Dirhodium(II) Carbenes : The Chiral Product Cascade

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ABSTRACT: The last decade has witnessed enormous growth in the spectrum of highly efficient asymmetric synthetic transformations. One prominent example of this progress is the application of dirhodium (II) carbenes generated from diazo-precursors. Innovative construction of ‘designer’ catalysts has played a integral role in extending the breadth of the synthetic cascade of non-racemic products now available through the range of cyclopropanation, C-X insertion, aromatic cycloaddition-rearrangement, and ylide-based reaction types. This review deals briefly with an overview of the important catalytic systems and maintains as its primary focus the cascade of diverse optically enriched products that flow from their applications.
1. Introduction

1.1 The Need for Asymmetric Synthesis

The world around us is chiral. Most organic compounds are chiral. The chemistry of perfumes, nutrients, pesticides, and pharmaceuticals involves chiral compounds whose physiological or pharmacological properties depend upon their recognition by chiral receptors. Public opinion and associated legislation surrounding the pharmaceutical industry demands, especially since the thalidomide disaster (Figure 1), the preparation and testing of enantiopure compounds. This has, in part, caused asymmetric synthesis to become the single greatest “growth industry” within organic chemistry over the past 25 years. Once the important factors that control reaction stereoselectivity were recognized, development has exploded throughout the arena of organic synthesis (Ager and East, 1996; Gawley and Aubé, 1996; Seyden-Penne, 1995).

Of the handful of approaches to asymmetric synthesis, catalysis has the advantage over stoichiometric synthesis with chirons (enantiomerically pure substrate fragments) or chiral auxiliaries (temporary enantiomerically pure attachments), particularly in terms of large-scale or industrial processes. Catalytic asymmetric reactions have been the subject of research investigations for many years and, particularly over the last decade, the number of catalytic asymmetric processes (some giving enantioselectivities of greater than 99%) has burgeoned (Brünner and Zettlmeier, 1993; Jacobsen et al, 1999). Whilst broad scope and high enantioselectivity are important for any catalytic asymmetric transformation, they alone are not necessarily sufficient to ensure that a process will become widely used, especially on industrial scale. To reach this goal, the process additionally needs to be economical and easy to perform. For this reason, many of the new wave of catalysts are either already commercially available, or are designed for easy or in situ preparation.

1.2 Carbene Reactions

The general group of transformations referred to as “carbene reactions” forms a versatile class of transition metal catalysed processes. These reactions are characterised by the involvement of a transition
metal stabilized carbene that is formed from the decomposition of a diazo compound in the presence of the transition metal catalyst. Further reaction of the carbene may follow a number of pathways including insertion and addition reactions, as well as ylide generation. Recent investigations have focussed on the development of catalysts that control the selectivity of what had traditionally been thought of as non-selective reactions of “free carbenes". Of these, dirhodium catalysts have emerged as arguably the most versatile for a wide range of stereoselective transformations (Doyle et al, 1993a, 1994a, 1996a, 1997a, 1998a, 1998b, 1998c, 1999; Ene and Doyle, 1998; Ye and McKervey, 1994; Roos and Raab, 1997).

Given the rapid growth within this area of endeavor, this review seeks to place these developments in context via the published literature through mid-1999. The specific focus is on homochiral catalysts and therefore excludes chiron-based syntheses, and only pertinent examples of diastereoselectivity via chiral auxiliaries are covered. Previous reviews have tended to focus on details of catalyst development or of subsequent reaction type that the carbene undergoes. Outside of essential introductory material, this review seeks primarily to highlight the wealth of diverse enantiomerically enriched chiral products that are available via the numerous highly chemoselective, regioselective, and stereoselective transformations brought about by dirhodium(II) catalyst systems. Some of these have a high potential for commercial adaptation. Readers seeking further details on access to diazo compounds, catalyst design and preparation, as well as mechanistic aspects are referred to the alternative specialist reviews cited throughout.

![Figure 1. Thalidomide enantiomers](image-url)

2. Generation of Dirhodium(II) Carbenes

2.1 Diazo Compounds

Diazo compounds are derivatives of diazomethane, and as such have stabilities and reactivities that reflect their substituents. Generally, the stabilities of diazo compounds towards diazo decomposition are increased by electron withdrawing substituents, and decreased by electron donating substituents (Figure 2). For this reason, the most widely employed diazo compounds for metal catalysed reactions are diazocarbonyl compounds. Numerous synthetic methodologies are now available for the synthesis of diazo compounds and these have been reviewed by Regitz and Maas (1986) and Doyle et al (1998a).
2.2 Metal-Catalysed Diazo Decomposition

Since diazo decomposition is an acid promoted process, transition metal complexes that are effective catalysts for diazo decomposition are of necessity Lewis acids (Doyle, 1986). Their catalytic activity depends on the metal centre being coordinatively unsaturated, which allows them to react as electrophiles with diazo compounds.

\[
\begin{align*}
Z, Y &= R, OR, NR_2 \\
R &= \text{alkyl, aryl, H}
\end{align*}
\]

Increasing Stability

\[
\begin{align*}
\text{Z, Y = R, OR, NR}_2 \\
\text{R = alkyl, aryl, H}
\end{align*}
\]

Increasing Reactivity

In the generally accepted mechanism for catalytic diazo decomposition, electrophilic addition of the catalyst to the diazo compound causes the loss of dinitrogen from a diazonium ion adduct \(1\) to produce a metal-stabilized carbene \(2\) (Scheme 1). The electrophilic carbene is transferred to an electron-rich substrate (S:) to form the product of the carbene reaction (SCR\(_2\)), with release of the transition metal catalyst to complete the catalytic cycle.

2.3 Dirhodium(II) Catalysts

A wide range of other metals such as copper, cobalt, palladium, ruthenium, osmium, iron, nickel, and zinc have been employed with varying success in catalytic systems (Roos and Raab, 1997; Doyle et al., 1998a). Rhodium, and more specifically dirhodium(II) complexes have proven to be the most effective and versatile catalysts for diazo decomposition (Maas, 1987; Padwa and Krumpe, 1992; Davies, 1993a; Padwa and Austin, 1994; Ye and McKervey, 1994; Doyle, 1995a). Generally, rhodium-mediated carbene reactions proceed under much milder conditions than is common for classical synthetic methodology with copper(II) catalysts (Padwa and Austin, 1994).
Their versatility arises from the large variety of bridging ligands that can be coordinated to the dirhodium(II) skeleton, and in their marked influence on reactivity and selectivity. Dirhodium(II) catalyst complexes are divided into two major groups, those bridged with carboxylate ligands and those bridged with carboxamidate ligands. It is through the tuning of these ligands that particular catalysts are able to provide appropriate chemical properties as well as specific reactivity and selectivity profiles for desired transformations. The dirhodium(II) catalysts are based on the parent dirhodium(II) tetraacetate, \( \text{Rh}_2(\text{OAc})_4 \), first introduced by Paulissen et al. (1973). Since that time, this has been the single most widely used catalyst for metal carbene transformations. \( \text{Rh}_2(\text{OAc})_4 \) possesses four bridging acetate ligands and has \( D_{4h} \) symmetry, leaving one vacant axial coordination site on each metal for carbene attachment (Boyar and Robinson, 1983). A multitude of dirhodium(II) catalysts is available by replacement of the acetate ligands with other carboxylate or carboxamidate ligands. Many of these catalysts have unique properties or synthetic uses (Doyle et al., 1998a, 1998b).

