 169. In particular, ylide formation was prohibited altogether when X = NMe_2. However, yields of up to 66% were achieved with more electron deficient N-benzoyl substituents (Scheme 39). These results are surprising given the remote position of the different substituents, but may be due to the facility of amide bond rotation.

Azetidine and aziridine derived catalysts 170, 160, and 171 were synthesized by Zwanenburg co-workers to explore the effect of ring size on catalysis (Scheme 40). Davies had previously explored azetidine catalyst 160 and obtained promising results. Excellent diastereoselectivities were obtained in the cyclopropanation of styrene with methyl phenyldiazoacetate 70 utilizing catalysts 160 and 171. However, enantioselectivities were dramatically lower.
lower than those obtained with proline derived Rh\textsubscript{2}(S-TBSP)\textsubscript{4}. Similar trends were also observed in the cyclopropanation of α-methylstyrene. Thus, five-membered amino acid derived ligands appear to be critical to enantioselective success.

In some additional examples of the utility of the Rh\textsubscript{2}(S-DOSP)\textsubscript{4} (155c) catalyst and diazo substituent effects, Davies and co-workers demonstrated high levels of enantiocontrol in reactions of cycloheptatriene with both phenyl- and vinyldiazoacetates. Unlike ethyl diazoacetate which reacted solely via cyclopropanation to give product \textsubscript{174} in only 6% ee (Scheme 41), phenyldiazoacetate \textsubscript{70} instead led almost exclusively to allylic insertion in 95% ee. Excellent enantioselectivity was also seen for vinyldiazoacetate \textsubscript{61a}, which yielded C–H insertion/Cope rearrangement product \textsubscript{176} in 99% ee. Under refluxing conditions, a second Cope rearrangement led to the desired C–H insertion product \textsubscript{177} with no loss of enantiopurity.

The enormous body of work compiled by Davies and co-workers has proven many researchers wrong in their belief that the chirality in Rh(II) carboxylates is too far removed from the reactive carbened center to create a chiral environment. With the use of proline catalysts such as Rh\textsubscript{2}(S-DOSP)\textsubscript{4}, excellent enantiocontrol was achieved. As seen with achiral catalysts, carbenoid substitution in rhodium(II) proline catalyzed reactions was also crucial in obtaining exemplary diastereo- and enantioselectivities. Incorporating both an electron-withdrawing substituent such as an ester and an electron donating substituent such as phenyl or vinyl was absolutely necessary for stereosecontrol. Diazoo substrates lacking either functionality, i.e. ethyl diazoacetate, dimethyl diazomalonate, phenyldiazoacetamide, and vinyldiazoacetamide, exhibited substantially reduced stereoselectivity. This methodology has not only been utilized in olefin cyclopropanations, but also in tandem cyclopropanation/Cope rearrangements and intermolecular Si–H and C–H insertions. In all cases, excellent diastereo- and enantioselectivities were achieved.

### 3.2 Carboxamidate Ligands

Chiral rhodium(II) carboxamidate catalysts derived from pyrrolidinones and oxazolidinones were initially reported by Doyle and co-workers in the same year that Ikegami and McKervey disclosed their findings on chiral carboxylate catalysts. Rh\textsubscript{2}(4S-IPOX)\textsubscript{4} and Rh\textsubscript{2}(4S-BNOX)\textsubscript{4} derived from 4-isopropyl- and 4-benzylazolidinones, and Rh\textsubscript{2}(5S-ME PY)\textsubscript{4} from the 5-methyl ester of pyrrolidinone (Figure 8), were investigated in the cyclopropanation of styrene with d- and l-methyl diazoacetate (Scheme 42). Although diastereoselectivities ranged from 2:1 to 3:1 in favor of the trans-cyclopropane \textsubscript{182}, enantioselectivities were substantially higher for the cis-isomer. Rh\textsubscript{2}(5S-MEPY)\textsubscript{4} gave the best enantiocontrol when matched with d-methyl diazoacetate \textsubscript{181}, providing cis-\textsubscript{182} in 88% ee. To prove that the stereoselectivity was a result of the chiral catalyst and not of the chiral auxiliary, use of achiral Rh\textsubscript{2}(OAc)\textsubscript{4} afforded cis-cyclopropane in a mere 13% ee.

