Catalytic Enantioselective C−H Activation by Means of Metal−Carbenoid-Induced C−H Insertion

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1. Introduction

The demand for more efficient ways to construct complex chemical structures from simple, readily available precursors continues unabated. A very attractive way to meet this demand would be through selective functionalization of unactivated carbon−hydrogen (C−H) bonds.[1−6] The successful development of practical C−H activation methods would revolutionize the strategies available for the synthesis of natural products, pharmaceuticals, and other industrially relevant targets.[7,8] Due to the ubiquitous nature of C−H bonds in organic molecules, such an approach is very challenging because it would require reagents that are sufficiently reactive to cleave the strong C−H bond but still able to be selective and controllable.

The activation of unfunctionalized C−H bonds has been extensively studied over the past 20 years, but the development of a practical catalytic method has proven to be very demanding.[1−16] Although activation of C−H bonds through oxidative addition of a highly reactive metal complex has been explored at length (Scheme 1), the difficulty associated with regeneration of the highly reactive complex has complicated the efforts toward achieving a catalytic process.[3]

An alternative approach that shows great promise is C−H activation by means of metal−carbenoid-induced C−H insertions (Scheme 2).[17] In the past, the C−H insertion chemistry of metal carbenoids has rarely been mentioned in reviews on C−H activation,[1−6] but as will become apparent in this review, the metal−carbenoid approach is a spectacular method for the functionalization of unactivated C−H bonds.[17] In metal−carbenoid-induced C−H activation the metal atom is not thought to interact directly with the alkane C−H bond.[17,18] Thus, the mechanism of the carbene complex reaction is different from those of other C−H activation reactions that involve metal/C−H interactions. Furthermore, the transient metal−carbenoids are conveniently formed from diazo compounds.[17−21] The metal complex that initiates the reaction is readily regenerated, and so the chemistry is very amenable to being a catalytic process.[17] A number of alternative reaction pathways, however,

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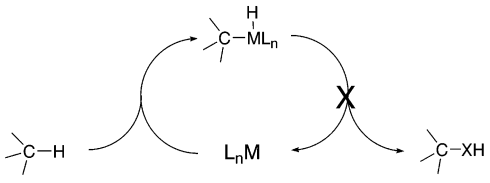
Rohan E. J. Beckwith was born in Chelmsford, England, in 1975. He received his M.Sci. degree from the University of Bristol in 1998 and his Ph.D. degree from the University of Nottingham in 2001, the latter under the guidance of Professor Nigel S. Simpkins. His doctoral research focused on novel applications of η^6-chromiumtricarbonyl complexes. In February 2002, with a fellowship from The Royal Commission for the Great Exhibition of 1851, he took up a postdoctoral position in the research group of Professor Huw Davies. His research interests are in the development of new methods in asymmetric catalysis and the synthesis of biologically relevant compounds.

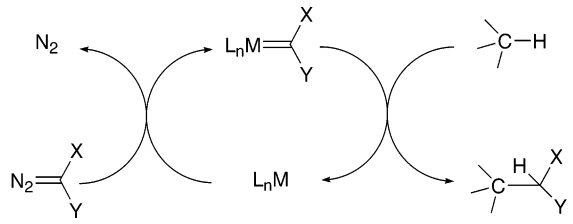
Scheme 1



are open to the carbenoid intermediates.[17,18,20–33] Controlling this diverse reactivity has been the central requirement for the effective development of synthetically useful carbenoid-induced C−H activations.

In the past few years, fantastic advances have been made in catalytic asymmetric C−H activation. Initially, the breakthroughs were made in the intramolecular processes,[17,18,20,26–40] but very recently, the intermolecular version has also been shown to have great breadth and utility.[41–45] Several recent reviews have emphasized many aspects of metal−carbenoid chemistry[17,18,20,21,23,24,26–34,36–55] including overviews of the metal−carbenoid-induced C−H activations.[17,18,20,26,28–34,36–49,51–53,55] This review aims to establish a general overview of catalytic asymmetric C−H activation, bringing together all of the recent advances in the field. A distinctive feature of this review is the classification of the carbenoid intermediates into three major groups according to the carbenoid functionality: acceptor, acceptor/acceptor, and donor/acceptor (Figure 1). The majority of earlier

Scheme 2



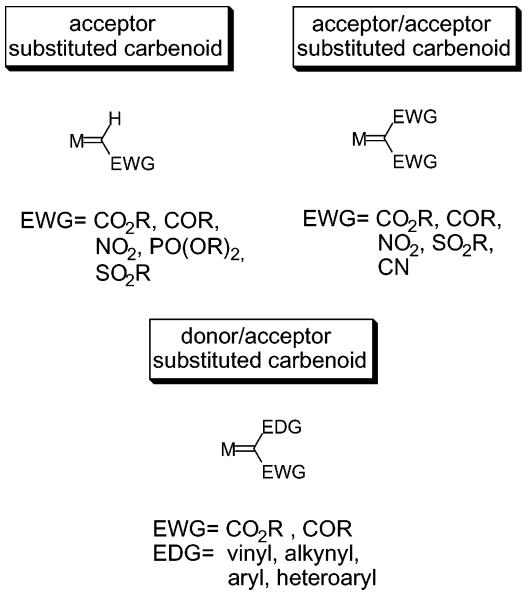


Figure 1. Classification of carbenoid intermediates.

reviews have not emphasized this distinction, but in recent years it has become increasingly apparent that the reactivity profile of carbenoids is very dependent on the carbenoid structure.[44,45,56–60] For example, the recent success of the intermolecular C−H activation is due to the introduction of the highly chemoselective donor/acceptor-substituted carbenoids.[44,45] Furthermore, the effectiveness of the majority of the chiral catalysts used in C−H activation is influenced by the carbenoid structure.[17,18,20,26,28–30,32,34–45] To achieve a successful asymmetric C−H activation, a judicious selection of catalyst, reagent, and substrate is required. This review will highlight the major trends of the C−H activation chemistry and, it is hoped, serve as a useful guide for accessing which approach to use in which situation.

The next section of the review will give an overview of the general aspects of the C−H activation chem-

istry. This material has been covered in detail in earlier reviews,[17,20,28,34,40,46−49,51−53,55] and only the most pertinent material will be covered here. The third section of the review will expand on the classification system that is being used for the carbenoid intermediates. The fourth section will give an overview of the range of chiral catalysts that have been developed for asymmetric C−H activation. Considering that asymmetric intramolecular C−H activation was the first to be developed, this field will be described initially (section 5). This will be followed by an overview of the recent advances in intermolecular C−H activation (section 6). Both sections will illustrate the scope and limitations of the chemistry and demonstrate the versatility of the approach with regard to target synthesis. The models that have been developed to account for the observed relative and absolute stereochemistry will then be discussed followed by a conclusion, which will describe the future opportunities and challenges associated with this area of chemistry.

The transient metal-stabilized carbenoids are most readily derived from metal-catalyzed decomposition of diazo compounds.[17−21] This review will be limited to carbenoid intermediates derived from this source. Other carbenoid precursors such as phosphonium ylides, iodonium ylides, sulfonium ylides, sulfoxonium ylides, and thiophenium ylides have been explored, including some enantioselective approaches.[18,61−69] These are not discussed in detail in this review because the chemistry usually parallels that of carbenoids derived from diazo compounds.[65] The success of chiral catalysis has reduced the use of chiral auxiliaries for asymmetric induction in C−H insertion reactions, and the latter will not be covered in this review.[70−75] Substrate-induced diastereoselectivity[76−85] will also not be covered except for those systems that exploit double-stereodifferentiation and kinetic resolution through the use of the above along with a chiral catalyst. Another powerful C−H activation approach, which is outside the scope of this review, is alkylidene C−H insertion chemistry.[86−90] Chiral catalysis has not been shown to induce asymmetry in these alkylidene C−H insertions, although several diastereoselective examples using substrate control are known. The apparent C−H activation of aromatic C−H bonds will also not be covered as this reaction proceeds via an electrophilic addition of the rhodium carbenoid to the aromatic ring followed by proton transfer rather than via a direct C−H insertion mechanism.[91−95]

2. General Trends in Carbenoid C–H Activation Chemistry

C−H activation through carbene-induced insertion reactions has been recognized for over 60 years.[20] Free carbenes are capable of reacting with organic compounds in several ways, but these processes are typically unselective and uncontrollable and, as a result, are of little synthetic value.[17,18,96] Highly selective transformations, however, can be achieved by modulating the high reactivity of free carbenes through their association with a suitable metal complex.

Proficient C−H activation requires the appropriate level of electrophilic character at the metallocarbenoid carbon center.[18,44,45,56−60] If the carbenoid intermediate is too electrophilic, it will exhibit poor regio- and stereocontrol and will be susceptible to other competing reaction pathways. A carbenoid with insufficient electrophilicity will lack the reactivity to insert into the unactivated C−H bond. The degree of electrophilicity available to the metallocarbenoid intermediate is governed by the nature of the metal catalyst[56,58,59,97−103] and the nature of the substituents adjacent to the carbene carbon.[56−59] An electron-withdrawing substituent, typically a carbonyl moiety, causes the carbenoid to be highly electrophilic and capable of undergoing insertion into an unactivated C−H bond.[17,18] A wide variety of metal complexes can be used to generate metal−carbenoids from diazo compounds.[17,18,29−31,47] They all need to have an accessible site for coordination of the diazo compound, whereupon nitrogen is lost and the carbenoid intermediate is formed. The metal complexes that tend to be the best catalysts bind to the carbene through strong σ-acceptor interactions and weak π-back-donation interactions, which stabilize the carbene somewhat but still ensure that the carbenoid retains its highly electrophilic character. Often the catalyst would have electron-withdrawing ligands, which would further enhance the electrophilic character of the carbenoid. The most effective catalysts for carbenoid C−H activation have been found to be rhodium(II) complexes, although copper(I) complexes can also be effective.[17,18,20,47] Other metal complexes such as those of ruthenium, which appear to generate a very stabilized carbenoid complex, are not effective at catalytic C−H activation but are very useful for other reactions such as cyclopropanation.[21]

Even though selective C−H activation of a complex organic molecule might at first glance appear to be an insurmountable problem, metal−carbenoid intermediates of appropriate reactivity display remarkable regiochemistry (Figure 2).[17,44,45] The electronic

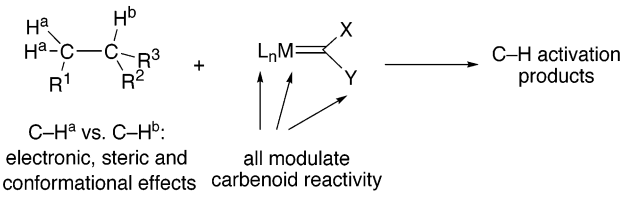


Figure 2. Controlling factors for chemoselectivity of C−H activation.

influence of the substituents adjacent to the site of C−H activation can have a profound effect.[104−107] C−H activation preferentially occurs at sites that stabilize buildup of positive charge at the carbon undergoing C−H cleavage.[58,100,104−107] Electron-donating groups such as alkoxy substituents direct C−H activation to the adjacent C−H bond, whereas electron-withdrawing groups such as ester and acetoxy groups are strongly deactivating. Electronic preferences, however, are not totally dominant in this chemistry. Depending on the system, the electronic effects may be outweighed by steric and even conformational factors inherent in the substrate and the

metallocarbenoid complex.[56−58,108−111] The subtle balance between electronic, steric, and conformational effects can often result in outstanding regiocontrol in this chemistry. Hence, the choice of catalyst is often crucial as the ligands will influence the electrophilicity of the metallocarbenoid.[39,56,58,98,100,111,112]

A very important stage in the development of the carbenoid-induced C−H activation was the introduction of the dirhodium tetracarboxylates as catalysts for carbenoid chemistry.[47,113] Seminal studies by Teyssié and co-workers demonstrated that the dirhodium tetracarboxylates were superior at inducing C−H activation compared with the older copper catalysts.[113−116] A series of detailed studies were published on intermolecular C−H activation of alkanes, demonstrating that the carbenoid displayed some selectivity between different C−H bonds and that the nature of the catalyst can influence the selectivity.[113−120] In these earlier studies mixtures of C−H activation products were invariably formed, and, consequently, the intermolecular C−H activation was not considered to be a synthetically viable process.[17,20,121] This led several groups to explore the intramolecular version in which entropic effects would be expected to improve the chemoselectivity of the process.[17] The order of reactivity of C−H bonds in competing C−H activation processes is methine > methylene ≫ methyl, and the rhodium-catalyzed intramolecular insertion reactions proceed with retention of stereochemistry.[104,122] Several groups have demonstrated that five-membered ring formation is greatly favored over other ring sizes[20,48,51−53] and that heteroatoms, such as oxygen and nitrogen, can activate an adjacent C−H bond for insertion.[53] Heteroatom activation of an adjacent methylene group or conformational effects in restricted systems can cause the formation of four- or six-membered rings to be favored over five-membered ring formation.[57,108,123,124] Very recently, it has been found that the intermolecular C−H activation can be made into a very useful synthetic process as long as donor/acceptor-substituted carbenoids are used.[44,45]

3. Carbene Precursors: Diazocarbonyl Compounds

The electrophilicity of the metal−carbenoid intermediate is known to have a marked influence on the chemo-, regio-, and stereoselectivity of the C−H activation reaction.[39,56−60,97,98,100,111,112,123,125−129] This electrophilicity stems not only from the effect of the associated ligated metal complex[58,59,97,98,100,127,128] but also from interactions with substituents on the carbenoid carbon.[56−60] The nature of the carbonyl group and indeed the identity of the additional substituent at the carbene carbon can dramatically influence the stability of the metallocarbenoid complex.

In recognition of the critical role of the carbenoid functionality on the outcome of the C−H activation chemistry, the metal−carbenoid will be presented under three subdivisions in this paper, namely, carbenoids containing a single acceptor group, two acceptor groups, and both an acceptor and a donor group. The terms "donor" and "acceptor" refer, respectively, to electron donation or withdrawal through resonance effects. An acceptor group will tend to make the carbenoid more electrophilic and reactive, whereas a donor group will make the carbenoid more stable and chemoselective.[17]

The acceptor-substituted carbenoids are derived from diazo compounds with a single electron-withdrawing substituent (Figure 3).[17,20] Nitrogen extrusion from these diazo compounds can be achieved with a variety of catalysts to generate a highly reactive metallocarbenoid species. A major problem that needs to be avoided with this class of carbenoid is the formation of carbene dimers. Acceptor-substituted carbenoids have been widely applied in intramolecular C−H activation reactions, where the high reactivity can be tamed by entropic factors.[17,20] The most utilized acceptor-substituted α-diazocarbonyls in metallocarbenoid chemistry are alkyl diazoacetates. The carbenoids from diazoketones are usually more reactive than the carbenoids from diazoacetates, whereas the carbenoids from diazoacetamides are the least reactive.[17] α-Alkyl α-diazoacetates have been less explored because the resulting carbenoid is prone to alkene formation by a 1,2-hydride shift. A few significant examples of intramolecular asymmetric C−H activation by carbenoids derived from alkyl-substituted diazoacetates are known, and the presence of the alkyl group appears to enhance the enantioselectivity.[130]

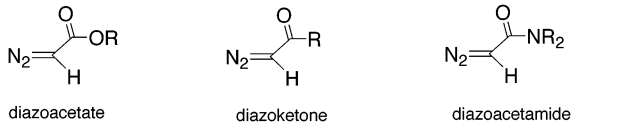


Figure 3. Common precursors to acceptor-substituted carbenoids.