Dirhodium(II) perfluorobutyrate, \( \text{Rh}_2(\text{pfb})_4 \), is the most reactive dirhodium(II) catalyst, and its selectivity in diazo decomposition reactions is often correspondingly poor (Doyle et al., 1993b). In contrast, dirhodium(II) carboxamidates such as \( \text{Rh}_2(\text{acam})_4 \), which have two nitrogen and two oxygen donor atoms at each rhodium, with the two nitrogens arranged \( cis \) to each other (a \( [2,2-cis] \) configuration)
ROOS, RAAB, and AL-HATMI

(Ahsan et al, 1986) are less reactive than the dirhodium(II) carboxylates in diazo decomposition, but are often more selective in the subsequent carbene reactions (Doyle et al, 1989a,b; Doyle et al, 1991a).

Homochiral dirhodium(II) carboxylate catalysts 6 for asymmetric carbene reactions were simultaneously developed in three laboratories (Brunner et al, 1989; Kennedy et al, 1990; Hashimoto et al, 1990; Roos and McKervey, 1992) from enantiomerically pure carboxylic acids. More recent refinements have demonstrated highly successful proline 7 (McKervey and Ye, 1992; Davies et al, 1993b, 1996; Doyle et al, 1996b) and phthalimide 8 derivatives (Hashimoto et al, 1994; Watanabe et al, 1995, 1996a). A recent report (Buck et al, 1998) has employed parallel array techniques to screen rapidly for novel carboxylate catalysts.

In contrast to the dirhodium(II) carboxylates, the rhodium(II) carboxamidates allow placement of an inducing chiral centre adjacent to nitrogen in closer proximity to the axial carbene centre. A series of more than twenty structurally varied homochiral dirhodium(II) carboxamidates derived from chiral cyclic amide ligands has been developed by Doyle and co-workers (Doyle, 1994b, 1996a). In general, dirhodium(II) carboxamidate catalysts based on chiral 2-oxopyrrolidine 9 (Doyle et al, 1993c, 1994c) 2-oxazolidinone 10 (Doyle et al, 1993d, 1995b), N-acylimidazolidinone 11 (Doyle, 1995c, 1996c, 1997b; Roos et al, 1998), and 2-azetidinone 12 (Doyle et al, 1996d) ligands, especially those bearing pendant carboxylate groups, afford the highest levels of enantioselectivity.

Dirhodium(II) complexes 13 bearing chiral phosphate ligands derived from binaphthol have been reported to provide moderate enantioselectivities in a number of carbene reactions (McCarthy et al, 1992; Pirrung and Zhang, 1992). In addition, Estevan et al (1995) prepared a novel set of C$_2$-symmetric catalysts 14 bearing two cis carboxylate ligands along with two orthometallated phosphine ligands.

$$\text{Insertion}$$

$$\text{Cyclopropanation}$$

$$\text{Ylide generation}$$

$$\text{Aromatic cycloaddition}$$

Scheme 2. Diversity of metal carbene reactions
DIRHODIUM(II) CARBENES: THE CHIRAL PRODUCT CASCADE

- **9**
  - a. $A = \text{CO}_2\text{Me}$; Rh$_2$(5S-MEPO)$_4$
  - b. $A = \text{CO}_2\text{CH}_2\text{CMe}_3$; Rh$_2$(5S-NEPO)$_4$
  - c. $A = \text{CO}_2\text{CH}_2\text{Me}$; Rh$_2$(5S-ODPO)$_4$
  - d. $A = \text{CONMe}_2$; Rh$_2$(5S-DMP$_4$

- **10**
  - a. $A = \text{CO}_2\text{Me}$, $R = \text{H}$; Rh$_2$(4S-MEPO)$_4$
  - b. $A = \text{CO}_2\text{Me}$, $R = \text{CH}_3$; Rh$_2$(4S-THREPO)$_4$
  - c. $A = \text{CH}_2\text{Ph}$, $R = \text{H}$; Rh$_2$(4R-BNOPO)$_4$
  - d. $A = \text{iPr}$, $R = \text{H}$; Rh$_2$(4R-IPOX)$_4$
  - e. $A = \text{Ph}$, $R = \text{H}$; Rh$_2$(4R-PHOX)$_4$

- **11**
  - a. $A = \text{CO}_2\text{Me}$, $R = \text{CH}_3$; Rh$_2$(4S-MACPO)$_4$
  - b. $A = \text{CO}_2\text{Me}$, $R = \text{Ph}$; Rh$_2$(4S-MBOPO)$_4$
  - c. $A = \text{CO}_2\text{Me}$, $R = \text{PhCH}_2$; Rh$_2$(4S-MPAPPO)$_4$
  - d. $A = \text{CO}_2\text{Me}$, $R = \text{PhCH}_2\text{CH}_2$; Rh$_2$(4S-MPPPO)$_4$
  - e. $A = \text{CO}_2\text{Me}$, $R = \text{c-C}_6\text{H}_{11}\text{CH}_2$; Rh$_2$(4S-MCHPO)$_4$

- **12**
  - a. $A = \text{CO}_2\text{CH}_2\text{Ph}$; Rh$_2$(4S-BAZPO)$_4$
  - b. $A = \text{CO}_2\text{CH}_2\text{CHMe}_2$; Rh$_2$(4S-BAZPO)$_4$

- **13**
  - a. Rh$_2$(5S-BNHP)$_2$(HCO$_3$)$_2$
  - b. Rh$_2$(5R-BNHP)$_4$

- **14**
  - a. $X = \text{H, F, CH}_3, \text{CF}_3$
3. Reaction Products From Dirhodium(II) Carbenes

The metal-carbenes resulting from the diazo decomposition of α-diazocarbonyl compounds by a transition metal catalyst, are versatile electrophilic reagents. Dirhodium(II) catalysed diazo decompositions provide the greatest versatility in subsequent carbene reactions, and provide many synthetically useful transformations. This includes inter- and intramolecular reactions as diverse as cyclopropanation, cyclopropenation, insertion, aromatic cycloaddition, and ylide generation (Scheme 2). As a result, the range of stereoselectively generated product types is large.

Researchers in this area have tested a variety of fundamental approaches to the asymmetric production of chiral compounds via dirhodium(II)-catalysed reactions (Scheme 3). Thus, (a) diastereoselective reaction of achiral catalysts with diazo substrates containing chiral auxiliaries, (b) enantioselective reaction between chiral catalysts and achiral substrates, and in a few instances (c) a double diastereoselective approach with both chiral catalyst and substrate have been used. For the purpose of orderly classification, the range of product molecules has been grouped according to the reaction type via which they are generated.