![Figure 8](1150) Chiral rhodium(II) carboxamidate catalysts.
Many additional modes of reactivity were investigated by Doyle co-workers comparing oxazolidinone and pyrrolidinone derived catalysts. In all cases, Rh$_2$(5S-MEPY)$_4$ catalysis was paramount for high enantioselectivity. Intramolecular cyclopropanation of diazoketone 183 afforded a modest 56% ee with Rh$_2$(4R-BNOX)$_4$, but increased to 98% ee with Rh$_2$(5S-MEPY)$_4$ (Scheme 43). Similarly dramatic results were obtained for intramolecular aliphatic C–H insertion.

Rhodium(II) carboxamide catalysts of this design exist in a cis-2,2 configuration (Figure 8). Determination of equilibrium constants for acetonitrile association demonstrated that oxazolidinone derived catalysts were more reactive than their pyrrolidinone counterparts. However, their increased reactivity was compromised by lower enantiocontrol.

In an extensive investigation of the stereochemical consequences of olefin substitution in Rh$_2$(5S-MEPY)$_4$ catalyzed intramolecular cyclopropanation, Doyle, Martin, and co-workers found internal olefin substitution diminished enantioselectivities almost completely. For example, the parent olefin 185a ($R^t = R^c = R^i = H$) provided cyclopropanation in 95% ee. However, methyl substitution at the internal position produced cyclopropane 186b in only 7% ee (Scheme 44). Bulky trans-substitution also decreased enantiocontrol. On the other hand, cis-substitution was highly tolerated and imparted no loss in enantiocontrol.

A transition state model for olefin approach was constructed to explain the experimental results of alkene substitution. Molecular modeling revealed that the carbenoid complex of Rh$_2$(5S-MEPY)$_4$ allowed for the approach of a tethered olefin as depicted in Figure 9. Applying this model directly to allylic diazoacetates 185 illustrated the steric constraints of $R^t$ and $R^i$ substitution.

Imidazolidinone ligands were also used for chiral rhodium(II) carboxamidate catalysts and further enhanced enantiocontrol (Scheme 45). In particular, Rh$_2$(4S-MACIM)$_4$, 187 and the more sterically demanding Rh$_2$(4S-MPPIM)$_4$, 188 were synthesized and compared to Rh$_2$(5S-MEPY)$_4$, the most promising carboxamide catalyst thus far. Formation of cyclopropanated $\gamma$-lactones was investigated with various alkene substituents and excellent enantioselectivities were achieved in all cases with Rh$_2$(4S-MPPIM)$_4$. In particular, high levels of enantiocontrol were obtained in the formation of products with a quaternary center with Rh$_2$(4S-MPPIM)$_4$. This was in stark contrast to the results obtained with Rh$_2$(5S-MEPY)$_4$, in which the $\gamma$-lactone was formed in only 7% ee.

Substantial improvements were also observed for Rh$_2$(4S-MPPIM)$_4$ catalyzed intramolecular aliphatic C–H insertion. The yield and enantioselectivity dramatically improved from 35% yield and 36% ee in the case of Rh$_2$(5S-MEPY)$_4$ catalyzed reaction of diazoester 189 to 75% yield.
and 92% ee for Rh$_2$(4S-MPPIM)$_4$ catalysts (Scheme 46). Additionally, aliphatic C–H insertion to form γ-lactones was highly favored over the formation of β-lactones under Rh$_2$(4S-MPPIM)$_4$ catalysis. This regioselectivity was diminished, however, with Rh$_2$(5S-MEPY)$_4$ and mixtures of products were obtained.

Scheme 46

Although the pyrrolidinone Rh$_2$(5S-MEPY)$_4$ catalyst has proven to be highly stereoselective in many cases, limitations exist with this catalyst. For example, Rh$_2$(4S-MEPY)$_4$ catalyzed cyclopropanation of styrene yielded a slight preference for the trans-isomer in 58% ee, while the cis-isomer was obtained in a modest 33% ee.$^{34}$ In an effort to determine if ligand ring size substantially impacted diastereo- and enantioselectivity, azetidinone catalysts 191a–c were prepared. In particular, Rh$_2$(4S-IBAZ)$_4$ catalyzed cyclopropanation of styrene with ethyl diazoacetate afforded predominantly the cis-isomer in a 2:1 ratio and 73% ee (Scheme 47). Increasing the steric bulk of the diazoester further improved enantiocontrol.

Scheme 47 Reactions employing Doyle’s chiral azetidinone catalysts.