The acceptor/acceptor-substituted carbenoids are derived from diazo compounds with two electron-withdrawing substituents (Figure 4).[20] This includes carbenoids derived from diazoacetoacetates, diazomalonates, diazodiketones, diazoacetoacetamides, and α-methoxycarbonyl-α-diazoacetamides. Due to the added stabilization of the diazo compound by the presence of the second electron-withdrawing group, very active catalysts are required to decompose the diazo compound.[17] The carbenoid once formed is highly electrophilic and very capable of undergoing C−H activation. Common side reactions for this carbenoid system are carbene dimerization and hydride transfer to form zwitterionic intermediates. Again, intramolecular C−H insertion reactions are the most synthetically useful.[17] Even though the acceptor/acceptor-substituted carbenoids would be expected to be less selective than the acceptor-

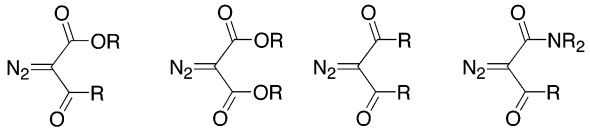
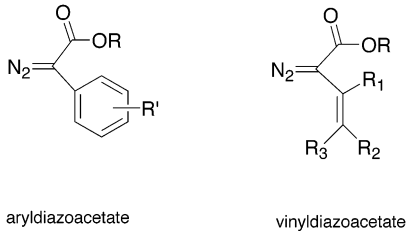


Figure 4. Common precursors to acceptor/acceptor-substituted carbenoids.

substituted carbenoids, there is evidence that the opposite is the case, at least in cyclopropanation reactions.[131]

The third group, the donor/acceptor-substituted carbenoids, is a late arrival to the field of metal−carbenoid chemistry (Figure 5).[41−43,132,133] In this



aryldiazoacetate vinyldiazoacetate

Figure 5. Common precursors to donor/acceptor-substituted carbenoids.

group a donor substituent is present, such as vinyl or aryl, that is capable of stabilizing the carbenoid through resonance. Very few reports on this class of metal−carbenoid existed prior to 1985, and the first example of C−H activation with this class of carbenoid was reported in 1997.[134] In the past few years, this situation has changed dramatically with the recognition that the donor/acceptor carbenoids are capable of undergoing highly chemoselective intermolecular C−H activation.[44,45] The aryl and vinyl groups also stabilize the diazo precursor, and so very active catalysts are required to effectively decompose this class of diazo compounds.

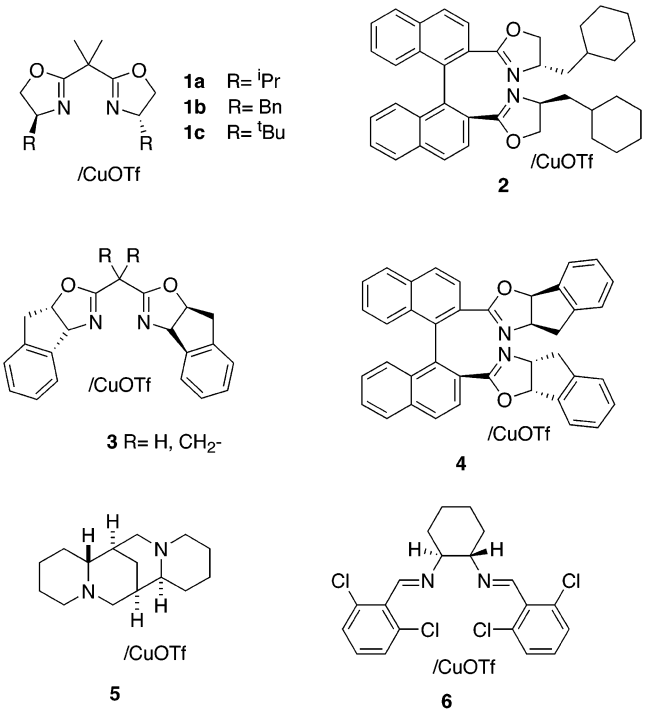
4. Chiral Catalyst Design for Asymmetric C–H Activation

Activation of a C−H bond requires a metallocarbenoid of suitable reactivity and electrophilicity.[39,56−60,97,98,100,111,112,123,125−129] To create such a species, a catalyst possessing sufficiently electron-withdrawing ligands around an electron-deficient metal core is desired.[18] Judicious choice of the metal−ligand combination is essential, however, as increased electron withdrawal by the ligands on the metal generates a more reactive carbenoid that undergoes bond formation through an earlier transition state, resulting in reduced selectivity.[17,51,58] Selective C−H activation is proposed to occur through a relatively late transition state in which cleavage of the metal−carbene bond is involved.[17,58,135] A catalyst possessing enantiopure ligands is therefore capable of inducing chirality in the products of C−H activation reactions.[17,58,135] In addition to enantiocontrol, the nature of the catalyst is also found to have a major influence on the level of chemo-, regio-, and diastereoselectivity of the reaction.[17,26,28,34,39,100,136]

The development of chiral catalysts for metal−carbenoid transformations has been a prolific field of research.[17,21,22,26,28−31,35,38−40,43,65,137−149] The vast majority of catalysts were developed for asymmetric intermolecular cyclopropanations.[21] Only those chiral catalysts that have been shown to be effective in asymmetric C−H activation will be described here.

4.1. Copper(I) Catalysts

Virtually all of the early literature on metal-catalyzed carbenoid reactions used copper complexes as the catalysts.[17,29,47] Copper catalysts tend to be highly electrophilic and so typically generate carbenoids that are too reactive to undergo selective C−H activation reactions. Even so, a few isolated cases have been reported of impressive asymmetric induction in copper-catalyzed C−H activation reactions.[65,150] The most widely studied ligands are C_2 symmetric bisimines, and the complexes are usually formed in situ by reaction of the ligands with copper triflate or hexafluorophosphate. The most effective chiral copper catalysts have been the C_2 symmetric bisoxazoline complexes **1**, particularly bis(*tert*-butyl)-



oxazoline (**1c**), which has achieved enantioinduction of up to 74% ee in intramolecular C−H activation.[65,72,130,150−153] The binaphthyl complex **2** has also been recently applied to C−H activation chemistry, achieving moderate enantioinduction in the cyclization reactions of α-diazo-*β*-ketoesters.[65] Several other chiral copper complexes, **3**−**6**, with C_2 symmetric ligands have been briefly explored, but the enantioselectivity with these complexes has been moderate, ranging from 15 to 60% ee.[29,65,66,130,154−156]

4.2. Rhodium(II) Catalysts

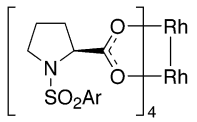
The scope of carbenoid-induced C−H activation expanded greatly with the introduction of dirhodium complexes as catalysts.[17,47] A major factor behind the success of rhodium(II) complexes, specifically in the realm of C−H activation chemistry, is thought to be due to the dirhodium bridge caged within a "lantern" structure.[51,129,135] Nakamura suggested that only one of the two rhodium centers functions as a carbene-binding site; the second rhodium atom assists the C−H insertion reaction by acting as an electron sink to enhance the electrophilicity of the carbene moiety and facilitates cleavage of the rhodium−carbene (Rh−C) bond on completion of the reaction.[135] Such a supporting role is not available to single metallic

complexes such as a copper−carbenoid species. In addition, Pirrung proposed that binding at one rhodium site weakens the binding at the other site (via the trans effect), again suggesting that only one site might be catalytically active at any given time.[129]

Building on initial findings from achiral catalysts,[51] four types of chiral rhodium(II) complexes have been developed for enantioselective catalysis in C−H activation reactions. They are rhodium(II) carboxylates, rhodium(II) carboxamidates, rhodium(II) phosphates, and ortho-metalated arylphosphine rhodium(II) complexes.

4.2.a. Rhodium(II) Carboxylates

Rhodium(II) carboxylates are kinetically very active at decomposing diazo compounds, much more so than copper or rhodium(II) carboxamidate catalysts.[43,51] Originally, the dirhodium tetracarboxylate framework was not considered to be a promising scaffold for the design of chiral catalysts,[157,158] but major advances have been made in the past few years that refute this viewpoint.[40,43] McKervey and co-workers explored a variety of *N*-protected L-proline derivatives for enantioselective C−H activation reactions. The most successful catalyst that McKervey developed was the *N*-benzenesulfonyl-protected Rh_2(*S*-BSP)$_4$ (**7a**).[130,159−162] Davies then discovered that dirhodium

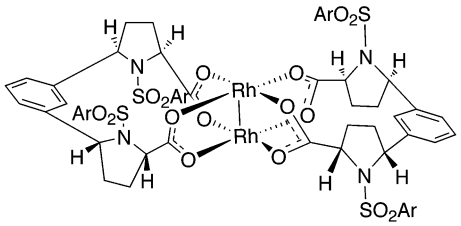


7a	Ar= C_6H_5	Rh_2(*S*-BSP)$_4$
7b	Ar= *p*-^{t}BuC_6H_4	Rh_2(*S*-TBSP)$_4$
7c	Ar= *p*-($C_{12}H_{25}$)C_6H_4	Rh_2(*S*-DOSP)$_4$

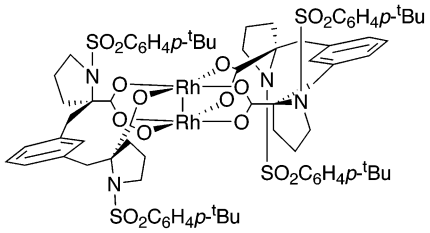
tetraprolinates were exceptional chiral catalysts for the donor/acceptor-substituted carbenoids, even though these catalysts gave low to moderate enantioselectivity with other carbenoid systems.[43,163−166] As the prolinate catalysts gave enhanced asymmetric induction in reactions conducted in nonpolar solvents, the hydrocarbon soluble prolinate catalysts, *N*-*p*-*tert*-butylbenzenesulfonyl derivative Rh_2(*S*-TBSP)$_4$ (**7b**) and *N*-*p*-dodecylbenzenesulfonyl derivative Rh_2(*S*-DOSP)$_4$ (**7c**), were developed.[41,43,163,164] Spectacular results in intermolecular C−H activation chemistry have been observed with these prolinate catalysts, especially Rh_2(*S*-DOSP)$_4$, which has been found to maintain catalytic activity even at −78 °C.[43−45]

The enhancement of stereocontrol in hydrocarbon solvents has been proposed to be the result of a solvent-induced orientation of the prolinate ligands leading to a complex of overall D_2 symmetry.[43,167] From these findings a second generation of catalysts was developed possessing a rigid bridged structure, which could therefore give optimum asymmetric induction even in non-hydrocarbon solvents. The most prominent in C−H activation chemistry have been Rh_2(*S*-biTISP)$_2$ **8a** and Rh_2(*S*-biDOSP)$_2$ **8b**.[168] Another bridged catalyst that has been developed and explored briefly in intramolecular C−H activation is the C_2 symmetric bridged prolinate **9**.[169] These catalysts are essentially locked in a D_2 symmetric conformation with the *N*-arylsulfonyl groups orientated in an "up-down-up-down" arrangement.[43,164]

Hashimoto and Ikegami developed dirhodium(II) tetracarboxylates **10** incorporating *N*-phthaloyl-(*S*)-



8a Rh_2(*S*-biTISP)$_2$: Ar = 2,4,6-tri-^{i}PrC_6H_2
8b Rh_2(*S*-biDOSP)$_2$: Ar = *p*-($C_{12}H_{25}$)C_6H_4



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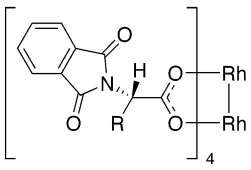
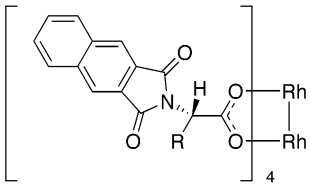
amino acids as ligands.[170] Recently a set of second-generation catalysts **11** were developed in which the

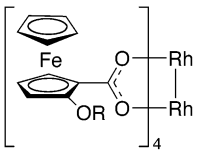




10a	R= Bn	Rh_2(*S*-PTPA)$_4$	**11a**	R= Bn	Rh_2(*S*-BPTPA)$_4$
10b	R= Me	Rh_2(*S*-PTA)$_4$	**11b**	R= Me	Rh_2(*S*-BPTA)$_4$
10c	R= ^{i}Pr	Rh_2(*S*-PTV)$_4$	**11c**	R= ^{i}Pr	Rh_2(*S*-BPTV)$_4$
10d	R= ^{t}Bu	Rh_2(*S*-PTTL)$_4$	**11d**	R= ^{t}Bu	Rh_2(*S*-BPTTL)$_4$
10e	R= Ph	Rh_2(*S*-PTPG)$_4$			

phthalimido wall has been extended by an additional benzene ring.[22] The catalysts have a C_2 symmetric conformation with the phthalimido groups aligned in a "down-down-up-up" arrangement. The bulky Rh_2(*S*-PTTL)$_4$ has been the most universally successful of this breed of catalyst, being proficient in the intramolecular cyclizations of aryldiazoacetates into methylene sites,[171] certain α-diazo-β-ketoesters,[172] and the generation of γ-lactams from α-methoxycarbonyl-α-diazoacetamide precursors.[173] The methyl-substituted Rh_2(*S*-PTA)$_4$ is most adept at β-lactam formation from α-methoxycarbonyl-α-diazoacetamides,[174] and Rh_2(*S*-PTPA)$_4$ has found relative success in catalyzing the cyclizations of α-diazo-β-ketoesters.[40,175] An (*S*)-2-benzyloxyphenylacetic acid-based catalyst also developed by Hashimoto and Ikegami proved not to be especially effective at asymmetric induction in C−H activation chemistry.[170]

Ito and co-workers developed a range of 2-alkoxyferrocenecarboxylic acids for use as chiral ligands in a number of metal-mediated processes including asymmetric C−H activation reactions.[176] The resultant rhodium(II) 2-alkoxyferrocenecarboxylates **12** have proven to be only moderately effective in C−H activation chemistry, although a thorough analysis has yet to be conducted.

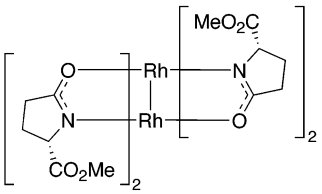


12a R= Bn
12b R= CH_2(1-naphthyl)
12c R= Me
12d R= Et

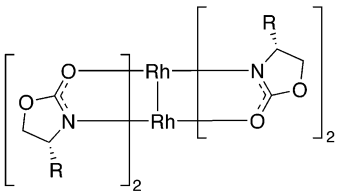
4.2.b. Rhodium(II) Carboxamidates

Doyle's rhodium(II) carboxamidate complexes are undisputedly the best catalysts for enantioselective cyclizations of acceptor-substituted carbenoids derived from diazoesters and diazoacetamides, displaying outstanding regio- and stereocontrol.[17,38,39,143,145,146] These carboxamidate catalysts consist of four classes of complexes: pyrrolidinones **13**,[138,177] oxazolidinones **14**,[178,179] imidazolidinones **15**,[139,179] and azetidinones **16**.[138,139,142,144,180,181] A number of Doyle's catalysts have proven to be effective in particular intramolecular transformations with specific substrate types.[39] The imidazolidinone-based catalysts Rh_2(*S*-MPPIM)$_4$ and Rh_2(*S*-MACIM)$_4$ produce excellent regio- and stereocontrol in cyclizations of acceptor-substituted diazoacetates owing to the restricted access available to the reacting carbenoid center due to the pendant acyl chains on the chiral ligands. With more sterically encumbered diazoacetates, the more open structures of the pyrrolidinone-based catalyst Rh_2(*S*-MEPY)$_4$ or the oxazolidinone-based catalyst Rh_2(*S*-MEOX)$_4$ tend to provide greater regio- and stereoselectivity. The enhanced reactivity of the azetidinone-based complexes compared to the other classes of carboxamidates means that catalysts such as Rh_2(*S*-IBAZ)$_4$ and Rh_2(*S*-MEAZ)$_4$ are reactive enough to decompose aryldiazoacetates and generate β- or γ-lactones with moderate to good enantiocontrol.[124,144,182]

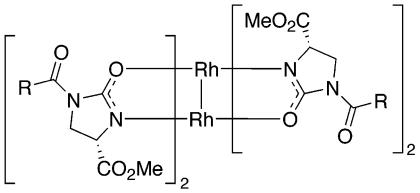
The general structure of the carboxamidate catalysts is more rigid than in rhodium(II) carboxylates and involves four bridging amine ligands around the dirhodium core, with two oxygen and two nitrogen donor atoms bound to each rhodium in a cis configuration.[17] The chiral center of the enantiopure ligand is positioned in such a manner as to influence the approach of the substrate C−H bond and also the orientation of the carbene carbon, thereby influencing regioselectivity as well as stereoselectivity.