3.1 Cyclopropanes and Cyclopropenes

Due to their biological significance and synthetic utility, cyclopropanes and cyclopropenes are extremely important target molecules (Rappoport, 1987; Binger and Büch, 1987; Baird, 1988; Salaün, 1989). They are often present as structural sub-units in natural and non-natural products (Rappoport, 1987; Burke and Grieco, 1979; Hudlicky et al, 1985; Ho, 1988; Burgess and Ho, 1994), are frequently used as mechanistic probes to elucidate reaction pathways (Suckling, 1988; Silverman et al, 1993; Newcomb and Chestney, 1994; Caldwell and Zhou, 1994; Husbands et al, 1994), and are increasingly valuable as synthetic intermediates (Wong et al, 1989; Davies, 1991; Reissig, 1995).
Since the availability of enantiomerically pure cyclopropanes is critical to many applications, a number of useful methods for their enantioselective synthesis have been developed. These include the cyclopropanation of chiral bicyclic lactams to give optically pure di- and trisubstituted cyclopropanes; highly diastereoselective Simmons-Smith cyclopropanation of chiral auxiliary-derivatised allylic ethers; enantioselective Simmons-Smith cyclopropanation of allylic alcohols using diethylzinc that is coordinated with chiral ligands; and enzymatic resolutions of meso-cyclopropanes. In the field of asymmetric synthesis, cyclopropanation of electron-rich olefins by catalytic diazo decomposition of α-diazocarbonyl compounds with chiral catalysts equation 1, particularly copper and rhodium, has become an attractive and important route to optically active cyclopropanes (Maas, 1987; Doyle, 1993a, 1998a, 1998d; Ye and McKervey, 1994, Singh et al, 1997). Cyclopropanation may either be performed intermolecularly or intramolecularly. A successful example of the former is the commercial synthesis (by the “Sumitomo process”) of optically pure cilastatin 15, an in vivo stabiliser of the antibiotic imipenem (Doyle, 1995a). Generally it has been found that copper-based systems are the better catalysts for intermolecular cyclopropanation with traditional diazoacetates, whilst dirhodium catalysts provide the better results in intramolecular variants (Roos and Raab, 1997; Doyle et al, 1998a).

3.2 Intermolecular Processes

Initial attempts at asymmetric intermolecular cyclopropanations by means of chiral auxiliaries bonded to diazoacetates were largely unsuccessful (equation 1, Z = chiral auxiliary). Chiral N-(diazoacetyl)oxazolidinones 16 and 17 underwent Rh$_2$(OAc)$_4$ catalysed cyclopropanation of styrene in
good yield but with low diastereoselectivity (Doyle et al, 1990). High diastereoselectivities in the catalytic cyclopropanation of diazo compounds bearing chiral auxiliaries have only been achieved in select cases (Davies et al, 1993c; Doyle et al, 1993e). These reports now include diastereomeric excesses of up to 97% in the dirhodium(II) octanoate catalysed cyclopropanation of styrenes and vinyl ethers with (R)-pantolactone- and (S)-lactate-substituted vinyl diazomethane 18 with (Table 1) (Davies et al, 1993c, 1997a). These workers (Davies et al, 1998a) have shown that appropriate choice of vinyl diazo substituent allows facile subsequent transformation of the cyclopropyl products to 2,3-dihydrofurans with high asymmetric induction.

Table 1. Diastereoselective intermolecular cyclopropanation with vinyl diazoacetates containing chiral auxiliaries.

<table>
<thead>
<tr>
<th>R</th>
<th>Diazo</th>
<th>de, %</th>
<th>Abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>18a</td>
<td>89</td>
<td>(1R,2R)</td>
</tr>
<tr>
<td>Ph</td>
<td>18a</td>
<td>97</td>
<td>(1R,2R)</td>
</tr>
<tr>
<td>pClC₆H₄</td>
<td>18a</td>
<td>&gt;95</td>
<td>(1R,2R)</td>
</tr>
<tr>
<td>pMeOC₆H₄</td>
<td>18a</td>
<td>&gt;95</td>
<td>(1R,2R)</td>
</tr>
<tr>
<td>AcO</td>
<td>18a</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>EtO</td>
<td>18a</td>
<td>92</td>
<td>-</td>
</tr>
<tr>
<td>Ph</td>
<td>18b</td>
<td>67</td>
<td>(1S,2S)</td>
</tr>
</tbody>
</table>

This methodology has been extended to diene systems, furans (Davies et al, 1996b) to give 8-oxabicyclo[3.2.1]octan-3-ones and pyrroles (Davies et al, 1997b) to give tropanes (Scheme 4). The fundamental reaction sequence has allowed the preparation of the oxabicycles 20-22 and a series of 2β-acyl-3β-aryltropanes 23 (Davies et al, 1994a, 1996c), which are important building blocks in further synthesis.
Enantioselective approaches have surveyed two distinct types of homochiral dirhodium(II) carboxylates. Brünner et al (1989) used carboxylate ligands of the type $R_1R_2R_3CCOO$, as in catalysts 6 (substituents varied from H, Me, and Ph; to OH, NHAc, and CF$_3$) and Kennedy et al (1990) pursued the chiral prolinate derivatives 7 ($Z = H$). They found that enantioselectivities in the cyclopropanation of styrene with ethyl diazoacetate were less than 12% ee and 30% ee respectively. More recently, Davies et al (1993b, 1996b, 1997) have used modified prolinate catalysts with vinyldiazoacetates to achieve enantioselectivities of $\geq 90\%$, with correspondingly high diastereoselectivities (Table 2). It has further been shown that with suitably fuctionalised vinyldiazoacetates, the cyclopropyl products can afford cyclopentenes with high stereoselectivity (Davies et al, 1998b). A recent catalyst, based on an axially
Table 2. Dirhodium(II) prolinate catalyzed intermolecular cyclopropanation with vinyldiazoacetates

\[
\begin{array}{ccc}
\text{R} & \text{ee, % with} & \text{ee, % with} \\
 & \text{Rh}_2(\text{TBSP})_4 & \text{Rh}_2(\text{DOSP})_4 \\
\text{Ph} & 90 & 98 \\
p\text{ClC}_6\text{H}_4 & 89 & >97 \\
p\text{MeOC}_6\text{H}_4 & 83 & 90 \\
\text{AcO} & 76 & 95 \\
\text{EtO} & 59 & 93 \\
n\text{Bu} & >90 & - \\
\text{Et} & >95 & - \\
i\text{Pr} & 95 & - \\
\end{array}
\]

dissymmetric biphenyl, does as yet not appear to offer any significant advantages over existing examples (Ishitani and Achiwa, 1997).