Another limitation of the Rh$_2$(5S-MEPY)$_4$ catalyst is its inability to generate the rhodium carbeneoid of dimethyl diazomalonate.$^{35}$ Vinyl diazomalonates are also unreactive with Rh$_2$(5S-MEPY)$_4$ and, instead, lead to pyrazole products at elevated temperatures.$^{36}$ Doyle and co-workers found that shrinking the ring system from the five-membered pyrrolidinone to the four-membered azetidinone while maintaining the methyl ester allowed for unprecedented reactivity of chiral rhodium(II) carboxamidates. The enhanced reactivity is presumably due to the longer Rh–Rh bond in the azetidinone catalyst, which arises from the coordinating geometry of the azetidinone. Rh$_2$(5S-MEPY)$_4$, Rh$_2$(S-TBSP)$_4$, and Rh$_2$(S-TBSP)$_4$ catalysts developed by Davies were typically used to achieve high levels of enantiocntrol in intermolecular cyclopropanations with vinyl- and phenyldiazoacetates (vide supra). However, results were less than desirable for intramolecular variants. In comparison, Rh$_2$(4S-MEAZ)$_4$ allowed for substantially improved enantioselectivity for both vinyl- and phenyldiazoacetates intramolecular reactions (Scheme 48).

Scheme 48

To further improve rhodium(II) carboxamidate reactivity with vinyl- and phenyldiazoacetates and diazomalonates, fluorinated versions of Rh$_2$(4S-IBAZ)$_4$ and Rh$_2$(4S-MEPY)$_4$ were prepared (Figure 10).$^{37}$ Although these catalysts were significantly more reactive toward carbenoid generation, enantioselectivity suffered in the cyclopropanation of styrene. Rh$_2$(4S-dFIBAZ)$_4$ gave more promising results for ylide generation and subsequent [2,3]-sigmatropic rearrangement than its nonfluorinated counterpart. Still, only moderate diastereo- and enantioselectivities were achieved.

Figure 10 Difluorinated carboxamidate catalysts.

Of the oxazolidinone catalysts, Rh$_2$(4S-MEOX)$_4$, bearing a methyl ester, displayed high levels of enantiocntrol and often opposite chemoselectivity compared to Rh$_2$(5S-MEPY)$_4$. For example, two modes of reactivity were possible for substrates such as 200, in which an alkyn and diazoacetate were tethered by naphthalene.$^{38}$ While Rh$_2$(5S-MEPY)$_4$ afforded a slight preference for cyclopropanation in 62% ee, Rh$_2$(4S-MEOX)$_4$ exclusively provided norcaradiene 202 in 73% ee (Scheme 49).
Regiocomplimentary transformations were also rapidly accessed with Rh₂(5S-MEPO)₄ and Rh₂(4S-MEOX)₄. For example, Doyle co-workers explored C–H insertion of steroidal diazoacetates for A-ring elaboration. In all cases investigated, Rh₂(5R-MEPO)₄ substantially favored formation of the γ-lactone from C-2 insertion (Scheme 50). However, this preference was completely altered when catalyzed by Rh₂(4S-MEOX)₄ and instead β-lactone 205 was formed via insertion at C-3. The α facial selectivity was the same in both cases.

Complimentary results, both chemoselectively and enantioselectively, were obtained when dirhodium(II) carboxylates such as Rh₂(5S-MEPO)₄ were compared to copper(I) bisoxazoline catalysts such as Cu(box)PF₆ (Scheme 51). Increasing the tether length between olefin and diazoacetate promoted large ring formation by cyclopropanation with Cu(box)PF₆. With this catalyst, enantioselectivity increased dramatically with increasing ring size. On the other hand, chiral carboxamidates afforded high enantiocontrol only for small rings formed via cyclopropanation. These values decreased with larger ring formation along with an increased propensity for C–H insertion. Again, catalyst choice is vital to chemo- and stereoselectivities.

As illustrated in Schemes 28–31, complexation of arenes by a chromium tricarbonyl moiety has profound effects on reactivity toward rhodium carbenoids. Further, the chromium imparts an element of chirality making the protons ortho to a side chain in a mono substituted arene enantiotopic. While complexation served to protect an arene from aryl C–H insertion with simple rhodium acetate catalysis (Scheme 31), use of carboxamide ligands on rhodium had remarkable results (Scheme 52). Not only did product 210 arise from aryl C–H insertion on the complexed ring formed in 75% yield, but a 90% ee was obtained using the Rh₂(5S-MEPO)₄ catalyst. The only other example of construction of a planar chiral product via aryl C–H insertion is a synthesis of a chiral ferrocene using a chiral copper catalyst.