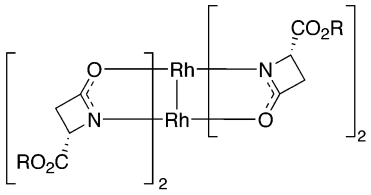
13 Rh_2(5*S*-MEPY)$_4$



14a R= CO_2Me Rh_2(4*S*-MEOX)$_4$
14b R= Bn Rh_2(4*R*-BNOX)$_4$
14c R= Ph Rh_2(4*R*-PHOX)$_4$



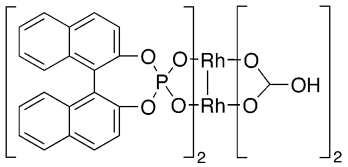
15a R= CH_3 Rh_2(4*S*-MACIM)$_4$
15b R= $BnCH_2$ Rh_2(4*S*-MPPIM)$_4$
15c R= *c*-$C_6H_{11}CH_2$ Rh_2(4*S*-MCHIM)$_4$

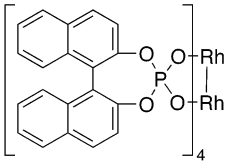


16a R= Me Rh_2(4*S*-MEAZ)$_4$
16b R= ^{i}Bu Rh_2(4*S*-IBAZ)$_4$
16c R= Bn Rh_2(4*S*-BNAZ)$_4$
16d R= *c*-C_6H_{11} Rh_2(4*S*-CHAZ)$_4$
16e R= CH_2CMe_3 Rh_2(4*S*-NEPAZ)$_4$

4.2.c. Rhodium(II) Phosphates

Chiral rhodium(II) binaphtholphosphates have been developed independently by McKervey and Pirrung. McKervey prepared Rh_2(*S*-BNP)$_2$(HCO$_3$)$_2$ **17** and



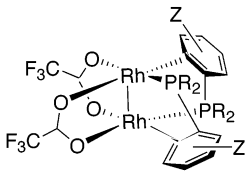


17 Rh_2(*S*-BNP)$_2$(HCO$_3$)$_2$.5H$_2$O **18** Rh_2(*R*-BNP)$_4$

Pirrung prepared Rh_2(*R*-BNP)$_4$ **18**, both of which have had limited use to date in C−H activation chemistry.[183,184]

4.2.d. Ortho-Metalated Arylphosphine Rhodium(II) Complexes

Lahuerta, Pérez-Prieto, and co-workers recently introduced a family of novel rhodium(II) catalysts **19**;



19a R= C_6H_5 Z= H
19b R= *p*-MeC_6H_4 Z= *p*-CH_3
19c R= *m*-MeC_6H_4 Z= *m*-CH_3
19d R= 3,5-$Me_2C_6H_3$ Z= 3,5-CH_3
19e R= *p*-^{t}BuC_6H_4 Z= *p*-^{t}Bu
19f R= *p*-FC_6H_4 Z= *p*-F
19g R= CH_3 Z= H

the chirality of these catalysts did not originate from chiral ligands but instead was inherent in the system.[35,136,185−187] The complexes possess C_2 symmetry and consist of two ortho-metalated arylphosphines and two carboxylate ligands in a cis arrangement. These catalysts have had reasonable success

in the cyclization reactions of acceptor-substituted diazoketone systems.[35]

5. Intramolecular Carbenoid C–H Activation

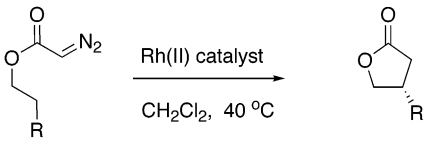
Intramolecular C−H activation reactions permit remote functionalization through C−C bond formation, presenting a general approach for the synthesis of a variety of carbocyclic and heterocyclic structures in a regio- and stereocontrolled manner. Several excellent reviews have been published covering the general aspects of intramolecular C−H activation by metal carbenoids.[17,20,46−49,51−53,55] The following section highlights the major advances made in asymmetric intramolecular C−H activation with particular emphasis on the relationship between carbenoid structure and catalyst efficiency.

5.1. Acceptor-Substituted Carbenoids

5.1.a. Carbenoids Derived from α-Diazoacetates

The most effective catalysts for intramolecular C−H activation of diazoacetates have been Doyle's chiral carboxamidate complexes.[17,28,30,34,38,39] In addition to achieving very high asymmetric induction in this system, the catalysts have considerable influence on the chemoselectivity and regioselectivity of the chemistry. For instance, $Rh_2(OAc)_4$ or rhodium(II) caprolactamate-catalyzed decomposition of 2-substituted ethyl diazoacetates (**20**) typically generates products arising from intermolecular processes such as carbene dimerization and insertion into adventitious water.[188] However, the corresponding reactions conducted with chiral Rh(II) carboxamidates favor formation of the γ-butyrolactone **21** (Table 1).[188−191]

Table 1. Asymmetric Synthesis of 4-Substituted γ-Butyrolactones



20 **21**

compd	R	catalyst	yield, %	ee,[a] %
a[b]	$CH_2C_6H_5$	Rh_2(5*R*-MEPY)$_4$	23	72 (*R*)
a[b]	$CH_2C_6H_5$	Rh_2(4*S*-MEOX)$_4$	42	51 (*S*)
a[b]	$CH_2C_6H_5$	Rh_2(4*S*-MPPIM)$_4$	50	87 (*S*)
a[b]	$CH_2C_6H_5$	Rh_2(4*R*-MPPIM)$_4$	56	91 (*R*)
b	CH_2Ar[c]	Rh_2(4*R*-MPPIM)$_4$	59	97 (*R*)
c[b]	C_2H_5	Rh_2(4*S*-MPPIM)$_4$	52	96 (*S*)
d[b]	$CH_2CH(CH_3)_2$	Rh_2(4*S*-MPPIM)$_4$	60	95 (*S*)
e	OCH_3	Rh_2(4*S*-MPPIM)$_4$	>98	93 (*S*)
f	*p*-ClC_6H_4	Rh_2(4*S*-MPPIM)$_4$	81	95 (*S*)

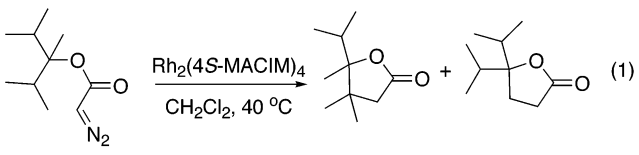
[a] Configurational assignment in parentheses. [b] β-Lactone product also formed (<5% yield). [c] Ar = 4-benzyloxy-3-methoxybenzene.

All of the chiral carboxamidates studied in the reaction of diazoacetate **20a** generally displayed the same levels of chemo- and regioselectivity, showing a strong tendency for five-membered ring formation over benzylic C−H activation.[188,191,192] The first-generation catalysts, the pyrrolidinone $Rh_2(MEPY)_4$ and the oxazolidinone $Rh_2(MEOX)_4$, gave moderate asymmetric induction (51−72% ee), whereas the second-generation imidazolidinone catalyst Rh_2(MPPIM)$_4$ was far superior (87−97% ee).[188,193] The unrivaled success of $Rh_2(MPPIM)_4$ is thought to be due to the greater steric influence of the *N*-3-phenylpropanoyl attachment, which provides greater control over the orientations of the carbenoid intermediate than with the more open structures of Rh_2(MEPY)$_4$ and $Rh_2(MEOX)_4$.[194] The formation of **21e** has also been conducted using a polymer-bound Rh_2(5*S*-MEPY)$_4$ catalyst.[195]

The asymmetric synthesis of γ-butyrolactones by intramolecular C−H activation has been elegantly applied to the synthesis of various lignans such as isodeoxypodophyllotoxin **22** and enterolactone **23** (Scheme 3).[188,190] The chemistry has also been utilized in the synthesis of (*S*)-(+)-imperanene **24**[191] and (*R*)-(−)-baclofen **25**.[193]

Intramolecular C−H activation of secondary alkyl diazoacetates enables rapid construction of chiral 4,5-disubstituted γ-butyrolactones (Table 2, $R^2 = H$).[196−198] With simple alkyl groups such as 3-pentyl diazoacetate **26a**, β-lactone formation also occurred (2−11% yield) and the regio- and diastereoselectivity as well as the enantioselectivity of the reaction were largely dependent on the choice of catalyst.[197] Doyle's imidazolidinone catalysts Rh_2(4*S*-MCHIM)$_4$ and Rh_2(4*S*-MPPIM)$_4$ gave the best results, forming the cis isomer **27a** in 81−87% yield with ≥94% de and 99% ee. With the related substrate **26b** containing alkoxy substituents, the activating influence of the ether oxygen strongly favored γ-lactone formation with the cis products **27b** predominating in 65−81% yield with 82−88% de and 97−98% ee using Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$ as catalysts.[196,198] These reactions have been used to construct 3,5-dialkyl-2-deoxyxylactones, which are useful chiral building blocks.[196] The reactions of the tertiary alkyl diazoacetate **26c** gave rise to the γ-lactone **27c** in 76% ee.[189] The generation of lactone **27c** required the rhodium−carbenoid intermediate to differentiate between two enantiotopic methyl groups in the C−H activation reaction. As a result, the newly formed stereocenter is adjacent to the site of insertion.

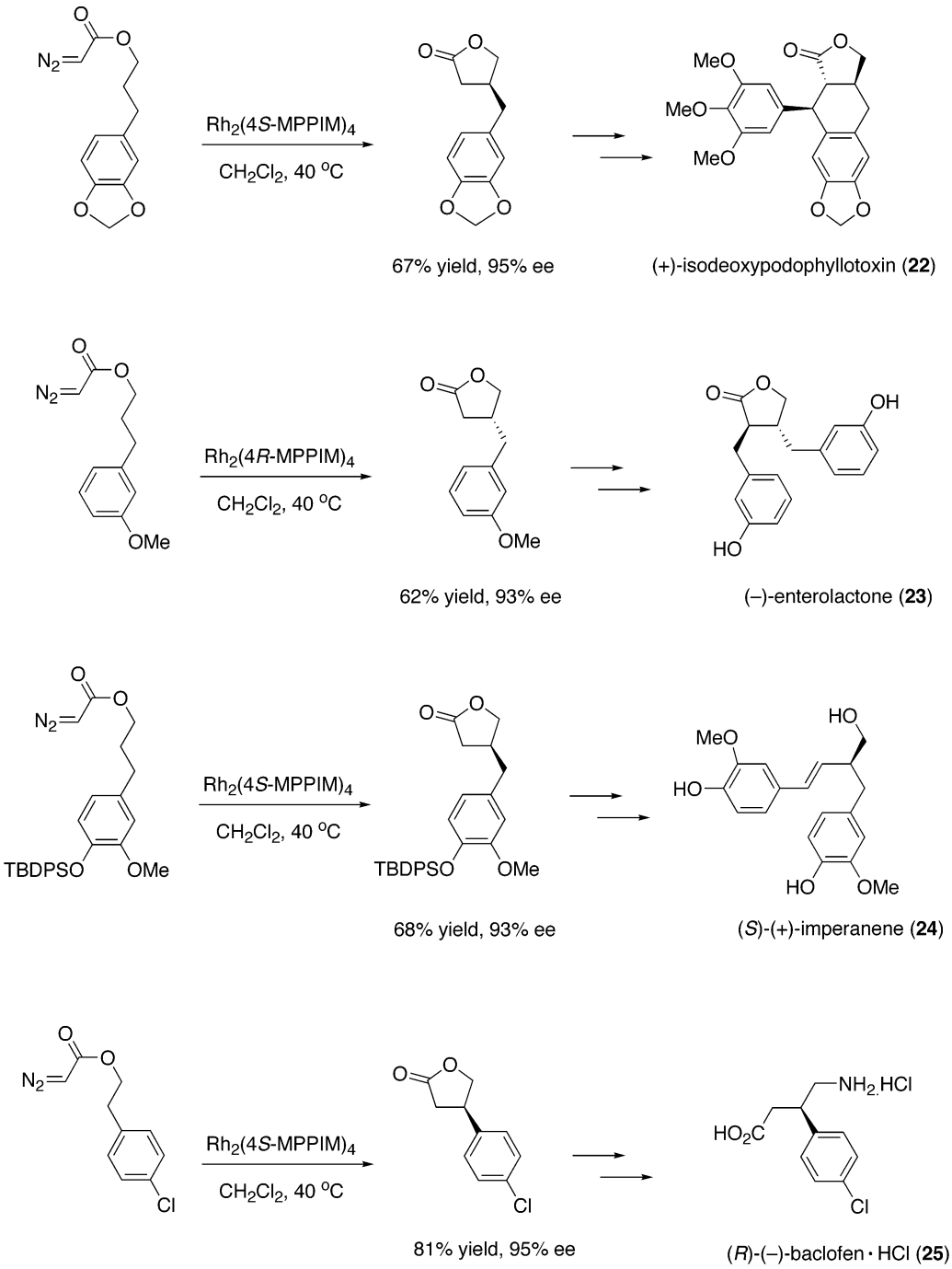
Intramolecular C−H activation is also effective at methine sites, as illustrated in the reaction of the tertiary alkyl diazoacetate **29** (eq 1).[99,189] The highest



29 **30** 61% yield, 85% ee **31** 13% yield

levels of asymmetric induction have been obtained using Rh_2(4*S*-MACIM)$_4$ as the catalyst, but, overall, the enantioselectivity is not as high as the insertions into methylene C−H bonds.[196−198] Furthermore, the reactions tend not to be as regioselective, irrespective of the choice of carboxamidate catalyst; for instance, the reaction of diazoacetate **29** results in competition between methine and methyl C−H insertion, leading

Scheme 3

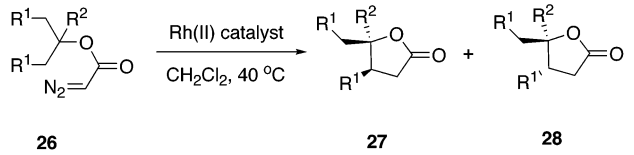


to the formation of a mixture of the butyrolactones **30** and **31**.[99,189]

Cycloalkyl diazoacetates are also capable of undergoing highly regio- and stereoselective cyclization reactions.[197,199,200] In the reaction of cyclohexyl diazoacetate **32**, the more sterically encumbered imidazolidinone catalysts $Rh_2(4S\text{-MPPIM})_4$ and $Rh_2(4S\text{-MACIM})_4$ provide exceptional diastereoselectivity for the cis isomer **33** (Table 3). This remarkable diastereocontrol is thought to stem from the *N*-acyl appendages on the chiral ligands of $Rh_2(4S\text{-MPPIM})_4$ and $Rh_2(4S\text{-MACIM})_4$, which restrict the trajectory of the substrate C−H bond and effectively fix the carbenoid center in a single orientation.[197] Similar results are seen in the cyclizations of seven- or eight-membered ring cycloalkyl diazoacetates, with the $Rh_2(4S\text{-MPPIM})_4$- or $Rh_2(4S\text{-MACIM})_4$-catalyzed process affording excellent stereoselectivity.[199] The corresponding $Rh_2(4S\text{-MEOX})_4$- or $Rh_2(5S\text{-MEPY})_4$-mediated processes give much poorer diastereoselectivity. In cyclopentyl diazoacetates the reactions are highly selective for the cis isomer irrespective of the choice of catalyst, but only sterically demanding catalysts such as $Rh_2(4S\text{-MPPIM})_4$ produce outstanding asymmetric induction.[197,200]

It is well established that metallocarbenoids derived from cyclohexyl diazoacetates favor insertion into an equatorial C−H bond over an axial C−H bond.[194,199] As a result of interchange between the two cyclohexyl chair conformers, equatorial C−H insertion can lead to both *cis*-lactone **33** and *trans*-lactone **34**.[199,200] The strong preference for C−H activation

Table 2. Asymmetric Synthesis of 4,5-Disubstituted γ-Butyrolactones

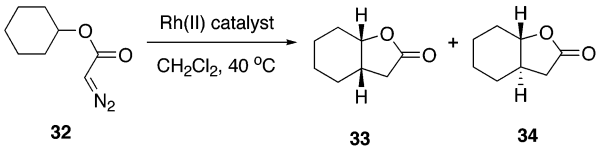


26 27 28

compd	R^1	R^2	catalyst	yield, %	ratio **27**:**28**	ee **27**, %	ee **28**, %
a[a]	CH_3	H	Rh_2(4*S*-MCHIM)$_4$	87	98:2	99	
			Rh_2(4*S*-MPPIM)$_4$	81	97:3	99	
			Rh_2(5*S*-MEPY)$_4$	70	78:22	98	71
			Rh_2(4*S*-MEOX)$_4$	75	69:31	98	92
b	OMe	H	Rh_2(5*S*-MEPY)$_4$	65−81	94:6	97[b]	45[c]
			Rh_2(4*S*-MEOX)$_4$	65−81	91:9	98[b]	76[c]
c	H	Ph	Rh_2(5*S*-MEPY)$_4$	30		76[d]	

[a] β-Lactone also isolated in 2−11% yield depending on the catalyst. [b] Configurational assignment determined as (4*S*,5*S*). [c] Configurational assignment determined as (4*R*,5*S*). [d] Configurational assignment determined as (4*R*).