Scheme 5. Stereoselective synthesis of cyclopropaneamino acids

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{Ph} \quad \text{Ph} \\
\text{CO}_2\text{Me} \\
\text{Ph} \quad \text{Ph} \\
\text{CO}_2\text{H} \\
\text{Ph} \\
\text{NH}_2\cdot\text{HCl} \\
\text{HCl/EtOAc} \\
\text{NEt}_3, \text{DPPA}, \text{tBuOH; [(CH}_3)_3\text{COCO]}_2\text{O; NaOH/H}_2\text{O/THF; HCl/EtOAc} \\
a: \text{RuCl}_3/\text{NaIO}_4 \quad b: \text{K}_2\text{CO}_3, \text{Me}_2\text{SO}_4 \quad c: \text{LiOH, MeOH} \quad d: \text{NEt}_3, \text{DPPA, tBuOH; [(CH}_3)_3\text{COCO]}_2\text{O; NaOH/H}_2\text{O/THF; HCl/EtOAc} \\
94\% \quad 78\% \quad 66\%
\end{array}
\]
The vinyl functionality that exists in the cyclopropane offers a number of opportunities for further transformations. One generally useful application is for the stereoselective synthesis of cyclopropaneamino acids (Scheme 5) (Davies et al, 1993b, 1996b). This approach has been utilised in a recent synthesis of the antidepressant sertraline (Scheme 6) (Corey and Grant, 1994).

The extension of asymmetric vinylcarbenoid cyclopropanation to dienes affords a good general entry into seven-membered rings equation 2 (Davies et al, 1994b). The stereoselectivity that occurs results in a strong preference for the formation of cis-divinylcyclopropanes, and the subsequent Cope rearrangement follows with a predictable stereochemical outcome.
This methodology, which represents a formal [3 + 4]-cycloaddition, has been well exploited by Davies et al (1994b) (Scheme 7) (Table 3).

Table 3. Enantioselective synthesis of bicyclo[3.2.1]octadienes

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>ee % with $\text{Rh}_2(S\text{-TBSP})_4$</th>
<th>ee % with $\text{Rh}_2(S\text{-DOSP})_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>75</td>
<td>93</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>CH=CH$_2$</td>
<td>H</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>63</td>
<td>-</td>
</tr>
<tr>
<td>CO$_2$Et</td>
<td>H</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td>H</td>
<td>OTBS</td>
<td>42</td>
<td>-</td>
</tr>
</tbody>
</table>

Although the dirhodium(II) carboxamidate catalysts 9-12 are able to provide substituted cyclopropanes with reasonable levels of enantioselectivity, they suffer the drawback of poor
diastereoselective when diazoacetates are employed, with mixtures of trans- and cis-adducts being formed (Table 4) (Doyle et al., 1993d; Müller et al., 1995; Watanabe et al., 1996b). Diastereoselectivity can only be effectively induced when sterically demanding diazo esters can be employed. The most noteworthy recent examples have been reported with the catalysts Rh₂(4S-IBAZ)₄ 12b (Doyle et al., 1996d) and Rh₂(S-PTPI)₄ (Kitagaki et al., 1997) where enantioselectivities of up to 95% have been achieved in selected systems. The situation has been somewhat improved by the discovery that methyl phenyl diazoacetate 24 is an excellent substrate for intermolecular cyclopropanation (Table 5) (Davies et al., 1996d; Doyle et al., 1996b).

Homochiral dirhodium(II) carboxamidates, in particular 9a, have proven to be exceptional catalysts for highly enantioselective intermolecular cyclopropanation (Table 6) (Doyle et al., 1994d). Since the cyclopropene products can be quantitatively reduced to cis-cyclopropanes, this provides an alternative route to these products in high enantiomeric purity.

Table 4. Dirhodium(II) carboxamide catalyzed intermolecular cyclopropanation

<table>
<thead>
<tr>
<th>R</th>
<th>Catalyst</th>
<th>Trans yield % (de %)</th>
<th>Cis yield % (de %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-menthyl</td>
<td>Rh₂(5S-MEPY)₄</td>
<td>57 (31)</td>
<td>43 (88)</td>
</tr>
<tr>
<td>Et</td>
<td>Rh₂(5S-MEPY)₄</td>
<td>56 (58)</td>
<td>44 (33)</td>
</tr>
<tr>
<td>l-menthyl</td>
<td>Rh₂(4S-PHOX)₄</td>
<td>27 (40)</td>
<td>73 (72)</td>
</tr>
<tr>
<td>Et</td>
<td>Rh₂(4S-PHOX)₄</td>
<td>34 (24)</td>
<td>66 (57)</td>
</tr>
<tr>
<td>d-menthyl</td>
<td>Rh₂(4R-BNOX)₄</td>
<td>67 (34)</td>
<td>33 (62)</td>
</tr>
<tr>
<td>Et</td>
<td>Rh₂(4R-BNOX)₄</td>
<td>46 (8)</td>
<td>54 (13)</td>
</tr>
<tr>
<td>cyc-(C₆H₁₁)₂CH</td>
<td>Rh₂(4S-IBAZ)₄</td>
<td>34 (77)</td>
<td>66 (95)</td>
</tr>
<tr>
<td>Et</td>
<td>Rh₂(4S-IBAZ)₄</td>
<td>36 (47)</td>
<td>64 (73)</td>
</tr>
<tr>
<td>Et</td>
<td>Rh₂(4S-MACIM)₄</td>
<td>43 (30)</td>
<td>57 (37)</td>
</tr>
</tbody>
</table>

3.3 Intramolecular Processes

Because of geometric constraints, intramolecular cyclopropanations of unsaturated diazocarbonyl compounds can produce only one fused bicyclic cyclopropane (the cis isomer). Tanimori et al. (1997) have reported a chiral auxiliary approach to intramolecular cyclopropanation of a diazoacetate in their synthetic route to the carbocyclic moiety of the anti-HIV agent carbovir. This is, however, a rare diastereoselective approach, since the dirhodium(II) carboxamide catalysts 9-12 have proven to be
most efficient and selective for reactions of diazoacetates and diazoacetamides (Doyle et al, 1995c, 1997c, 1998d).

Table 5. Enantioselective intermolecular cyclopropanation with phenyldiazoacetate

![Cyclopropanation with phenyldiazoacetate](image)

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>Catalyst</th>
<th>ee of Z, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>Rh₂(S-TBSP)₄</td>
<td>87</td>
</tr>
<tr>
<td>pCl₆H₄</td>
<td>H</td>
<td>Rh₂(S-TBSP)₄</td>
<td>85</td>
</tr>
<tr>
<td>pMePC₆H₄</td>
<td>H</td>
<td>Rh₂(S-TBSP)₄</td>
<td>88</td>
</tr>
<tr>
<td>EtO</td>
<td>H</td>
<td>Rh₂(S-DOSP)₄</td>
<td>66</td>
</tr>
<tr>
<td>nBuO</td>
<td>H</td>
<td>Rh₂(S-DOSP)₄</td>
<td>64</td>
</tr>
<tr>
<td>nBu</td>
<td>H</td>
<td>Rh₂(S-DOSP)₄</td>
<td>77</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Rh₂(S-TBSP)₄</td>
<td>97</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>Rh₂(S-TBSP)₄</td>
<td>85(E), 81(Z)</td>
</tr>
</tbody>
</table>

Table 6. Enantioselective intermolecular cyclopropenation

![Cyclopropenation](image)