Recently, Doyle and co-workers demonstrated that Rh₂(5S-MEPO)₄ could be immobilized by converting one methyl ester to a link to either polystyrene or polyethylene oxide extended polystyrene (Tentagel). Interestingly, catalyst immobilization did not limit selectivity or diminish product yields, but actually slightly enhanced enantioselectivity and turnover numbers in some cases. The catalysts could be recovered and reused up to seven times without a reduction in enantioselectivity.

In 2001, Timmons and Doyle addressed in a review ‘the art of chiral carboxamidate catalyst selection’. The catalysts compared included Rh₂(5S-MEPO)₄, Rh₂(4S-MEOX)₄, Rh₂(4S-MPPIM)₄, Rh₂(4S-MEOX)₄, and Rh₂(4S-IBAZ)₄. Table 1 summarizes years of research in this field and provides trends for optimal catalyst choice for the desired transformation.

### 3.3 Phosphate Ligands

In 1992, back-to-back articles from McKervey and Pirrung described the potential of chiral phosphate catalysts. McKervey and co-workers developed rhodium(II) phosphate catalysts based on axially chiral bidentate binaphthol (Scheme 53). Three separate modes of reactivity were explored with Rh₂{HCO₃}₂{(+-Phos)}₂SₗH₂O (211): [2,3]-simatropic rearrangement, intramolecular aliphatic C–H insertion and intramolecular...
Buchner reaction. A high yield and a 60% ee were achieved for the Buchner reaction, while modest enantioselectivities were obtained in the other two reaction pathways. This report was the first to demonstrate stereocontrol in a [2,3]-sigmatropic rearrangement.

The following article introduced a second binaphthol phosphate catalyst, (BNP)_4 Rh_2 (216). This preliminary report by Pirrung and Zhang focused on ylide generation and subsequent dipolar cycloaddition with furan derivatives. Thus, cycloadduct 218 was obtained in 50% ee (Scheme 54).

Hodgson co-workers recently undertook an extensive investigation of ylide generation and subsequent intramolecular trapping with an olefin to synthesize highly complex tricyclic systems. Attempts to catalyze the reaction with widely used chiral catalysts such as Cu(box)PF_6, rhodium(II) carboxamidates, and rhodium(II) carboxylates gave unsatisfactory results. The most promising catalyst was Pirrung’s (BNP)_4 Rh_2 catalyst, affording the desired product in 65% ee. Based on this, several other binaphthol phosphate derivatives were examined. Of the second generation catalysts, Rh_2{(R)-ddbn} (219) improved enantioselectivities significantly to afford 222 in high yield and 89% ee (Scheme 55).

### 3.4 Phosphine Ligands

Rhodium(II) catalysts bearing ortho-metalated phosphine ligands are highly chemoselective for olefin cyclopropanation over both aliphatic and aryl C–H insertion (Scheme 56). Such catalysts exist as atropisomeric enantiomers and are readily separated. With rhodium(II) carboxamidate catalysts, minimal enantiocontrol was possible in intramolecular cyclopropanations with diazoketones, unlike that observed with their diazoacetate counterparts. In contrast, enantioselectivities ranging from 80–95% were achieved for cyclopropanes utilizing phosphine-derived catalysts in pentane (Scheme 56). These high levels of stereocontrol were comparable to those achieved with Pfaltz’s semicorrin-copper catalyst, however, yields were significantly higher with catalysts 223a,b. This new class of chiral dirhodium(II) catalysts compliments the widely used chiral carboxylate and carboxamidate catalysts by providing high levels of enantiocontrol previously unattainable for certain substrates.
4. Conclusions

Rhodium(II) catalyzed reactions of α-diazo carbonyl compounds are extremely useful for a wide variety of synthetic transformations. However, attention to detail in all regards is crucial for high levels of chemo-, diastereo-, and enantioselectivity. Steric, electronic, and conformational variations play an enormous role in determining the favored reaction pathway and product ratios. These variations prove to be important not only in catalyst ligands, but in diazo and substrate substitution patterns as well. Thus, tremendous control can be achieved in C–H insertion, cyclopropanation, Buchner reaction, and ylide generation with the appropriate structural choices. Researchers new to the area and desiring to exploit this chemistry would be well advised to carefully consider literature precedents as they design their experiments in order to attain the most from this powerful chemistry.

References