Table 3. C−H Activation of Cycloalkyl Diazoacetate 32



32 33 34

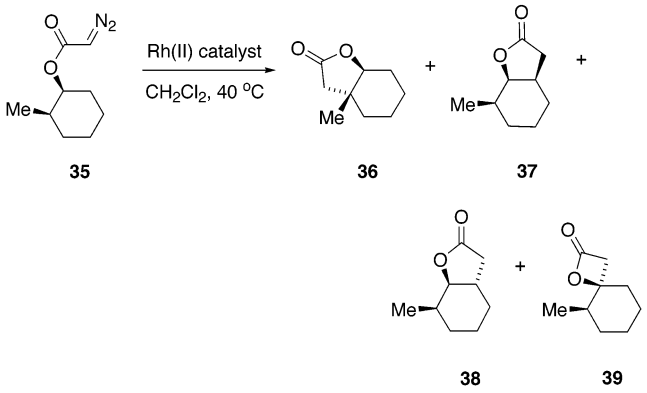
entry	catalyst	yield, %	ratio **33**:**34**	ee **33**,[a] %	ee **34**,[b] %
1[c]	Rh_2(4*S*-MPPIM)$_4$	−[e]	96:4	98	−[e]
2[c]	Rh_2(4*S*-MACIM)$_4$	70	99:1	97	65
3[d]	Rh_2(5*S*-MEPY)$_4$	30	75:25	95	90
4[c]	Rh_2(4*S*-MEOX)$_4$	50	55:45	96	95

[a] Absolute configuration determined as (4*S*,9*S*). [b] Absolute configuration determined as (4*S*,9*R*). [c] Reaction conducted by Doyle group. [d] Reaction conducted by Müller group. [e] Not reported in publication.

of an equatorial bond along with the influence of catalyst configuration has been exploited by Doyle and Müller in stereodifferentiation reactions to achieve exceptional levels of regio- and diastereocontrol in addition to enantiocontrol.[99,182,194,198−200] For example, catalytic decomposition of enantiopure (1*S*,2*R*)-diazoacetate **35** with a selection of dirhodium(II) carboxamidates gave, in most instances, the γ-lactones **36** or **37** preferentially even though there are four possible C−H activation products, **36**−**39**. Table 4 displays the results obtained for the Rh_2(MEPY)$_4$-catalyzed reactions and demonstrates that selection of **36** versus **37** is controlled by catalyst configuration.[194] The Rh_2(5*S*-MEPY)$_4$ catalyst directed the reaction toward formation of γ-lactone **36**, whereas the corresponding (*R*)-enantiomer gave preference to formation of γ-lactone **37**.

Having established that pure enantiomer **35** was capable of undergoing remarkably regioselective and diastereoselective C−H activation, it followed that highly efficient enantiomeric differentiation of (±)-**35** could be accomplished.[194] Hence, the Rh_2(5*S*-MEPY)$_4$-catalyzed reaction of (±)-**35** effectively gave

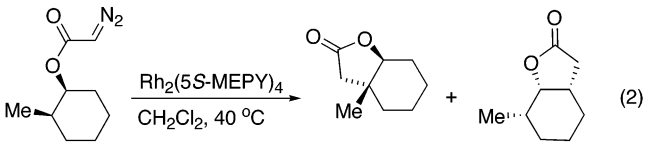
Table 4. Stereodifferentiation in Intramolecular C−H Activation



35 36 37 38 39

entry	catalyst	yield **36** + **37** + **38** + **39**, %	ratio **36**:**37**:**38**:**39**
1	Rh_2(5*S*-MEPY)$_4$	96	94:1:0:5
2	Rh_2(5*R*-MEPY)$_4$	79	4:91:3:2

close to a 1:1 mixture of enantioenriched γ-lactones **36** (91% ee) and *ent*-**37** (98% ee) (eq 2). Other equally



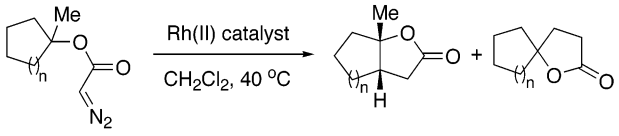
(2)

(±)-**35** **36** 91% ee *ent*-**37** 98% ee

spectacular examples of diastereo- and regiocontrol via chiral rhodium carboxamide catalysts in cyclic and acyclic diazoacetate systems have been reported.[99,182,194,198−200]

The C−H activation of tertiary cycloalkyl diazoacetates suffers from competing sites of reaction in a parallel manner to the acyclic analogues reported earlier.[99,200] Again, the imidazolidinone Rh_2(4*S*-MACIM)$_4$ has been shown to be the most effective catalyst for controlling the regioselectivity and enantioselectivity of the process (Table 5). The reaction

Table 5. C−H Activation of Tertiary Cycloalkyldiazoacetates



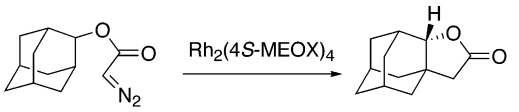
40 41 42

compd	*n*	catalyst	yield, %	ratio **41**:**42**	ee **41**, %
a	1	Rh_2(4*S*-MEOX)$_4$	61	83:17	33
	1	Rh_2(5*S*-MEPY)$_4$	52	94:6	36
	1	Rh_2(4*S*-MACIM)$_4$	56	90:10	85
b	2	Rh_2(4*S*-MEOX)$_4$	60	78:22	40
	2	Rh_2(5*S*-MEPY)$_4$	63	90:10	75
	2	Rh_2(4*S*-MACIM)$_4$	68	90:10	90

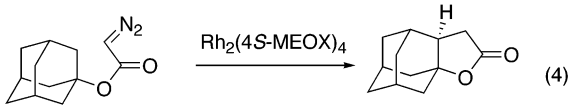
of the diazoacetate **40b** catalyzed by Rh_2(4*S*-MACIM)$_4$ afforded a 9:1 mixture of **41b** and **42b**, the secondary and primary site C−H activation products, in

which **41b** was formed as a single diastereoisomer in 90% ee.

The open framework of the oxazolidinone catalyst $Rh_2(4S\text{-MEOX})_4$ is particularly suited for sterically demanding diazoacetates (eqs 3 and 4).[179] The $Rh_2(4S\text{-MEOX})_4$ mediated reaction of adamantane derivatives **43** and **45** through C−H activation at tertiary and secondary sites to form **44** and **46** was accomplished with excellent enantioinduction.

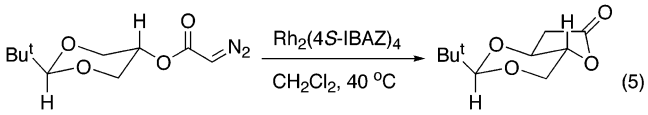


43 **44** 98% ee



45 **46** 90% ee

C−H activation in cyclic ethers has also been accomplished and has been employed as an alternative approach to the carbohydrate precursor 2-deoxy-xylono-1,4-lactone.[127,196,198] Interestingly, the presence of an ether oxygen in the cyclic system can have a dramatic influence on the level of enantioselectivity observed. For example, the $Rh_2(5S\text{-MEPY})_4$-catalyzed reaction of *trans*-2-(*tert*-butyl)-1,3-dioxan-5-yl diazoacetate (**47**) afforded **48** as a single diastereomer (only insertion into the equatorial C−H bond is observed), in a modest 52% ee.[198] Cyclization of the corresponding carbocyclic system, *trans*-4-*tert*-butylcyclohexyl diazoacetate, however, gave the related γ-lactone in 95% ee.[198,199] The lower level of enantioinduction witnessed in acetal **48** is attributed to repulsive interactions between the 1,3-dioxane oxygens and the oxygens in the catalyst's carboxamidate ligands in the transition state of the C−H insertion reaction.[198] The highest level of asymmetric induction obtained with *trans*-2-(*tert*-butyl)-1,3-dioxan-5-yl diazoacetate (**47**) was via a $Rh_2(4S\text{-IBAZ})_4$-mediated reaction; the open framework of the azetidinone catalyst is thought to allow for a conformation in which the unfavorable oxygen−oxygen interactions are substantially reduced, affording **48** in 81% ee (eq 5).[198]

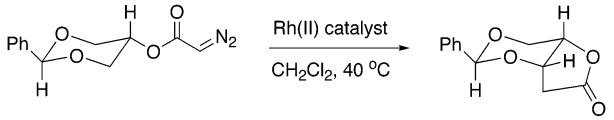


47 **48** 81% ee

Doyle suggested that such unfavorable interactions are avoided in the corresponding *cis*-acetal diazoacetate system; hence, the related *cis*-*tert*-butylcyclohexyl and *cis*-2-(*tert*-butyl)acetal systems both display comparable levels of enantiocontrol, (96% ee in both cases).[198]

The reaction was even more intriguing when the *tert*-butyl group was replaced by an aromatic species (**49**) as the product **50** arises from insertion into an axial C−H bond (Table 6).[198] In this case the $Rh_2(5S\text{-MEPY})_4$-catalyzed reaction results in the best asymmetric induction (94% ee). It is thought that the aryl substituent encourages axial C−H activation through resonance stabilization of positive charge buildup in the transition state.[198] Alternative possibilities and an explanation as to the reversal in expected enantiomer preference have also been addressed.[198]

Table 6. C−H Activation in Cyclic Ethers

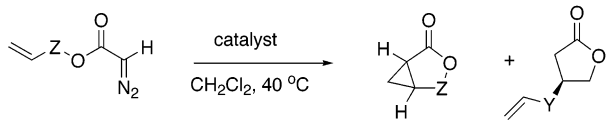


49 **50**

entry	catalyst	yield, %	ee, %
1	$Rh_2(4S\text{-IBAZ})_4$	85	88
2	$Rh_2(4S\text{-MEOX})_4$	48	67
3	$Rh_2(5S\text{-MEPY})_4$	71	94
4	$Rh_2(5R\text{-MEPY})_4$	75	94

A highly insightful study into catalyst and substrate influence in competitive cyclopropanation versus intramolecular C−H activation reactions was recently conducted by Doyle and Phillips (Table 7).[150]

Table 7. Effect of Catalyst on Cyclopropanation versus C−H Activation



51 **52** **53**

compd	−Z−	−Y−	catalyst	ratio **52**:**53**	ee **53**, %
a[a]	$(CH_2)_3$	CH_2	$Rh_2(OAc)_4$	>99:<1	
			$Rh_2(5S\text{-MEPY})_4$	42:58	93
			$Rh_2(4S\text{-MEOX})_4$	19:81	98
			$Rh_2(4S\text{-MPPIM})_4$	47:53	98
			$Rh_2(4S\text{-IBAZ})_4$	92:8	
			$Rh_2(S\text{-TBSP})_4$	>99:<1	
			$CuPF_6$/**1c**	>99:<1	
b[a]	$(CH_2)_4$	$(CH_2)_2$	$Rh_2(OAc)_4$	84:16	
			$Rh_2(5S\text{-MEPY})_4$	14:86	95
			$Rh_2(4S\text{-MEOX})_4$	9:91	97
			$Rh_2(4S\text{-MPPIM})_4$	13:87	>97
			$Rh_2(4S\text{-IBAZ})_4$	50:50	50
			$Rh_2(S\text{-TBSP})_4$	82:18	10
			$CuPF_6$/**1c**	>99:<1	74
c[b]	$CH_2OCH_2CH_2$	OCH_2	$Rh_2(OAc)_4$	82:18	
			$Rh_2(5S\text{-MEPY})_4$	<1:>99	91
			$Rh_2(4S\text{-MEOX})_4$	<1:>99	96
			$Rh_2(4S\text{-IBAZ})_4$	5:95	91
			$Rh_2(S\text{-TBSP})_4$	95:5	19
			$CuPF_6$/**1c**	*c*	

[a] Combined yield for **52** and **53** was <50% with all catalysts. [b] Combined yield for **52** and **53** was in the range 50−95% with all catalysts. [c] The major product was that formed from intramolecular oxonium ylide[2,3]sigmatropic rearrangement.

In a series of alkenyl diazoacetates **51**, when linker Z was a methylene or ethylene unit, only cyclopro-

panation product **52** was formed irrespective of the catalyst used. Presumably the construction of a five- or six-membered ring system through cyclopropanation was far more appealing to the intermediate metallocarbenoid complex than C−H activation to afford the respective four- or five-membered lactone. Lengthening of appendage Z results in less favorable formation of cyclopropanes fused to medium- to large-sized rings. With these systems, five-membered ring formation through C−H activation becomes a competitive process. The more electrophilic catalytic species, such as the copper complex, the rhodium(II) carboxylates, and the azetidinone-ligated Rh_2(4*S*-IBAZ)$_4$, all favored the cyclopropanation pathway, owing to the highly electrophilic metallocarbenoid species that they create.[17,39,150] The preference for γ-lactone formation can be seen to gradually increase with increasing ring size of the cyclopropanation product (compare results for substrate **51a** with those for substrate **51b**).[150] The less electrophilic rhodium(II) carboxamidates, especially Rh_2(4*S*-MEOX)$_4$, favor the C−H activation pathway, which occurs in a highly enantioselective manner (up to 98% ee), whereas the rhodium prolinate catalysts gave low asymmetric induction (10−19% ee). The preference for C−H activation is even greater when the site of insertion is adjacent to oxygen (Table 7, entries 16 and 17).[150] Particular attention should be paid to the spectacular reversal in selectivity witnessed in the azetidinone catalyst Rh_2(4*S*-IBAZ)$_4$ in the reaction of **51c** (entry 18). Interestingly, macrocyclization via intramolecular carbenoid C−H activation has been accomplished to afford a nine-membered ring product, although the yields and enantioselectivity were poor (<15% yield, 4−37% ee).[201]

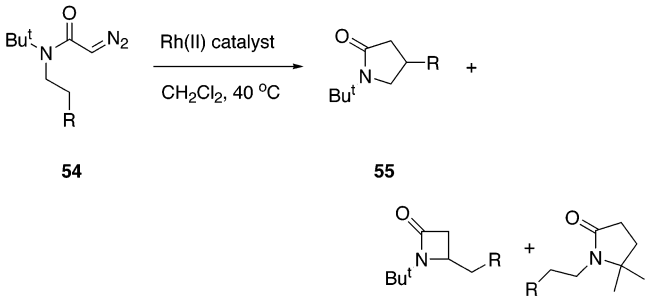
Rhodium(II) carboxamidates are clearly superior to all other types of catalysts in effecting highly chemo-, regio-, diastereo-, and enantioselective intramolecular C−H activation reactions of carbenoids derived from diazoacetates. Specifically, Rh_2(4*S*-MPPIM)$_4$ is the catalyst of choice for C−H activation reactions of simple primary and secondary alkyl diazoacetates. Likewise, Rh_2(4*S*-MACIM)$_4$ thus far has been the most successful catalyst with tertiary alkyl diazoacetates, whereas for primary acceptor-substituted diazoacetates with a pendant olefin side chain, Rh_2(4*S*-MEOX)$_4$ has proven to be highly selective.

5.1.b. Carbenoids Derived from α-Diazoacetamides

The intramolecular C−H activation of carbenoids derived from diazoacetamides typically results in a competition between β- and γ-lactam formation.[97,108,109,202] β-Lactam formation is favorable because of the activating influence of the amide nitrogen, whereas the γ-lactam is the generally favored ring size for intramolecular C−H activation.