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(OEt)₂</td>
<td>OMe</td>
<td>42</td>
<td>≥ 98</td>
</tr>
<tr>
<td>CH₃OMe</td>
<td>O'Bu</td>
<td>52</td>
<td>78</td>
</tr>
<tr>
<td>CH₃OMe</td>
<td>OEt</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td>CH₂OMe</td>
<td>OEt</td>
<td>85</td>
<td>57</td>
</tr>
<tr>
<td>CH₂OMe</td>
<td>NMe₂</td>
<td>22</td>
<td>≥ 94</td>
</tr>
<tr>
<td>CH₂OMe</td>
<td>NMe₂</td>
<td>47</td>
<td>89</td>
</tr>
</tbody>
</table>
Excellent enantioselectivities have been reported in a series of allylic diazoacetates 25 (n = 1, Z = O) catalysed by Rh₂(5S-MEPLY)₄ (S-9a), and Rh₂(5R-MEPLY)₄ (R-9a) to give fused cyclopropyl lactones 26 (n = 1, Z = O) equation 4 (Doyle et al, 1991b, 1995c, 1996e). Cyclopropanation of homoallylic diazoesters 25 (n = 2, Z = O) (Martin et al, 1992a) and N-tert-butyl diazoacetamides 25 (n = 2, Z = N- tBu) equation 4 (Doyle et al, 1994e) proceeded with moderate to high enantioselectivities with the same catalysts.

It has further been shown that enantioselectivities obtained in the catalysed cyclopropanation of allylic diazoacetates 27a-g to give the cyclopropyl γ-lactones 28a-g, were largely dependent on the position of vinylic substitution (Table 7) (Doyle et al, 1995c). As is shown in Table 7, careful selection of the catalyst becomes necessary in order to optimise the enantioselectivity (Doyle et al, 1995d, 1997c). Application of the enantiomeric catalysts to the cyclopropanation of these allylic diazoacetates provide the cyclopropyl lactone products with the same enantiomeric excesses, but with the opposite absolute configurations. A recent contribution to the area by Martin and Hillier (1998) has investigated the complimentarity of chiral diazoacetates and chiral catalysts in a form of double diastereodifferentiation-cyclopropanation.

Several pharmacologically important molecules have been synthesized through the use of the above methodology, using either of the enantiomeric catalysts 9a. As outlined in Scheme 8, Martin et al (1992b, 1993) synthesized trisubstituted cyclopropanes as conformationally restricted peptide isosteres for renin 29 and collagenase inhibitors, and Rogers et al (1995) have synthesizes presqualene alcohol 30. In addition, the products of these cyclopropanation reactions may serve as synthetic precursors to cis-chrysanthemic acid (Mukaiyama et al, 1983) and the pheromone R-(-)-dictyopterene C (Schotten et al, 1986).

With homoallylic diazoacetates 31 (n = 2, R⁴ = H) (Martin et al, 1992a; Doyle et al, 1995c) and allylic diazopropionates 31 (n = 1, R⁴ = Me) (Doyle and Zhou, 1995e), there is a moderate reduction in the enantioselectivity with a similar selection of dirhodium catalysts (Table 8).
Table 7. Enantioselective intramolecular cyclopropanation of allylic diazoacetates

![Diagram of cyclopropanation reaction]

<table>
<thead>
<tr>
<th>27</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Catalyst</th>
<th>Yield % (ee %)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>9a</td>
<td>75 (95)</td>
<td>(1R,5S)</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>9a</td>
<td>89 (98)</td>
<td>(1S,5R)</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>9a</td>
<td>72 (7)</td>
<td>(1R,5S)</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>11d</td>
<td>75 (89)</td>
<td>(1S,5R)</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>9a</td>
<td>70 (≥94)</td>
<td>(1R,5S)</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>9a</td>
<td>78 (68)</td>
<td>(1R,5S)</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>11d</td>
<td>61 (96)</td>
<td>(1R,5S)</td>
</tr>
<tr>
<td>f</td>
<td>Pr</td>
<td>H</td>
<td>H</td>
<td>9a</td>
<td>93 (85)</td>
<td>(1R,5S)</td>
</tr>
<tr>
<td>f</td>
<td>Pr</td>
<td>H</td>
<td>H</td>
<td>11d</td>
<td>83 (95)</td>
<td>(1R,5S)</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>iPr</td>
<td>H</td>
<td>9a</td>
<td>85 (≥94)</td>
<td>(1R,5S)</td>
</tr>
</tbody>
</table>

Analogous intramolecular cyclopropanation of N-allyl diazoacetamides 32 (n = 1) (Doyle et al., 1995c, 1996f) and N-tert-butyl-N-homoallylic diazoacetamides 32 (n = 2) (Doyle et al., 1994e) to give the cyclopropyl lactams have progressively been refined to high yielding, highly enantioselective processes (Table 9).

![Diagram of lactam formation]

Although diazoacetates and diazoacetamides generally undergo dirhodium(II)-catalysed intramolecular cyclopropanation with high enantiocontrol, the same is not true for diazoketones. Here the best results were obtained from copper-based catalysts (Doyle et al., 1997d).

The Davies group has demonstrated the applicability of their formal [3 + 4]-cycloaddition in an intramolecular example as part of a synthesis of 5-epitremulenolide equation 5 (Davies and Doan, 1996e).
Outside of two very recent preliminary reports from the Doyle group (Doyle et al., 1999b, 1999c), no widespread success with intramolecular cyclopropenation has been developed. These reactions often produce unstable fused cyclopropenes that undergo ring opening to vinylcarbenes that can react by a number of pathways, often giving rise to multiple products (Padwa et al., 1991, 1993).

Scheme 8. Applications of enantioselective intramolecular cyclopropanation

29 renin inhibitor

30 presqualene alcohol
Table 8. Enantioselective intramolecular cyclopropanation of homoallylic diazoacetates and allylic diazopropionates

\[
\begin{array}{ccccccccc}
\text{n} & \text{R}^1 & \text{R}^2 & \text{R}^3 & \text{R}^4 & \text{Cat.} & \text{Yield \% (ee \%)} \\
2 & \text{H} & \text{H} & \text{H} & \text{H} & 9a & 80 (71) \\
2 & \text{Me} & \text{Me} & \text{H} & \text{H} & 9a & 74 (77) \\
2 & \text{H} & \text{Ph} & \text{H} & \text{H} & 9a & 73 (88) \\
2 & \text{Ph} & \text{H} & \text{H} & \text{H} & 9a & 55 (73) \\
2 & \text{H} & \text{Et} & \text{H} & \text{H} & 9a & 80 (90) \\
2 & \text{H} & \text{H} & \text{Me} & \text{H} & 9a & 76 (83) \\
1 & \text{Me} & \text{Me} & \text{H} & \text{Me} & 10a & 81 (71) \\
1 & \text{H} & \text{nPr} & \text{H} & \text{Me} & 10a & 62 (85) \\
1 & \text{H} & \text{Ph} & \text{H} & \text{Me} & 10a & 65 (78) \\
\end{array}
\]

3.4 Insertion Products

Catalytically generated metal carbenes have been shown to be capable of highly versatile insertion into carbon-hydrogen and heteroatom-hydrogen bonds equation 6.

\[
\text{X–H} \quad + \quad \text{L}_n\text{M} \equiv \text{CR}_2 \quad \rightarrow \quad \text{R}_2\text{C}^\text{H} \quad + \quad \text{ML}_n \quad (6)
\]

Although generally indiscriminate, the advent of dirhodium(II) catalysts provided the required element of control to make these highly attractive C-C bond-forming processes (Maas, 1987; Doyle, 1986, 1995a; Ye and McKervey, 1994; Nefedov et al, 1992; Padwa and Krumpe, 1992). Although the
mechanism of the transition metal catalysed C-H insertion reactions has been the subject of considerable speculation (Taber, 1991; Doyle, 1992), there is general agreement that insertion occurs through a metal carbene intermediate. Doyle and co-workers have suggested the mechanism depicted below as a suitable model for the C-H insertion process (Scheme 9) (Doyle et al, 1993b).