In acyclic diazoacetamides **54** the substituents at the 2-position of the *N*-alkyl group have a pivotal role in controlling competing β- and γ-lactam-forming pathways.[203] With simple alkyl groups γ-lactam (**55**) formation is favored, although increasing the bulk of the R substituent can encourage β-lactam (**56**) formation (Table 8, cf. entries 1 and 2). The activating

Table 8. Effect of Structure and Catalyst on β- or γ-Lactam Formation



54 **55** **56** **57**

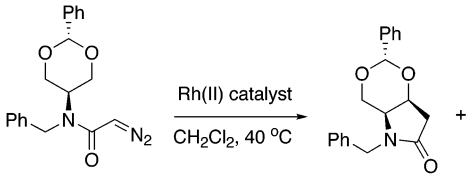
compd	R	catalyst	yield, %	ratio **55**:**56**:**57**	ee **55**, %	ee **56**, %
a	C_2H_5	Rh_2(4*S*-MEOX)$_4$	82	91:9:0	71	80
b	$^iC_3H_7$	Rh_2(4*S*-MEOX)$_4$	93	82:18:0	69	65
c	OC_2H_5	Rh_2(4*S*-MEOX)$_4$	97	100:0:0	78	
d	$CO_2C_2H_5$	Rh_2(5*S*-MEPY)$_4$	64	2:9:89		44
d	$CO_2C_2H_5$	Rh_2(4*S*-MEOX)$_4$	54	2:25:73		46
d	$CO_2C_2H_5$	Rh_2(4*S*-BNOX)$_4$	60	12:88:<1	16	20

influence of the ethoxy oxygen results in exclusive formation of γ-lactam **55c**, with oxazolidinone Rh_2(4*S*-MEOX)$_4$ giving the greatest level of enantiocontrol (78% ee). The deactivating influence of the carboethoxy functionality on the adjacent methylene group unexpectedly failed to favor formation of β-lactam **56d** with Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$. Instead, the major product was the pyrrolidinone **57d** via methyl C−H activation of the *tert*-butyl group.[203] This may have been due to steric factors or indeed unfavorable electronic interactions between the carboethoxy group and the ester substituents on the carboxamidate ligands. Evidence for the latter stems from the Rh_2(4*S*-BNOX)$_4$-catalyzed reaction.[203] Rh_2(4*S*-BNOX)$_4$ [which possess a benzylic functionality in place of the ester moiety on Rh_2(4*S*-MEOX)$_4$] gave β-lactam **56d** as the major product with only trace amounts of **57d** being formed. This last example highlights the subtle effect the catalyst has on the orientation of the carbenoid intermediate, and thereby plays an influential role in the regiochemical outcome as well as the enantioselectivity of the reaction.

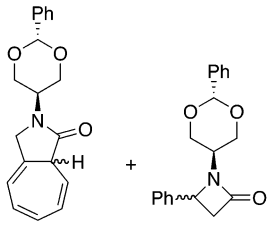
The rhodium(II)-catalyzed reactions of *trans*-5-(*N*-benzyldiazoacetamido)-2-phenyl-1,3-dioxane (**58**) afforded an interesting mixture of products.[192] In addition to C−H activation adjacent to oxygen (**59**), aromatic cycloaddition (**60**) and benzylic C−H activation (**59**) occurred in ratios that were largely catalyst dependent (Table 9). The Rh_2(5*S*-MEPY)$_4$-catalyzed reaction afforded γ-lactam **59** in 75% yield as a single diastereomer with 85% ee. The more electrophilic catalysts generated highly reactive carbenoids that were partial to aromatic cycloaddition to form **60** and showed less tendency toward forming β-lactam **61**.[192]

Although only moderate enantioselectivity has been achieved with acyclic terminal diazoacetamides, the related azacyclic systems display exceptional levels of enantiocontrol in certain cases.[204] C−H activation of azacycloheptane **62a** strongly favored formation of β-lactam **63a** (Table 10). Presumably the more rigid constraints of the cyclic structure pre-

Table 9. Intramolecular Reactions of *trans*-5-(*N*-Benzyldiazoacetamido)-2-phenyl-1,3-dioxane 58



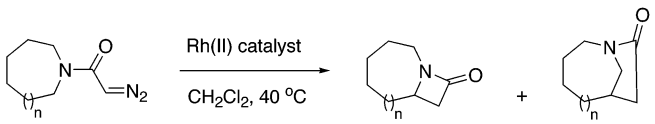
58 59



60 61

entry	catalyst	ratio **59**:**60**:**61**	yield **59**, %	ee **59**, %
1	$Rh_2(OAc)_4$	43:57:0	22	
2	$Rh_2(5S\text{-MEPY})_4$	95:5:0	75	85
3	$Rh_2(4S\text{-IBAZ})_4$	49:35:16	45	19
4	$Rh_2(5S\text{-MPPIM})_4$	53:18:29	48	37
5	$Rh_2(S\text{-TBSP})_4$	22:78:0	9	56

Table 10. Intramolecular C–H Activation of Cyclic Amides



62 63 64

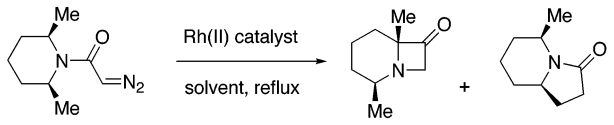
compd	*n*	catalyst	yield **63**, %	ee **63**, %	yield **64**, %	ee **64**, %
a	1	$Rh_2(5S\text{-MEPY})_4$	66	97	1	
	1	$Rh_2(4S\text{-MEOX})_4$	67	92	1	
b	2	$Rh_2(5S\text{-MEPY})_4$	31	31	46	97
	2	$Rh_2(4S\text{-MEOX})_4$	25	15	70	98
	2[a]	$Rh_2(4S\text{-MEOX})_4$	33	8	35	96
	2[a]	$Rh_2(4S\text{-MACIM})_4$	32	66	49	96

[a] Reaction conducted in 1,2-dichloroethane at reflux.

vented the intermediate rhodium–carbenoid complex from attaining sufficient orbital overlap for five-membered ring formation to be competitive.[204] The eight-membered diazoacetamide **63b** was sufficiently supple to enable both β- and γ-lactam formation to occur, with product distribution being catalyst and solvent dependent. The use of $Rh_2(4S\text{-MEOX})_4$ in CH_2Cl_2 gave the best results for γ-lactam formation, affording **64b** in 70% yield and 98% ee. Interestingly, conducting the reaction in refluxing dichloroethane resulted in an almost complete loss of regioselectivity, the higher reaction temperature enhancing the β-lactam pathway. The modest enantioselectivity obtained with the β-lactams generated from azacyclooctane **62b** is in sharp contrast to the exceptional levels witnessed for azacycloheptane **62a**. This is possibly a result of the more rigid structure of the latter and the more flexible structure of the former diazoacetamides.[204] Support for this theory comes from the 66% ee obtained in the reaction catalyzed by the sterically encumbered $Rh_2(4S\text{-MACIM})_4$ compared to the 8–31% ee obtained with the more open $Rh_2(4S\text{-MEOX})_4$ and $Rh_2(5S\text{-MEPY})_4$ systems.

Facile β-lactam formation was achieved in the reaction of the diazoacetamide derived from *cis*-2,6-dimethylpiperidine (**65**) (Table 11).[204] The preference

Table 11. Intramolecular C–H Activation of Diazoacetamide Derived from *cis*-2,6-Dimethylpiperidine



65 66 67

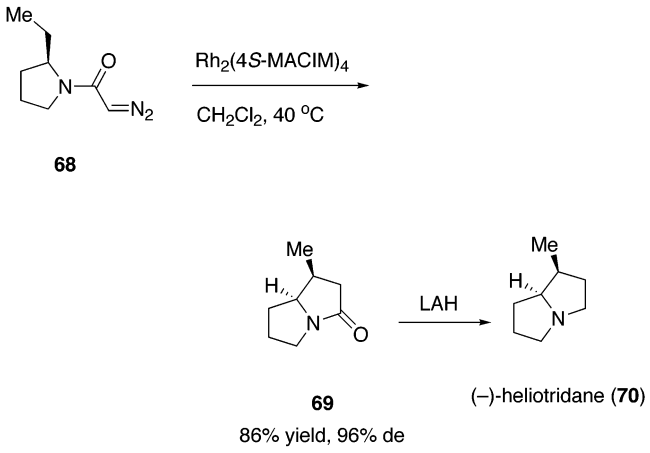
entry	catalyst	solvent	yield, %	ratio **66**:**67**	ee **66**, %
1	$Rh_2(5S\text{-MEPY})_4$	CH_2Cl_2	–[a]	85:15	86
2	$Rh_2(4S\text{-MEOX})_4$	CH_2Cl_2	78	89:11	86
3	$Rh_2(4S\text{-MACIM})_4$	$(CH_2Cl)_2$	–[a]	86:14	4

[a] Not reported in publication.

for the formation of β-lactam **66** over the γ-lactam **67** is thought to be due to a preferential chair conformation in the transition state in which the methyl groups adopt axial orientations to avoid steric interactions with the acetyl group.[204] Interestingly, in this rather crowded system $Rh_2(4S\text{-MACIM})_4$ gives very low asymmetric induction (4% ee).

γ-Lactam formation is strongly preferred with the corresponding 2-substituted pyrrolidine system (Scheme 4).[152] Indeed, exceptional double-diastereo-

Scheme 4



68 69

86% yield, 96% de

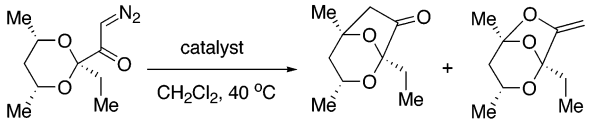
differentiation can be obtained in $Rh_2(MACIM)_4$- or $Rh_2(MPPIM)_4$-catalyzed cyclizations of enantiopure diazoacetpyrrolidinides, enabling easy access to pyrrolizidine bases such as (–)-heliotridane **70**. The matched reaction of $Rh_2(4S\text{-MACIM})_4$ or $Rh_2(4S\text{-MPPIM})_4$ with **68** displayed remarkable regioselectivity, forming exclusively **69** in 86–95% yield with great preference for the cis isomer (92–96% de). The mismatched reaction with the corresponding (*R*)-enantiomer produced **69** with 50% de. This reaction is uniquely suited for rhodium(II) carboxamidates

because the rhodium(II) carboxylate catalysts Rh_2-(*S*-BSP)$_4$ and Rh_2(*S*-PTPA)$_4$ gave low yields and poor selectivities.[152]

5.1.c. Carbenoids Derived from α-Diazoketones

Carbenoids derived from diazoketones are notoriously reactive, and harnessing this reactivity in enantioselective processes has generally proved to be problematic.[130,154,200,205,206] C−H activation reactions with enantiopure rhodium(II) carboxylate or carboxamidate catalysts typically generate little or no asymmetric induction. This is adequately demonstrated in a recent study on desymmetrization reactions by Wardrop and Forslund (Table 12).[205] Al-

Table 12. Desymmetrization Reaction of Diazoketone 71



71 72 73

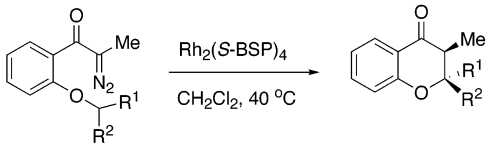
entry	catalyst	ratio **72**:**73**	yield **72**, %	ee **72**, %
1	$Rh_2(OAc)_4$	67:33	58	
2	$Rh_2(PTPA)_4$	78:22	36	20
3	$Rh_2(DOSP)_4$	100:0	31	7
4	$Rh_2(TBSP)_4$	77:23	17	<5
5	$Rh_2(MEPY)_4$	58:42	11	<5
6	$Cu(acac)_2$	33:67	15	

though the formation of bicyclic ketone **72** through transannular C−H activation appears to be particularly favorable (C−H insertion at a methine site adjacent to an activating oxygen functionality along with the propensity for five-membered ring formation), owing to the enhanced electrophilic nature of the carbenoid derived from α-diazoketone **71**, the activated methine C−H bond may actually be detrimental to the level of enantioinduction. The highly nucleophilic tertiary C−H bond is likely to interact with the electrophilic metallocarbenoid intermediate through an early transition state, thereby affording a lower level of enantioselectivity, as evident from Table 12. Clearly $Rh_2(OAc)_4$ was the most efficient catalyst at effecting cyclization to give **72**, whereas more electrophilic catalysts, especially $Cu(acac)_2$, tended toward formation of bicyclic enol ether **73**. The ether **73** is believed to arise from intramolecular hydride transfer to the initially formed metallocarbenoid followed by cyclization of the resulting zwitterionic species.[205] Notably, products analogous to **73** have been reported by several groups when attempting C−H activation reactions on terminal diazoketones.[207−211] As expected, no C−H insertion into the ethyl chain was observed.

The poor enantioselectivity commonly observed in the C−H activation reactions of diazoketones compared with that of diazoacetates or diazoacetamides has been attributed to two factors.[154] First, the carbenoids derived from diazoacetates or diazoacetamides have additional stability available to them through resonance of the carbonyl group with the heteroatom. Second, owing to the occurrence of carbonate or carbamate rotamers, diazoacetates and diazoacetamides, respectively, have additional conformational constraints that must be overcome to reach the transition state structure for C−H activation. As diazoketones do not suffer from such disruptions their transition state structure is more accessible and so less selective.[154]

McKervey and co-workers studied C−H activation in a number of α-diazoketone species as a means of constructing a variety of chromanone derivatives.[130,161] Attempted cyclization of the monosubstituted diazoketone corresponding to diazocarbonyl **74** with a range of copper and rhodium catalysts failed to give any of the desired C−H activation product.[130] Instead, products arising from a tandem oxonium ylide-[2,3] sigmatropic rearrangement reaction were obtained with all of the catalysts studied. C−H activation was accomplished through the limited stabilization provided by an additional α-methyl substituent on the carbenoid carbon (**74**). The formation of chromanones **75** was found to be catalyst dependent with highly electrophilic copper complexes generating solely products arising from sigmatropic rearrangement. In contrast, the considerably less electrophilic Rh_2(5*S*-MEPY)$_4$ complex proved to be completely ineffective, unable to generate a suitably reactive carbenoid species to undergo C−H activation. Of the dirhodium(II) and copper(I) complexes tested, the tetraprolinate catalyst Rh_2(*S*-BSP)$_4$ proved to be the most effective (Table 13). C−H activation of **74a**−**d** was accom-

Table 13. Asymmetric Synthesis of Chromanones



74 75

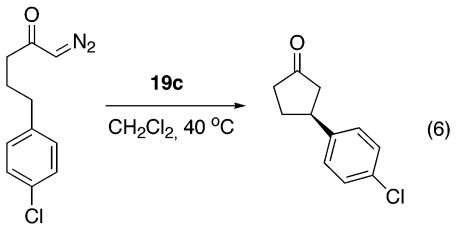
compd	R^1	R^2	yield, %	de, %	ee, %
a	H	CH_3	>98	50−78	82
b	H	$CH{=}CH_2$	97	86	60
b[a]	H	$CH{=}CH_2$	90	88	33
c	H	C_6H_5	92	50−78	62
d	CH_3	CH_3	>98		50
d[b]	CH_3	CH_3	>98		70

[a] Reaction catalyzed by Rh_2(*S*-BNP)$_2(HCO_3)_2$. [b] Reaction conducted at 0 °C.

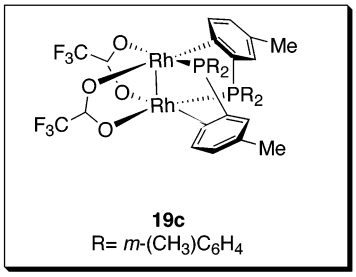
plished in excellent yield with a strong preference for the cis diastereomer in up to 82% ee. The highest enantioinduction was obtained for C−H insertion at a methylene site rather than a methine site (entry 1 vs entry 5) possibly due to steric factors. The binaphthyl phosphate catalyst Rh_2(*S*-BNP)$_2(HCO_3)_2$ was also explored in this reaction but gave a significantly lower level of enantioinduction (33% ee) compared with Rh_2(*S*-BSP)$_4$.[161]

A significant development in this field was the introduction of a family of ortho-metalated arylphosphine rhodium(II) catalysts by Lahuerta, Pérez-Prieto, and co-workers, which in certain cases proved to be effective in mediating the cyclization of a number of diazoketones.[35,136,185−187] The reactions

displayed wide variations in yield and enantioselectivity with the assorted ligated-rhodium complexes used, and no one catalyst proved to be consistently effective.[35] This underscores the importance of judicious choice of ligands when C−H activation reactions are conducted. The reactions were also highly sensitive to the influence of the substituents adjacent to the site of insertion, with electron-withdrawing groups tending to give the highest enantioinduction. For instance, the reaction of **76** catalyzed by catalyst **19c** generated the cyclopentanone **77** in 73% ee (eq 6). Presumably the electron-withdrawing nature of



76 (*S*)-**77**
87% yield, 73% ee (6)



19c
R= *m*-(CH3)C6H4

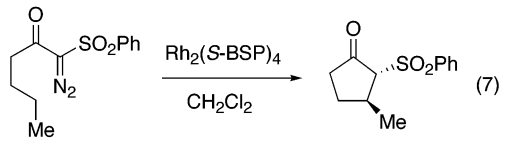
the *para*-chloro substituent afforded a less activated benzylic site, which therefore experienced a later, and thus more selective, transition state when interacting with the electrophilic rhodium−carbenoid.[35]

5.2. Acceptor/Acceptor-Substituted Carbenoids

Diazo compounds containing two acceptor groups are less reactive toward metal-catalyzed diazo decomposition than unsubstituted α-diazocarbonyls, so much so that most rhodium(II) carboxamidate complexes are unable to effect nitrogen extrusion in these systems at ambient temperatures, typically requiring temperatures of up to 80 °C.[66,144] Rhodium(II) carboxylates, however, are much more kinetically active than their carboxamidate counterparts and are capable of decomposing diazo compounds containing two acceptor groups even at temperatures below 23 °C.[43,51]

5.2.a. Carbenoids Derived from α-Diazo-β-ketosulfones

The first reported example of asymmetric induction in a carbenoid C−H activation reaction was by McKervey and co-workers in 1990 and involved the Rh_2(*S*-BSP)$_4$-catalyzed decomposition of α-diazo-β-ketosulfone **78** (eq 7).[160] Cyclopentanone **79** was obtained in excellent yield as a mixture of cis and trans isomers, although with poor enantioselectivity (12% ee).