Table 9. Enantioselective intramolecular cyclopropanation of N-allyl and N-homoallylic diazoacetamides

<table>
<thead>
<tr>
<th>n</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Cat.</th>
<th>Yield % (ee %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>10a</td>
<td>40 (98)</td>
</tr>
<tr>
<td>1</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>10a</td>
<td>91 (94)</td>
</tr>
<tr>
<td>1</td>
<td>H</td>
<td>Pr</td>
<td>H</td>
<td>Me</td>
<td>11d</td>
<td>88 (95)</td>
</tr>
<tr>
<td>1</td>
<td>Pr</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>11d</td>
<td>93 (92)</td>
</tr>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>11d</td>
<td>84 (44)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>iBu</td>
<td>9a</td>
<td>60 (60)</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>iBu</td>
<td>9a</td>
<td>75 (75)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>iBu</td>
<td>9a</td>
<td>94 (90)</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>iBu</td>
<td>9a</td>
<td>62 (67)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>iBu</td>
<td>9a</td>
<td>87 (78)</td>
</tr>
</tbody>
</table>

Scheme 9. Proposed mechanism of C-H insertion
3.4.1 Carbon-Hydrogen Insertion Products

Although examples of dirhodium(II) catalysed intermolecular C-H insertion reactions are known, they generally lead to multiple products and require highly electrophilic catalysts in order to minimise competitive reactions such as formal carbene dimer formation. The yields and regioselectivities of these reactions are highly dependant on the catalyst employed (Demonceau et al, 1981, 1984).

[Chemical structure and reaction scheme]

Scheme 10. Diastereoselective route to (+)-estrone methyl ether

Intramolecular C-H insertion reactions of diazocarbonyl compounds are more effective and selective, and they have become synthetically relevant, with the dirhodium(II) carboxylates and carboxamidates 7-12 as the catalysts of choice (Doyle 1994a, Watanabe et al, 1995; Doyle and McKervey, 1997a, Anada and Hashimoto, 1998a). Two diastereoselective approaches are worthy of note. Both groups have used 1-naphthylborneol 33 esters as the chiral auxiliary for asymmetric induction in C-H insertion reactions (Taber et al, 1987, 1998; Wee and Liu, 1996). Taber and co-workers achieved diastereoselectivities of 83:17-92:8, which corresponds to enantiomeric excesses for the hydrolysed ester of 66 to 84%.

This procedure was extended to a synthesis of (+)-estrone methyl ether 34 (Scheme 10). Wee and Liu (1996) used this auxiliary in the C-H insertion reactions of diazomalonamides equation 7.

Enantioselective adaptations have been a more recent development. The McKervey group (McKervey an Ye, 1992; Kennedy et al, 1990; Doyle and McKervey, 1997a) and others (Hashimoto et al, 1990, 1994; Anada and Hashimoto, 1998a, 1998b) have utilised dirhodium(II) carboxylates derived from N-protected amino acids (catalysts 7 and 8 respectively) to catalyse the enantioselective C-H insertion of diazoketone derivatives. Enantioselectivities in the C-H insertion reactions of α-diazo-β-ketosulphones catalysed by 7 (Z = H) were low (~12% ee), although yields were high Kennedy et al, 1990). With a series of methyl diazo ketones 35, the same catalyst yielded the corresponding chromanones with enantioselectivities (for the major cis isomers) of 62-82% ee equation 8 (McKervey an Ye, 1992). Taber and co-workers have very recently published a preliminary report on the preparation of a new type of chiral catalyst 36 (enantiomeric M and P) that has backbone chirality. Whilst this design strategy may
DIRHODIUM(II) CARBENES: THE CHIRAL PRODUCT CASCADE

have potential, the initial intramolecular C-H insertions with a diazoketone only afforded an enantioselectivity of 36% (Taber et al, 1999).

\[
\begin{align*}
&\text{R}^*\text{O}2\text{C} & \text{R}^*\text{O}2\text{C} \\
&\text{N}2 & \text{N}2 \\
&\text{N} & \text{N} \\
&\text{PMP} & \text{PMP} \\
\end{align*}
\]

\[
\begin{align*}
\text{Rh}_2(\text{OAc})_4 & \rightarrow \text{Rh}_2(\text{OAc})_4 \\
\text{PMP} & = \text{pMeOC}_6\text{H}_4 \\
\text{R}^* & = 33 \\
\text{R} & = \text{nHex} & 45\% \text{ ee (R)} \\
& = \text{cHex} & 98\% \text{ ee (S)} \\
& = \text{Ph} & 79\% \text{ ee (S)} \\
\end{align*}
\]

Hashimoto and co-workers obtained enantiomeric excesses of 24-76% ee in the intramolecular C-H insertion reactions of $\alpha$-diazoo-$\beta$-keto esters 37 catalysed by catalysts of type 8, to yield $\beta$-keto esters 38 equation 9 (Hashimoto et al, 1990). More recent results with this catalyst line have afforded good enantioselective routes to azetidinones (Anada and Hashimoto, 1998b) and 2-pyrrolidones (Anada and Hashimoto, 1998a). These successes are exemplified by their syntheses of intermediates for trinem $\beta$-lactam antibiotics 39 and a typical GABA$\beta$ receptor agonist ($R$)-(-)-baclofen 40 (Scheme 11).

\[
\begin{align*}
\text{R} & = \text{CH}_3, \text{Ph, CH}=$CH$_2$ \\
\end{align*}
\]

95
Scheme 11. Applications of enantioselective intramolecular C-H insertion
Doyle and co-workers have applied the homochiral dirhodium(II) carboxamidate catalysts to the enantioselective carbon-hydrogen insertion reactions of diazoesters and diazoamides (Doyle et al., 1993c, 1995b, 1996c). An early application of Rh$_2$(5S-MEPY)$_4$ 9a was in the diazo decomposition of alkyl diazoacetates such as 41 to give the corresponding γ-lactones 42 in high yield, since insertion into a C-H bond α to an ether oxygen is a facile process equation 10 (Doyle et al., 1991c). With primary alkyl diazoacetates other than 41, C-H insertion reactions catalysed by Rh$_2$(MEPY)$_4$ proceed with enantioselectivities that are < 70% ee. However, the introduction of 2-oxoimidazolidine catalyst variants 11 has led to enhanced enantioselectivities and excellent regiocontrol (Doyle et al., 1994f, 1995f-h; Müller and Polleux, 1994; Bode et al., 1996). For example, use of Rh$_2$(4S-MPPIM)$_4$ 11d provided γ-lactones 44 from diazoacetates 43 derived from primary alcohols equation 11. This methodology provided facile access to a series of naturally occurring lignans, for example (-)-enterolactone 45, (+)-arctigenin 46 and (+)-isodeoxypodophyllotoxin 47 (Bode et al., 1996).