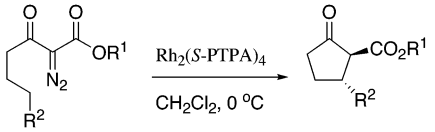


78 **79** (7)
>90% yield, 12% ee

5.2.b. Carbenoids Derived from α-Diazo-β-ketoesters

The most effective catalysts for intramolecular C−H activation of carbenoids derived from α-diazo-β-ketoesters have been the *N*-phthaloyl amino acid catalysts developed by Ikegami and Hashimoto.[40,170,175,212,213] The standard reaction that was used to evaluate these catalysts was the conversion of the α-diazo-β-ketoester **80** to the cyclopentanones **81** (Table 14). The *N*-phthaloyl phenylalanine catalyst

Table 14. Rh_2(*S*-PTPA)$_4$ Catalyzed Cyclization of α-Diazo-β-ketoester 80



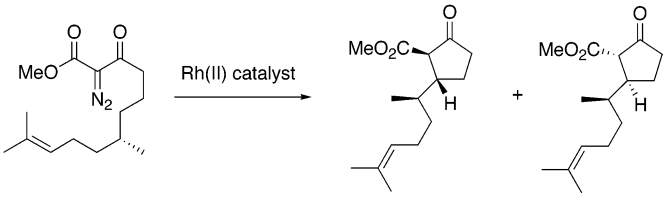
80 **81**

compd	R^1	R^2	yield, %	ee,[a,b] %
a	CH_3	CH_3	76	24
b	CH_3	C_5H_{11}	43	29
c	CH^iPr_2	C_5H_{11}	76	35
d	CH_3	$CH{=}CH_2$	44	38
e	CH_3	C_6H_5	96	46
f	^{t}Bu	C_6H_5	60	45
g	CH^iPr_2	C_6H_5	86	76[c]
h	CH^iPr_2	*p*-$MeOC_6H_4$	86	57
i	CH^iPr_2	*p*-$CF_3SO_3C_6H_4$	84	80

[a] Enantioselectivity determined following decarboxylation of **81**. [b] Absolute configuration determined as (3*R*). [c] The corresponding asymmetric copper-catalyzed phenyliodonium ylide decomposition reaction gave **81g** in up to 52% yield, 77% ee.[65,66]

Rh_2(*S*-PTPA)$_4$ was found to be the most efficient catalyst in these studies.[40,175,213] The enantioselectivity of the C−H activation process was found to be very dependent upon the size of the ester group and the nature of the substituents at the site of insertion.[40,175,213] The highest levels of asymmetric induction occurred with substrates containing very large ester groups and when the insertion occurred at benzylic sites in which the benzene ring had an electron-withdrawing substituent. The *N*-phthaloyl amino acid catalysts are ideally suited for this system, whereas very low asymmetric induction was obtained with Davies' Rh_2(*S*-DOSP)$_4$,[214] Doyle's Rh_2-(5*S*-MEPY)$_4$, [214] and Ito's rhodium(II) 2-alkoxyferrocene-carboxylate-ligated catalyst **11**.[176] The only other catalyst that has resulted in >50% ee has been a C_2 symmetric copper catalyst (**2**).[65,66] In addition, by using chiral ester substituents such as (+)-neomenthol, along with Rh_2(*S*-PTPA)$_4$, cyclopentanones in up to 80% ee were obtained through double-diastereoselection and then cleavage of the chiral auxiliary.[212,213] It is worthy of note that the corresponding acceptor-substituted α-diazoacetate system to **80d** is known to give solely the product from cyclopropanation of the pendant olefin chain with no reports of competing C−H activation (see

Table 15. C−H Activation of α-Diazo-β-ketoester 82



82 (*R*,*R*)-**83** (*S*,*R*)-**84**

	catalyst				
	$Rh_2(OAc)_4$	Rh_2(*S*-PTPA)$_4$	Rh_2(5*S*-MEPY)$_4$	Rh_2(*S*-DOSP)$_4$	Rh_2(*S*-biTISP)$_2$
yield, %	92	98	66	94	38
ratio **83**:**84**	57:43	74:26	57:43	64:36	79:21

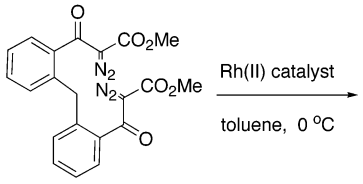
Table 7).[150] This result nicely illustrates the greater tendency of acceptor/acceptor-substituted carbenoids to undergo C−H activation compared to acceptor-substituted carbenoids.

Taber and Malcolm screened several chiral rhodium catalysts in an attempt to enhance the diastereoselectivity for the cyclization of enantiopure α-diazo-β-ketoester **82** (Table 15).[214] The bridged prolinate catalyst Rh_2(*S*-biTISP)$_2$ gave the best levels of diastereocontrol, affording **83** in up to 58% de, albeit in modest yield. The *ent*-**82** was also tested with the same range of catalysts. Only under the influence of Rh_2(*S*-biTISP)$_2$ was the reaction found to be catalyst controlled. In all other cases, the chirality inherent in the starting diazoacetoacetate **82** dominated the outcome of the reaction. Considering that Rh_2(*S*-biTISP)$_2$ outperforms Rh_2(*S*-PTPA)$_4$ in this reaction, it may be worthwhile to explore the utility of Rh_2(*S*-biTISP)$_2$ in other intramolecular C−H activation of carbenoids derived from α-diazo-β-ketoesters.

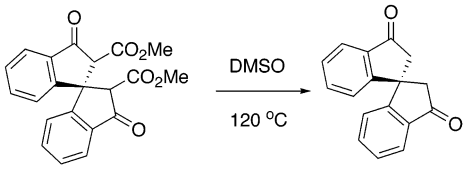
A very impressive example of the synthetic utility of this chemistry is the one-pot enantioselective double C−H activation reaction of **85** to generate chiral spiran **86**.[172] In this case the phthalimide catalyst Rh_2(*S*-PTPA)$_4$ was not especially effective (25% ee), but much better results were obtained with the bulkier Rh_2(*S*-PTTL)$_4$ catalyst (80% ee). Other rhodium carboxylates such as Rh_2(*S*-DOSP)$_4$ were found to be ineffective chiral catalysts for this chemistry. The asymmetric induction is believed to occur in the initial C−H insertion step and so relies on differentiating between the two enantiotopic hydrogens at the methylene site.[172] This possibly explains why only the exceptionally bulky Rh_2(*S*-PTTL)$_4$ catalyst was capable of high enantioselectivity (Table 16, entries 2 and 3). The subsequent C−H insertion is therefore thought to occur with retention of configuration, a well-established process in carbenoid C−H activation chemistry.[122]

Further evidence for the importance of α-substituent stabilization at the carbenoid carbon center is demonstrated by the Rh_2(*S*-BSP)$_4$-catalyzed reaction of β-keto diazoester **88**.[130] Whereas with the α-methyl-α-diazoketone the weak electron-donating effect of the alkyl group granted sufficient stabilization for productive C−H activation (see Table 13), the carbenoid derived from α-diazo-β-ketoester **88** was too unstable, undergoing tandem oxonium ylide formation-[2,3] sigmatropic rearrangement to produce **89** (eq 8) with no trace of the desired C−H activation product.[130] Rh_2(*S*-BSP)$_4$-catalyzed reactions of α-diazo-β-ketoesters generally suffer form poor enantiocontrol (5−14% ee).[215] Enhancement in selectivity has been achieved through substrate control utilizing ester chiral auxiliaries with the chiral catalyst, affording diastereoselectivities of up to 61% de.[215]

Table 16. Double C−H Activation to Form Spiran 87



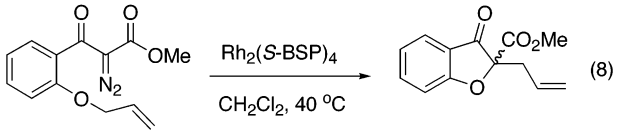
85



86 **87**

entry	catalyst	yield **87**, %	ee **87**, %
1	Rh_2(*S*-PTPA)$_4$	71	25
2	Rh_2(*S*-PTTL)$_4$	83	68
3[a]	Rh_2(*S*-PTTL)$_4$	78	80
4[b]	Rh_2(*S*-DOSP)$_4$	48	8

[a] Reaction conducted at −10 °C. [b] Reaction conducted at 23 °C.



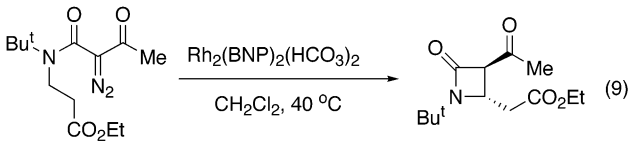
(8)

88 **89**
92% yield, 25% ee

5.2.c. Carbenoids Derived from α-Diazoacetoacetamides and Related Structures

C−H activation in α-diazoacetoacetamides typically favors β-lactam formation due to the activating influence of the adjacent nitrogen atom. However, as

the following section demonstrates, the observed regioselectivity is greatly influenced by the substituents on the amide nitrogen as well as α to the carbenoid carbon.[57,108,123] The binaphthyl phosphate $Rh_2(BNP)_2(HCO_3)_2$-catalyzed reaction of α-diazoacetoacetamide **90** exclusively gave the *trans*-*β*-lactam **91** with a modest 26% ee (eq 9).[183] No insertion



(9)

90 **91**
93% yield, 26% ee

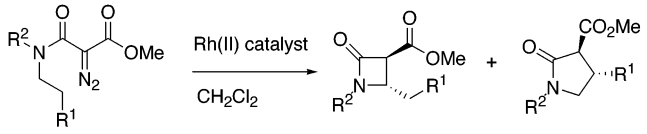
into the methyl C−H bond of the *tert*-butyl group was observed, unlike in the corresponding terminal diazoacetamide system (see Table 8).

The more stabilized acceptor/acceptor-substituted carbenoid derived from α-methoxycarbonyl-α-diazoacetamides **92** generated azetidinones **93** in a very efficient manner (Table 17).[216] Expanding on the initial findings of Wee,[57,217,218] Hashimoto and coworkers discovered that the regioselectivity of the C−H activation reaction could to some extent be controlled by careful choice of the *N*-protecting group.[173] For example, formation of the *β*-lactam **93** was completely suppressed by substituting the bulky *tert*-butyl group for a *p*-methoxyphenyl (PMP) group. Unfortunately, due to the high electron density of the PMP unit, aromatic C−H insertion was favored over benzylic C−H activation. Protecting the nitrogen with the less electron-rich *p*-nitrophenyl group discouraged the electrophilic aromatic substitution pathway, enabling exclusive formation of *trans*-3,4-pyrrolidinone **94** with no trace of the *β*-lactam product **93**. The enantioselectivity appears to be catalyst dependent, with Rh_2(*S*-PTTL)$_4$ and its naphthyl analogue Rh_2(*S*-BPTTL)$_4$ (both characterized by a bulky *tert*-butyl group) proving to be the catalysts of choice.[173] A range of substituents at R^1 were investigated in the Rh_2(*S*-PTTL)$_4$-catalyzed reaction, affording products in 72−84% yield with the enantioinduction being much higher for R^1 = aryl group (73−81% ee) than for R^1 = alkyl group (33−34% ee). In addition, the enantioselectivity for insertion adjacent to an electron-rich *p*-methoxyphenyl substituent was comparable to that for an electron-deficient *p*-nitrophenyl substituent (entries 13 and 14); therefore, the enantioselectivity was not dependent on the electronic effects of the substituents at the site of activation.

Hashimoto demonstrated the synthetic utility of the *N*-*p*-nitrophenyl substituent as a site-control element in the synthesis of some pharmaceutically relevant targets (Scheme 5). The $GABA_B$ receptor agonist, (*R*)-(−)-baclofen (**25**),[173] and phosphodiesterase type IV inhibitor (*R*)-(−)-rolipram (**95**)[219] were efficiently prepared with an intramolecular C−H activation being used as a key step.

Having established a highly regio- and stereoselective route to 4-substituted 2-pyrrolidinones, Hashimoto and co-workers readdressed selective formation of 2-azetidinones in an attempt to improve on the 74% ee previously obtained (Table 17, entry 3).[216] Following precedent form Ponsford and Southgate,[220] the incorporation of the amide nitrogen in a tetrahydro-1,3-oxazine system was found to create a rigid template for controlling the regio- and stereoselectivity of the C−H activation reaction. Indeed, highly selective *β*-lactam formation was accomplished in up to 94% yield and 96% ee using Rh_2(*S*-PTA)$_4$ (Table 18, entry 4).[174] Particularly insightful is a comparison of the C−H activation reactions of terminal α-diazoacetamide **96a**, α-diazoacetoacetamide **96b**, and α-methoxycarbonyl-α-diazoacetamide **96c**, which illustrate the beneficial influence of the stabilizing methoxycarbonyl group (Table 18).[174] Whereas the Rh_2(*S*-PTPA)$_4$-catalyzed reaction of diazoacetamide **96a** gave a complex mixture of products, cyclization of **96b** and **96c** proceeded to give the corresponding *β*-lactam product in good yield. However, in the case

Table 17. Intramolecular C−H Activation of α-Methoxycarbonyl-α-diazoacetamides



92 **93** **94**

compd	catalyst	R^1	R^2	product[a]	yield, %	de, %	ee, %
a	Rh_2(*S*-PTPA)$_4$	CO_2Et	^{t}Bu	**93**	98	>98	56
b	Rh_2(*S*-PTPA)$_4$	C_2H_5	^{t}Bu	**93**	97	>98	60
c	Rh_2(*S*-PTPA)$_4$	C_6H_5	^{t}Bu	**93**	>90	>98	74
d	Rh_2(*S*-PTPA)$_4$	C_6H_5	*p*-$MeOC_6H_4$	**94**	<5[b]		
e	Rh_2(*S*-PTPA)$_4$	C_6H_5	*p*-$NO_2C_6H_4$	**94**	82	>98	47
e	Rh_2(*S*-PTA)$_4$	C_6H_5	*p*-$NO_2C_6H_4$	**94**	83	>98	47
e	Rh_2(*S*-PTV)$_4$	C_6H_5	*p*-$NO_2C_6H_4$	**94**	82	>98	26
e	Rh_2(*S*-PTTL)$_4$	C_6H_5	*p*-$NO_2C_6H_4$	**94**	80	>98	74
e	Rh_2(*S*-TBSP)$_4$	C_6H_5	*p*-$NO_2C_6H_4$	**94**	87	>98	6
f	Rh_2(*S*-PTTL)$_4$	CH_3	*p*-$NO_2C_6H_4$	**94**	82	>98	33
g	Rh_2(*S*-PTTL)$_4$	C_2H_5	*p*-$NO_2C_6H_4$	**94**	84	>98	34
h	Rh_2(*S*-PTTL)$_4$	C_6H_5	*p*-$NO_2C_6H_4$	**94**	80	>98	74
i	Rh_2(*S*-PTTL)$_4$	*p*-$MeOC_6H_4$	*p*-$NO_2C_6H_4$	**94**	72	>98	81
j	Rh_2(*S*-PTTL)$_4$	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	**94**	81	>98	73

[a] Exclusive product. [b] Major product arose from electrophilic addition to aryl ring of *p*-methoxyphenyl.