\[
\begin{align*}
A = \text{Me, Ph, C}_5\text{H}_11, \text{CH}=\text{CH}_2 \\
\text{A} \text{COOR} \xrightarrow{\text{Rh}_2\text{L}_4^*} \text{CH}_2\text{Cl}_2 \rightarrow \text{A COOR} \\
\text{37} \\
\text{38} \; \text{24-76\% ee} \\
\end{align*}
\]
This methodology has been applied to the C-H insertion reactions of secondary cycloalkyl diazoacetates 48, where diastereoselectivity in the formation of cis- and trans-fused bicyclic lactones 49 and 50 is a critical control feature (Table 10) (Doyle et al, 1994f). Use of Rh₂(5S-MEPY)₄ 9a or Rh₂(4S-MEOX)₄ 10a produced insertion products with a high degree of enantiocontrol, but levels of diastereoselective were far lower. In the formation of the more strained fused cyclopentyl lactone, only the cis diastereomer is formed, but the levels of enantioselectivity are lower than those obtained with the larger ring-sizes. However, both high enantiocontrol and almost complete stereocontrol were achieved in the latter with the catalyst Rh₂(4S-MACIM)₄ 11a (Table 10) (Doyle et al, 1994f).

Investigation of the enantioselective C-H insertion reactions of tertiary cycloalkyl diazoacetates 51a,b catalysed by Rh₂(5S-MEPY)₄ 9a and Rh₂(4S-BNOX)₄ 10c have been carried out (Müller and Polleux, 1994). In contrast to the secondary cycloalkyl analogues above (Table 10), both enantioselectivities and yields obtained in the formation of the bicyclic lactones 52a,b were poor, although only cis products were observed. Again, Rh₂(4S-MACIM)₄ led to greatly improved results (Doyle et al, 1995f).

High levels of enantio- and diastereoselective control have been achieved with cis- or trans-4-alkylcyclohexyl diazoacetates (Doyle et al, 1994f; Müller and Polleux, 1994), and with 2-adamantyl diazoacetate (Doyle et al, 1995b) in the formation of lactones 53-55 respectively.

\[
\begin{align*}
\text{CH₃} & \quad \text{O} & \quad \text{C} & \quad \text{CHN₂} & \quad \text{Rh₂L₄}^* 9a & \quad \text{CH₂Cl₂} \\
51 \text{a } n = 1 & & \text{b } n = 2 & & \text{CH₃} & \quad \text{O} & \quad \text{O} & \quad \text{K} & \quad 52 \text{a } 85\% \text{ ee} \\
& & & & \text{b } 90\% \text{ ee} \\
\end{align*}
\]

Doyle and co-workers have described the use of Rh₂(5R-MEPY)₄ R-9a in the C-H insertion reactions of glycerol derived diazoacetates for the convenient synthesis of pure 2-deoxyxylolactone (Scheme 12) (Doyle et al, 1994g). The success of this reaction is probably based on the ether oxygen's
electronic activation of adjacent C-H bonds (Adams et al., 1989; Wang and Adams, 1994). In the absence of the ether oxygen, enantioselectivities in the C-H insertion reactions of alkyl diazoacetates remain high, but diastereoccontrol with Rh$_2$(MEPY)$_4$ catalysts tends to be relatively low.

Dirhodium(II) carboxamidate catalysed C-H insertion reactions of diazoacetamides derived from cyclic amines have been shown to afford β-lactam products preferentially, with a high degree of enantiocontrol equation 13 (Doyle and Kalinin, 1995i).
ROOS, RAAB, and AL-HATMI

Scheme 12. Enantioselective synthesis of 2-deoxxyxylolactone

3.4.2 Heteroatom-Hydrogen Insertion Products

The insertion of transition metal carbenes, particularly those derived from dirhodium(II) carboxylate catalysts, into a variety of nucleophilic heteroatom-H bonds have provided novel routes to the synthesis of many synthetically relevant compounds (Ye and McKervey, 1994; Doyle et al, 1998a). Of these, insertion into O-H, N-H and Si-H are the most prominent. Asymmetric variants of these reactions are, outside of those that are conducted on enantiomerically pure substrates, still in their infancy. Of the asymmetric variants reported, the diastereoselective chiral auxiliary approach has shown the most success. Recently, Moody and co-workers reported the Rh$_2$(OAc)$_4$ catalysed intermolecular O-H insertion reactions of chiral auxiliary-bearing diazoacetates with simple alcohols, with diastereomeric excesses of up to 53% being attained (Table 11) (Aller et al, 1995; Miller et al, 1999).

To date the N-H insertion reactions reported have shown disappointing levels of asymmetric induction (< 50% ee), and much more research is required before this becomes a useful synthetic tool (Aller et al, 1996; Garcia et al, 1996). On the other hand, Si-H insertion has shown greater promise. The Landais group (Landais, 1997) has provided the most significant results via a chiral auxiliary approach (Landais et al, 1994a, 1994b; Bulugahapitiya et al, 1997) equations 14, 15. Three groups have independently reported initial successful results in an enantioselective approach with chiral dirhodium...
catalysts, \( \text{Rh}_2(5S\text{-MEPY}) \) \( 9a \) (Buck et al, 1996; Bulugahapitiya et al, 1997) and \( \text{Rh}_2(5\text{-DOSP})_4 \) \( 7 \) (Davies et al, 1997c). The best results equation 16 were obtained with vinyldiazoacetates.

\[
\begin{align*}
\text{N}_2 & \quad \text{O} & \quad \text{O} \\
\text{N} & \quad \text{O}
\end{align*}
\]

\( \text{dr} = 72:28 \) (14)

\[
\begin{align*}
\text{Et}_3\text{SiH} & \quad \text{Rb}_2(\text{OAc})_4 & \quad \text{CH}_2\text{Cl}_2 \\
\text{dr} & = 85:15
\end{align*}
\]

(15)

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 & \quad \text{N}_2 & \quad \text{CO}_2\text{R}_3 \\
\text{SiMe}_2\text{Ph} & \quad \text{L} = (5\text{-DOSP}) & \quad \text{ee} 77-95\% \\
\text{L} = (5S\text{-MEPY}) & \quad \text{ee} 52-72\%
\end{align*}
\]

(16)

3.5 Aromatic Cycloaddition and Substitution Products

Transition metal catalysed carbene addition to aromatic rings may be considered a special class of cyclopropanation reaction. The high-yielding dirhodium(II) catalysed intramolecular reactions of \( \alpha \)-diazocarbonyl compounds form the fused bicyclic cycloheptatrienes such as \( 56 \) This was reduced to the bicyclodecanone \( 57 \) with a determined enantiomeric excess of 33% equation 17 (Kennedy et al, 1990). Asymmetric success has also been observed using chiral dirhodium(II) phosphates \( 13a \) and have yielded enantioselectivities of up to 60% ee equation 18 (McCarthy et al, 1992).

\[
\begin{align*}
\text{O} & \quad \text{N}_2 & \quad \text{O}
\end{align*}
\]

(17)
Table 11. Diastereoselective intermolecular O-H insertion by chiral auxiliary-bearing diazoacetates

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R*</th>
<th>ROH</th>
<th>Yield %</th>
<th>dr (major config)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 1" /></td>
<td>MeOH</td>
<td>95</td>
<td>52:48</td>
</tr>
<tr>
<td><img src="image" alt="Structure 2" /></td>
<td>H₂O</td>
<td>84</td>
<td>50:50</td>
</tr>
<tr>
<td><img src="image" alt="Structure 3" /></td>
<td>MeOH</td>
<td>75</td>
<td>54:46 (S)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 4" /></td>
<td>iPrOH</td>
<td>82</td>
<td>62:38 (S)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 5" /></td>
<td>H₂O</td>
<td>79</td>
<td>66:34 (R)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 6" /></td>
<td>MeOH</td>
<td>63</td>
<td>72:28 (R)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 7" /></td>
<td>iPrOH</td>
<td>85</td>
<td>68:32 (R)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 8" /></td>
<td>BuOH</td>
<td>40</td>
<td>76:24 (R)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 9" /></td>
<td>H₂O</td>
<td>85</td>
<td>75:25 (S)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 10" /></td>
<td>iPrOH</td>
<td>71</td>
<td>71:29 (R)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 11" /></td>
<td>H₂O</td>
<td>98</td>
<td>66:34 (R)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 12" /></td>
<td>iPrOH</td>
<td>82</td>
<td>74:26 (R)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 13" /></td>
<td>BuOH</td>
<td>37</td>
<td>75:25 (R)</td>
</tr>
</tbody>
</table>

The only diastereoselective approach to aromatic cycloaddition involves the recent novel use of a chiral diol auxiliary as a tether between the aromatic substrate and the diazo reagent (Sugimura et al, 1998). This has provided entry into a series of potentially useful tropilidenes as chirons for further synthesis equation 19.
Intramolecular aromatic substitution by metal carbenes represents a formal C-H insertion with tremendous potential for asymmetric synthesis via chiral catalysis. Although not many reports have appeared, there is evidence of early success. The Hashimoto group has exploited their amino acid phthalimide catalysts 8 to good effect in the synthesis of a range of indanones (Table 12) (Watanabe et al, 1995, 1996a).

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>58 yield %</th>
<th>58 % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>75</td>
<td>88</td>
</tr>
<tr>
<td>Et</td>
<td>H</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td>nPr</td>
<td>H</td>
<td>74</td>
<td>98</td>
</tr>
<tr>
<td>allyl</td>
<td>H</td>
<td>70</td>
<td>88</td>
</tr>
<tr>
<td>Me</td>
<td>CO₂Me</td>
<td>87</td>
<td>93</td>
</tr>
</tbody>
</table>
The same workers have exploited this protocol in the synthesis of the aspartate receptor antagonist FR 115427 (Scheme 13) (Watanabe et al., 1996a).

Scheme 13. Synthesis of antagonist FR 115427 via intramolecular aromatic substitution

3.6 Ylide Cascade Products

Metal carbenes derived from α-diazocarbonyl compounds are electrophilic enough to add to heteroatoms and form ylides equation 20. These then may undergo a wide range of reactions including [2,3]-sigmatropic rearrangements, [1,2]-insertion (Stevens rearrangements), hydride elimination, and dipolar cycloaddition (Doyle and Forbes, 1998e; Doyle et al., 1998a). This diverse reactivity, along with their often-competitive initial formation, has contributed to the relatively barren landscape in terms of their dirhodium-catalysed asymmetric synthesis. Successful asymmetric adaptation is only a very recent achievement, and is so far restricted to oxonium ylide systems.
The initial examples were provided by the McKervey group who exploited a tandem ylide formation-[2,3]-sigmatropic rearrangement sequence to produce benzofuranone derivatives with up to 60% ee equation 21 (McCarthy et al, 1992; Pierson et al, 1997). Dirhodium(II) carboxamidate catalysts were used in initial studies of catalytic asymmetric tandem ylide formation-cycloaddition (Doyle and Forbes, 1998e; Suga et al, 1998). However, these only produced ee values of < 30%. Very recent developments have produced the first examples with ee values approaching synthetically useful levels. Thus diazo ketesters were induced to give intramolecular cycloadducts with ee’s up to 53% equation 22 (Hodgson et al, 1997). The Hashimoto group has taken this development further with diazo ketones in the intermolecular cycloaddition to afford bridged bicyclic skeletons in good yield and high enantioselectivity equation 23 (Kitigaki et al, 1999).

\[
\text{\begin{align*}
\text{O} & \text{O} \\
\text{CO}_2R & \text{CH}_2n \\
\text{Rh}_2\text{L}_4^* & (Z = nC_{12}H_{25}) \\
\end{align*}}
\]

The Doyle group has provided the best enantioselective (ee up to 88%) example of ylide formation-[1,2]-insertion in their report on the decomposition of 1,3-dioxane diazoacetates equation 24 (Doyle et al, 1997e).

\[
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{Rh} \quad \text{N}_2 \quad \text{CO}_2\text{MeMeO}_2\text{C} \\
\text{MeO}_2\text{C} = \equiv - \text{CO}_2\text{Me} \\
\text{Rh}_2\text{L}_4^* \quad 8 \\
51-78\% \text{ yield} \\
70-92\% \text{ ee}
\]

\[
\text{\begin{align*}
\text{Me} & \text{O} \text{H}_2\text{Cl}_2 \\
\text{O} \text{CH}_2\text{N}_2 & \text{Me} \\
\text{Rh}_2\text{L}_4^* & 11d \\
86\%, 81\% \text{ ee}
\end{align*}}
\]

4. Conclusion

Over the past decade, the reports of chiral dirhodium(II) catalyst systems and their applications to asymmetric synthesis have burgeoned. As this technology is applied to a greater diversity of reaction systems, it seems inevitable that the spectrum of dirhodium(II)-carbene chemistry will continue to...
expand. Given the wide range of non-racemic products that can be targeted in this way, these developments auger well for asymmetric organic synthesis and the industries that depend thereon.

**Note added in proof**

The readers’ attention is drawn to the following noteworthy contributions which have appeared since original submission. Doyle et al (1999d) – intramolecular addition to remote furans; Davies and Panaro (1999) - improved D2-symmetric dirhodium(II) tetrapotassium cyclopropanation catalysts; Doyle et al (2000) – macrocycle formation via intramolecular cyclopropanation.

5. References


DIRHODIUM(II) CARBENES: THE CHIRAL PRODUCT CASCADE


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