Scheme 5

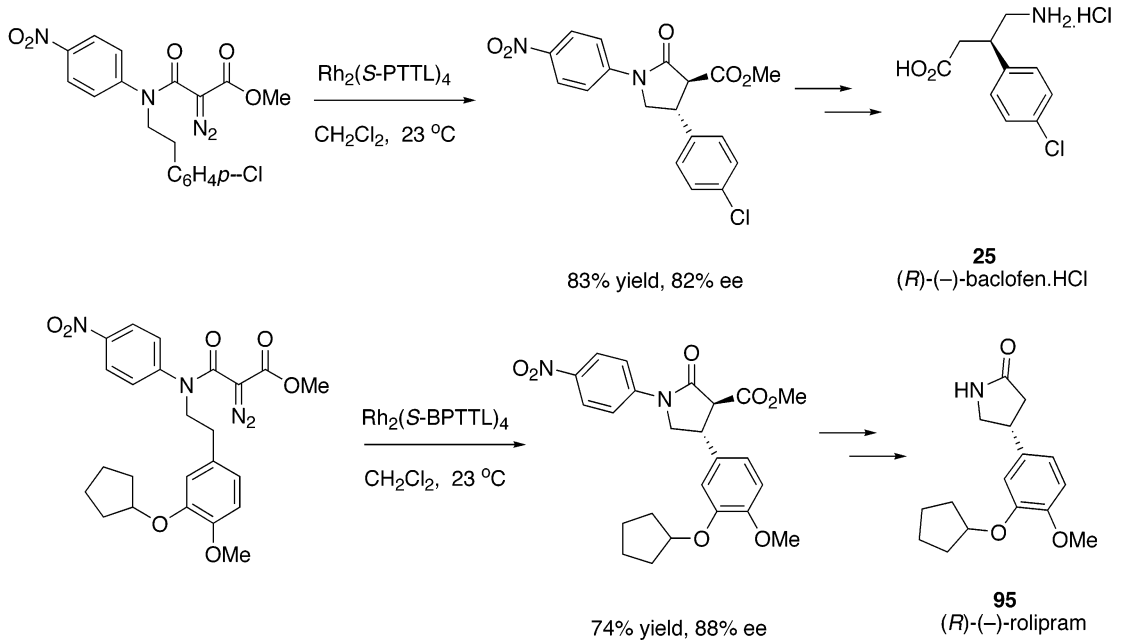
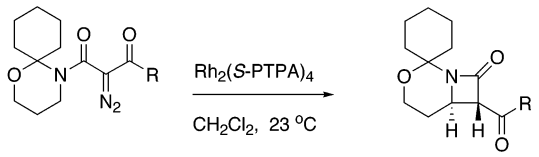


Table 18. Effect of Second Acceptor Group on Intramolecular C−H Activation

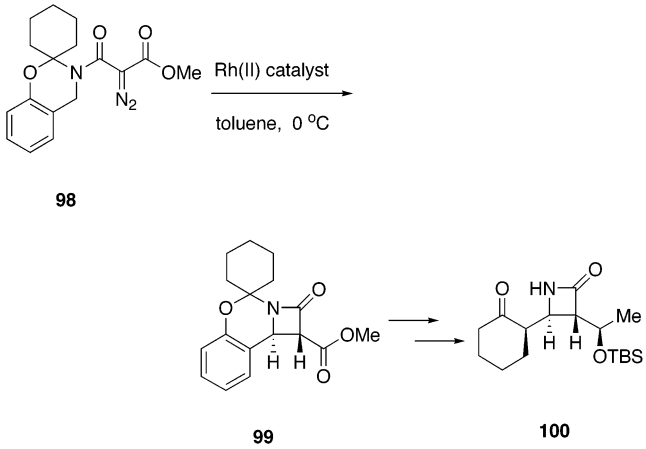


96 **97**

compd	R	yield, %	ee, %
a	H	—[a]	—
b	CH_3	84	0
c	OCH_3	89	90
d[b]	OCH_3	94	96

[a] Complex mixture of products obtained. [b] Reaction conducted at 0 °C using Rh_2(*S*-PTA)$_4$.

Table 19. Asymmetric Synthesis of Trinem 100



98 **99** **100**

entry	catalyst	yield **99**, %	ee **99**, %
1	Rh_2(*S*-PTA)$_4$	71	84
2	Rh_2(*S*-PTPA)$_4$	51	83
3	Rh_2(*S*-PTV)$_4$	56	45
4	Rh_2(*S*-PTPG)$_4$	78	10
5	Rh_2(*S*-PTLL)$_4$	66	84
6	Rh_2(*S*-TBSP)$_4$	—[b]	10
7[a]	Rh_2(5*S*-MEPY)$_4$	—[c]	

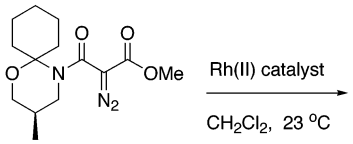
[a] Reaction conducted in 1,2-dichloroethane at reflux. [b] Yield not reported in publication. [c] Complex mixture of products.

of α-diazoacetoacetamide **96b**, the product **97b** was racemic, whereas the ester derivative **96c** gave **97c** in an excellent 90% ee. These results highlight the dramatic effect the substituent adjacent to the carbenoid carbon can have on the nature of the carbenoid with regard to regio- and stereocontrol. In particular, this elegantly underscores the subtle but important differences in the steric and electronic characteristics between acetyl and methoxycarbonyl groups at the α-position of the carbenoid carbon.[174]

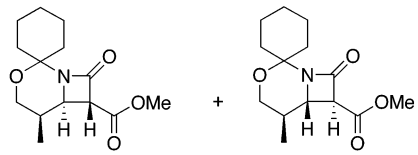
The 1,3-oxazine tether strategy was applied in a novel approach to a key intermediate (**99**) in the synthesis of trinem **100**.[221] Unlike the formation of γ-lactam **94**, in which bulky catalysts gave the greatest enantioselectivity,[173] formation of 2-azetidinone **99** was best conducted using Rh_2(*S*-PTA)$_4$, which contains a simple methyl substituent.[221] The enantioselectivity decreased on increasing the steric bulk of the ligand substitutent from methyl to isopropyl to phenyl (Table 19). Indeed, the bulky *tert*-butyl-substituted catalyst, Rh_2(*S*-PTTL)$_4$, caused a reversal in enantioselection. Hence, either enantiomer can be obtained by using either Rh_2(*S*-PTTL)$_4$ or Rh_2(*S*-PTA)$_4$ as a chiral catalyst. Rhodium(II) tetraprolinate catalyst Rh_2(*S*-TBSP)$_4$ achieved only 10% ee, whereas the carboxamidate, Rh_2(5*S*-MEPY)$_4$, was even less successful, affording an intractable mixture of products.[221]

Efficient double-asymmetric induction was effected in the Rh_2(*R*-PTPA)$_4$ matched reaction with nonracemic α-methoxycarbonyl-α-diazoacetamide **101** (Table 20).[222] Substantial reversal in the inherent diastereoselection occurred in the mismatched reaction of **101** with Rh_2(*S*-PTPA)$_4$ enabling convenient access to both diastereoisomers **102** and **103** by this approach.[222] With the corresponding α-diazoacetoaceta-

Table 20. Rh_2(PTPA)$_4$-Induced Double-Stereodifferentiation



101



102 103

entry	catalyst	yield **102** + **103**, %	ratio **102**:**103**
1	Rh_2(*R*-PTPA)$_4$	77	2:98
2	Rh_2(*S*-PTPA)$_4$	47	85:15

mide, the diastereomer ratio proved to be heavily dependent on the chirality of the substrate rather than that of the catalyst.[222]

Intramolecular C−H activation of acceptor/acceptor-substituted carbenoids has been dominated by Ikegami and Hashimoto's family of *N*-phthaloyl amino acid-based dirhodium(II) carboxylate catalysts. With α-diazo-*β*-ketoesters the catalyst of choice for cyclopentanone formation is the benzyl-substituted Rh_2(*S*-PTPA)$_4$. The regio- and stereoselectivity are highly sensitive to the substituents at the site of insertion and the size of the ester group adjacent to the carbenoid carbon. Higher enantioselectivities are generally obtained through cyclization of α-methoxycarbonyl-α-diazoacetamides, possibly as a result of the greater stability of the resultant carbenoids. Impressive site and stereoselectivity for *β*-lactam formation is exhibited by Rh_2(*S*-PTA)$_4$, whereas the bulkier Rh_2(*S*-PTTL)$_4$ and its second-generation derivative, Rh_2(*S*-BPTTL)$_4$, are best suited for *γ*-lactam formation. The nature of the nitrogen-protecting group is particularly relevant in influencing the regio- and enantioselectivity of the reaction.

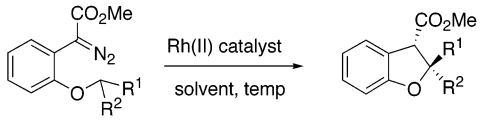
5.3. Donor/Acceptor-Substituted Carbenoids

The enhanced stability of donor/acceptor-substituted carbenoids means that they are able to undergo highly regio- and stereoselective C−H activation reactions.[42−45] Owing to the stability provided by the α-substituents at the carbenoid carbon, the carbene precursor is not so sensitive to the choice of the metal catalyst, and a range of chiral rhodium(II) carboxylates and rhodium(II) carboxamidates have been used with reasonable success in intramolecular cyclization reactions.[124,171,182,223] Metallocarbenoids generated from rhodium(II) carboxylates tend to give the best levels of selectivity, however, as they are sufficiently electrophilic to complement the enhanced stability of the donor/acceptor-substituted carbenoid. In this way a carbenoid of suitable electrophilicity is generated to undergo productive yet selective C−H insertion.

5.3.a. Carbenoids Derived from Aryldiazoacetates

The outstanding control and selectivity exhibited by donor/acceptor-substituted carbenoids in intramolecular reactions has been elegantly showcased in the construction of chiral dihydrobenzofurans. Independent studies by Davies[223] and Hashimoto[171] addressed C−H activation of aryldiazoacetates possessing an *ortho*-alkoxy substituent. Although C−H activation at the methyl ether position in **104a** was effected in excellent yield using prolinate catalyst Rh_2(*S*-DOSP)$_4$, the poor level of enantioinduction led Davies to investigate alternative catalysts (Table 21).[223] In

Table 21. Intramolecular C−H Activation of Aryldiazoacetates into Methyl and Methine C−H Bonds



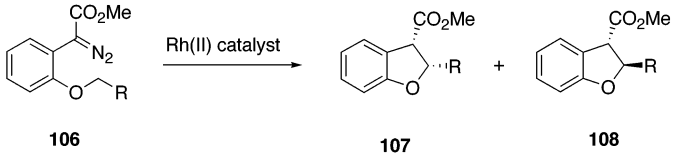
104 105

compd	R^1	R^2	catalyst	solvent	temp, °C	yield, %	ee, %
a[a]	H	H	Rh_2(*S*-DOSP)$_4$	hexane	23	98	<5
a[a]	H	H	Rh_2(*S*-biTISP)$_2$	CH_2Cl_2	−50	70	43
a[a]	H	H	**9**	CH_2Cl_2	−50	70	68
a[b]	H	H	Rh_2(*S*-PTTL)$_4$	toluene	−23	69	44
b[a]	CH_3	CH_3	Rh_2(*S*-DOSP)$_4$	hexane	−50	98	94
b[a]	CH_3	CH_3	Rh_2(*S*-biTISP)$_2$	CH_2Cl_2	−50	48	60
b[a]	CH_3	CH_3	**9**	CH_2Cl_2	−50	57	65
b[b]	CH_3	CH_3	Rh_2(*S*-PTTL)$_4$	toluene	−78	88	22
c[a]	c-C_4H_8		Rh_2(*S*-DOSP)$_4$	hexane	−50	93	90
d[a]	c-C_5H_{10}		Rh_2(*S*-DOSP)$_4$	hexane	−50	12	80

[a] Reaction conducted by Davies group. [b] Reaction conducted by Hashimoto group.

doing so, it was found that decomposition of **104a** at −50 °C in the presence of the bridged catalyst **9** generated **105a** in 70% yield and 68% ee. Using the *N*-phthaloyl catalyst Rh_2(*S*-PTTL)$_4$, Hashimoto and co-workers were able to effect the identical cyclization in comparable yield, although with a reduced level of asymmetric induction (69% yield, 44% ee).[171] The high yields for insertion into the methyl site are most impressive, considering that the reluctance of primary C−H bonds to undergo carbenoid C−H activation is well established for both the intra- and intermolecular processes.[17,44,45,104] Rh_2(*S*-DOSP)$_4$ proved to be the catalyst of choice for C−H activation at a tertiary site (entries 5−10), giving **105b** in an excellent 98% yield and 94% ee.[223] The reaction of **104b** with bridged prolinate catalysts Rh_2(*S*-biTISP)$_2$ (**8a**) and **9** occurred with enantiomer preference reversed from that obtained with Rh_2(*S*-DOSP)$_4$.[223] The Rh_2(*S*-PTTL)$_4$-catalyzed reaction gave **105b** with low asymmetric induction (22% ee) despite the lower reaction temperature.[171] Interestingly, although the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of cyclopentyl derivative **104c** proceeded in excellent yield, reaction of the corresponding cyclohexyl derivative **104d** gave the desired spirocycle **105d** in only 12% yield, with carbene dimerization being the predominant product.[223] The low yield is thought to result from conformational restrictions associated with the cyclohexane system.[223]

Table 22. Intramolecular C−H Activation of Aryldiazoacetates into Methylene C−H Bonds



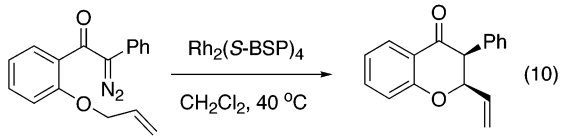
106 107 108

compd	R	catalyst	solvent	temp, °C	yield, %	de, %[a]	ee, %[b]
a[c]	CH_3	Rh_2(*S*-DOSP)$_4$	hexane	−50	85	60 (**107**)	60 (2*S*,3*R*)
a[c]	CH_3	Rh_2(*S*-biTISP)$_2$	CH_2Cl_2	−50	50	70 (**107**)	53 (2*R*,3*S*)
a[c]	CH_3	**9**	CH_2Cl_2	−50	70	75 (**107**)	45 (2*R*,3*S*)
a[d]	CH_3	Rh_2(*S*-PTTL)$_4$	toluene	−78	91	72 (**108**)	97 (2*R*,3*R*)
b[c]	c-C_6H_{11}	Rh_2(*S*-DOSP)$_4$	hexane	−50	72	95 (**107**)	63[e]
b[d]	c-C_6H_{11}	Rh_2(*S*-PTTL)$_4$	toluene	−78	63	92 (**107**)	96[e]
c[d]	C_6H_5	Rh_2(*S*-PTTL)$_4$	toluene	−78	86	>98 (**107**)	94 (2*R*,3*S*)

[a] Figure in parentheses denotes major diastereoisomer. [b] Configuration assignment given in parentheses. [c] Reaction conducted by Davies group. [d] Reaction conducted by Hashimoto group. [e] Absolute stereochemistry of the product was not determined.

Complementary diastereoselectivity was achievable for methylene insertion of **106** depending on the choice of catalyst.[171,223] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of the phenyldiazoacetate **106a** favored formation of the *cis*-dihydrofuran **107a**,[223] whereas the Rh_2(*S*-PTTL)$_4$-catalyzed approach favored the trans isomer **108a**[171] (Table 22). This latter result was actually a dramatic reversal in the typical diastereoselectivity observed with the Rh_2(*S*-PTTL)$_4$-catalyzed system, which appears to be superior to the Rh_2(*S*-DOSP)$_4$ system for intramolecular methylene C−H activation of aryldiazoacetates. This trend is different from that observed in the intermolecular C−H insertions, where reasonably high enantioselectivity generally occurs for Rh_2(*S*-DOSP)$_4$-catalyzed C−H activation of methylene C−H bonds.[44,45] Further studies have suggested that the presence of the aryl ring and the oxygen functionality adjacent to the site of insertion is required for high enantioinduction, at least with the phthaloylamino acid-derived catalysts.[171]

Steric factors can override electronic effects in influencing the level of asymmetric induction observed with aryldiazoacetates.[45] The enantioselectivity for the C−H activation product **110** (eq 10) obtained from the prolinate Rh_2(*S*-BSP)$_4$-catalyzed reaction of aryldiazoacetate **109** was much lower than

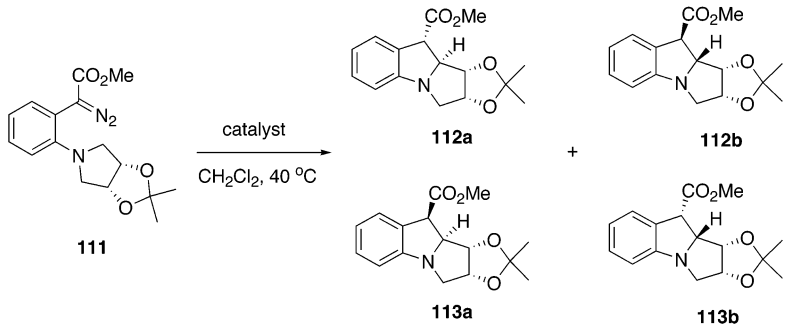


109 **110**
94% yield, 45% ee

that obtained with the corresponding α-methyl-α-diazoketone **74** (45% ee cf. 60% ee).[130] Despite the presumed greater stability of the carbene derived from aryldiazoacetate **109**, it is likely that the cyclization process is governed by steric factors, which quash the electronic preferences.[130]

The first effective asymmetric copper-catalyzed C−H activation reaction was reported by the group of Sulikowski in the reaction of the aryldiazoacetate **111** to form four diastereomeric products **112a**,**b** and **113a**,**b**[72,74] (Table 23). Rh_2(5*S*-MEPY)$_4$ was found to give racemic products, and Rh_2(*S*-TBSP)$_4$ gave only marginal enantioinduction (10% and 11% ee) in dichloromethane,[72] although the prolinate catalyst is known to perform much better in nonpolar solvents.[43] CuOTf and bisoxazoline **1c** gave improved, although still modest, enantioinduction (18% and 20% ee).[72] It should be noted that the overall enantioselectivity

Table 23. Intramolecular C−H Activation of 111



111 **112a** **112b** **113a** **113b**

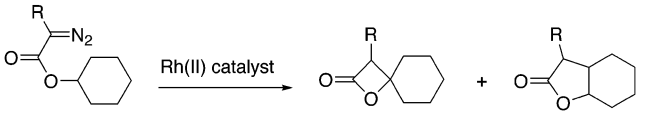
entry	catalyst	yield, %	ratio **112a**:**112b**:**113a**:**113b**	ee **112**,[a] %	ee **113**,[a] %
1	$Rh_2(OAc)_4$	95	45:5:37:13		
2	Rh_2(5*S*-MEPY)$_4$	88	3:58:2:37	0	0
3	Rh_2(*S*-TBSP)$_4$	95	54:6:30:10	10	11
4[b]	CuOTf/**1c**	94	38:38:17:7	48	20

[a] Enantiomeric excess obtained from oxidation of diastereomeric mixture. [b] Reaction conducted in $CHCl_3$ at reflux.

that was reported is not directly related to the carbenoid face selectivity during the insertion reaction as pairs of diastereomers were oxidized to the corresponding indole prior to the determination of enantioinduction.[72] A cyclic aryldiazoketone variant of **111** has also been utilized in a similar procedure. The copper-catalyzed reaction afforded the desired cyclic product in 8−15% ee.[73] High-throughput screening of the C−H activation of diazoacetate **111** was undertaken to ascertain the optimum metal, ligand, and solvent combination to use for the reaction.[155] The best stereoselectivities were observed in copper-based systems, although comparable diastereoselectivities were obtained with a silver-based catalyst.

Highly enantioselective C−H activation reactions have also been achieved on the ester substituents of phenyldiazoacetates rather than on the aryl substituent.[124,182] Doyle and May discovered that dirhodium(II) catalysts with chiral carboxylate or azetidinone ligands give high selectivity for insertion into tertiary C−H bonds to give β-lactones **115** with modest enantiocontrol and with only minor amounts of the corresponding γ-lactone **116** being produced.[124] This is yet another example of the subtle influence of steric effects in phenyldiazoacetates on the rhodium catalyst, as conducting the reaction with the corresponding acceptor-substituted diazoacetate largely favored γ-lactone (**33**) formation (Table 24).[194] Thus,

Table 24. Regioselectivity in Cyclization of 32 versus 114



32 R= H
114 R= C_6H_5

115

33 R= H
116 R= C_6H_5

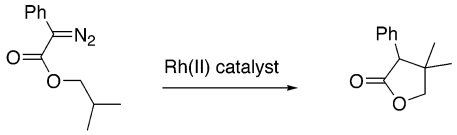
entry	R	catalyst	yield, %	ratio **115**:**116**	ee,[a] %
1	H	Rh_2(4*S*-MACIM)$_4$	70[b]	0:100[b]	97
2	C_6H_5	Rh_2(*S*-MEAZ)$_4$	67[c]	98:2	50
3	C_6H_5	Rh_2(*S*-IBAZ)$_4$	66[c]	97:3	51
4	C_6H_5	Rh_2(*S*-NEPAZ)$_4$	65[c]	97:3	42
5	C_6H_5	Rh_2(*S*-DOSP)$_4$	69[c]	98:2	63

[a] Enantiomeric excess of major product. [b] Fused bicycle **33** formed exclusively. [c] Product yield after separation of catalyst.

with phenyldiazoacetate **114** C−H activation was favored at the methine site, despite the adjacent deactivating ester functionality and the greater ring strain within the resultant β-lactone **115** than in γ-lactone **116**.[124]

Interestingly, positioning the tertiary center one carbon along the ester side chain resulted in only γ-lactone product being observed (Table 25), suggesting that the course of the C−H activation reaction is strongly influenced by the proximity of the tertiary C−H bond and to a much greater extent than witnessed in acceptor-substituted diazoacetates.[124] The effectiveness for asymmetric induction at tertiary sites using Rh_2(*S*-DOSP)$_4$ in intramolecular C−H activation is again highlighted (Table 24, entry 5; Table 25, entry 3; and Table 26, entry 4). The azetidinone-based catalysts Rh_2(*S*-MEAZ)$_4$ and

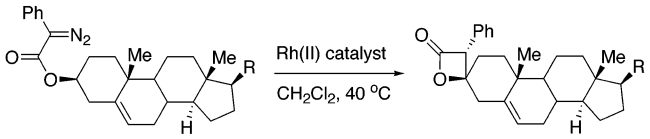
Table 25. Intramolecular C−H Activation of 117



117 **118**

entry	catalyst	yield, %	ee, %
1	Rh_2(*S*-MEAZ)$_4$	94	90
2	Rh_2(*S*-IBAZ)$_4$	89	84
3	Rh_2(*S*-DOSP)$_4$	89	86

Table 26. C−H Activation of Steroidal Phenyldiazoacetate 119



119 R=$CHCH_3(CH_2)_3CH(CH_3)_2$ **120**

entry	catalyst	yield,[a] %	de, %
1	$Rh_2(OAc)_4$	69	56
2	Rh_2(4*R*-MEAZ)$_4$	69	68
3	Rh_2(4*S*-MEAZ)$_4$	66	24
4[b]	Rh_2(*S*-DOSP)$_4$	69	80

[a] Product yield after separation of catalyst. [b] Reaction conducted in pentane at reflux.

Rh_2(*S*-IBAZ)$_4$ also gave good levels of asymmetric induction, demonstrating the increased reactivity of the azetidinone-based catalysts over the pyrrolidinone-based chiral rhodium(II) carboxamidate catalysts.[144]

Doyle exploited the strong tendency for aryldiazoacetates to form β-lactones in stereodifferentiation studies in steroidal systems (Table 26).[182] Results indicated that the chiral catalyst used strongly influenced the diastereoselectivity of the reaction, with the greatest selectivity achieved with Rh_2(*S*-DOSP)$_4$ of up to 80% de.

5.3.b. Carbenoids Derived from Vinyldiazoacetates

To date, there have been no reports on asymmetric intramolecular C−H activation reactions of vinyldiazoacetates, although it is very likely that this would be a feasible process.

The use of donor/acceptor-substituted carbenoids in asymmetric intramolecular C−H activation chemistry is still in its infancy, but results thus far have illustrated that highly regio- and stereoselective reactions can be conducted. C−H activation at tertiary sites seems to be generally most effective using the prolinate catalyst Rh_2(*S*-DOSP)$_4$, although in certain instances the azetidinone-based catalysts Rh_2(*S*-MEAZ)$_4$ and Rh_2(*S*-IBAZ)$_4$ have also produced good results. Outstanding enantioinduction has been achieved in methylene insertions using *N*-phthalimide *tert*-leucine catalyst Rh_2(*S*-PTTL)$_4$.

6. Intermolecular C–H Activation Reactions

Over the past few years the intermolecular C−H activation by carbenoids has undergone explosive

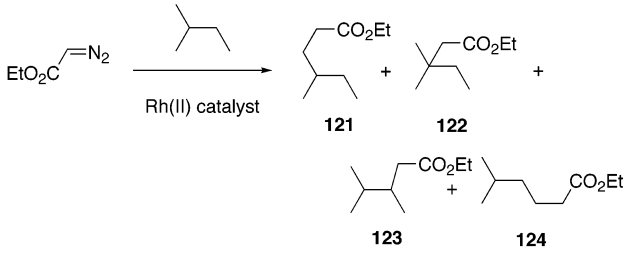
growth.[44,45] For a long time the intermolecular reaction was considered to be of little synthetic utility because the process displayed very poor chemoselectivity and carbene dimerization was a major competing reaction.[17,20,121] The situation has now totally changed with the development of the donor/acceptor-substituted carbenoids, which are exceptional reagents for intermolecular C−H activation.[44,45] This area of chemistry is probably the most graphic example of the huge difference in reactivity that exists between the carbenoid systems. To place this work in context, this section will be introduced by a brief description of the intermolecular C−H activation chemistry of acceptor- and acceptor/acceptor-substituted carbenoids, which then will be followed by the major advances that have been made with donor/acceptor-substituted carbenoids.

6.1. Acceptor-Substituted Carbenoids

6.1.a. C–H Activation of Alkanes

During the very early development of catalysts for metallocarbenoid transformations it was found that dirhodium tetracarboxylates were far superior to the copper catalysts at inducing intermolecular C−H activation.[47,113−116] The reaction, however, was not generally considered to be of much synthetic utility because the regioselectivity was poor and carbene dimerization dominated unless the diazo compound was added very slowly.[17,20,121] An example of the regiochemical challenges associated with this chemistry is the reaction of ethyl diazoacetate with 2-methylbutane (Table 27).[115] A mixture of all four of

Table 27. Intermolecular C−H Activation of 2-Methylbutane



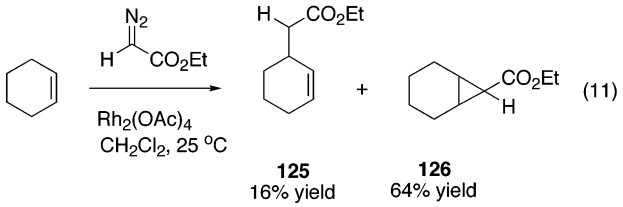
entry	catalyst	ratio **121:122:123:124**
1	$Rh_2(OAc)_4$	1:8:90:1
2	Rh_2(9-trp)$_4$ [a]	18:18:27:37
3	$Rh_2(TFA)_4$	5:25:66:4

[a] Dirhodium(II) tetrakis(9-triptycenecarboxylate).

the possible C−H activation products **121**−**124** was formed. Even though there was a preference for insertion into the methylene C−H bond and the catalyst did influence the ratio of products, no catalyst was capable of modulating the reaction such that only a single product was formed. These seminal results demonstrated not only that metal−carbenoid intermediates were capable of C−H activation of alkanes but also that much more chemoselective reagents would be required for this transformation to be of general practical utility.[113−116,134,224]

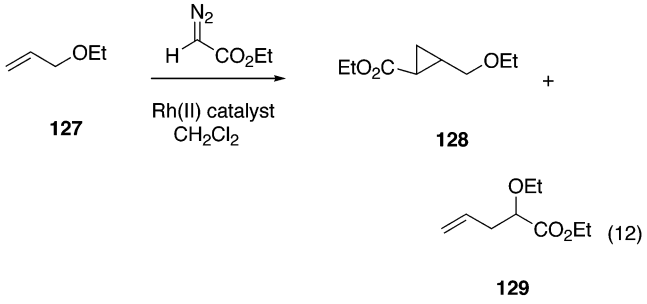
6.1.b. C–H Activation of Functionalized Organic Substrates

With the currently available catalysts, selective C−H activation reactions with ethyl diazoacetate would require the use of substrates possessing functionality to direct the reaction. C−H bonds at allylic and benzylic sites and α to oxygen or nitrogen functionalities are generally favored for C−H activation.[53,56−59] Unfortunately, the carbenoids derived from ethyl diazoacetate are so reactive that the additional functionality may not itself be inert to carbenoid chemistry. With allylic substrates acceptor-substituted diazoacetates routinely exhibit greater preference for cyclopropanation rather than C−H activation.[17,21] For example, $Rh_2(OAc)_4$-catalyzed decomposition of ethyl diazoacetate in the presence of cyclohexene favored cyclopropanation (**126**) over C−H activation (**125**) by a ratio of 4:1 (eq 11).[134,225] Other



compounds with highly activated allylic sites such as 1,3-cyclohexadiene, 1,4-cyclohexadiene, 1,3-cycloheptadiene, and 1,3,5-cycloheptatriene still preferentially undergo cyclopropanation to C−H activation.[225−227]

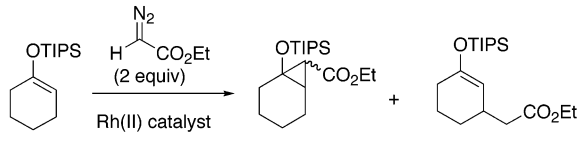
The allylic position in allyl ethers would be expected to be an exceptionally reactive site for C−H activation, but the reaction of allyl ethyl ether (**127**) with ethyl diazoacetate failed to form any C−H activation product (eq 12).[151] Irrespective of the



catalyst used, including Rh_2(*S*-TBSP)$_4$, Rh_2(5*S*-MEPY)$_4$, and Rh_2(4*S*-MEOX)$_4$, the only products were those arising from cyclopropanation (**128**) and ylide rearrangement (**129**).

Cyclopropanation is also favored over C−H activation when silyl enol ethers are used as substrates, although the nature of the catalyst does have an impact on the product ratio.[228] $Rh_2(OOct)_4$-catalyzed decomposition of ethyl diazoacetate in the presence of TIPS enol ether **130a** resulted in the formation of a 96:4 mixture of cyclopropane diastereomers **131** and C−H insertion product **132** (Table 28). A similar reaction using the prolinate catalyst Rh_2(*S*-DOSP)$_4$ afforded a 76:24 mixture of cyclopropane to the C−H insertion product.[228] The enhancement of C−H activation by the prolinate catalyst Rh_2(*S*-DOSP)$_4$ may be due to the bulkier nature of Rh_2(*S*-DOSP)$_4$ [43] or

Table 28. Cyclopropanation versus C−H Activation of Silyl Enol Ether 130a

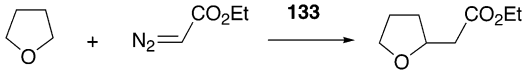


130a 131 132

catalyst	yield **131** + **132**, %	ratio **131**:**132**
$Rh_2(OOct)_4$	66	96:4
Rh_2(*S*-DOSP)$_4$	54	76:24

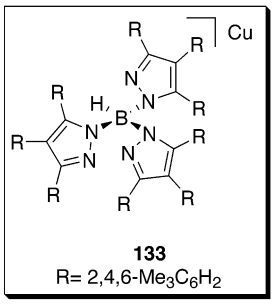
the more electrophilic character of the carbenoid derived from Rh_2(*S*-DOSP)$_4$.

One system that has been reported to undergo a selective C−H activation has been tetrahydrofuran.[120,229] In the earlier studies C−H activation of tetrahydrofuran catalyzed by rhodium(II) acetate was reported to occur α to oxygen, although the overall yields were low (20−40%).[120] Recently, higher yields in intermolecular C−H activations were reported using the bulky copper catalyst **133**, and in the reaction between ethyl diazoacetate and tetrahydrofuran the yield of the C−H activation product **134** was improved to 98% (eq 13).[229] The main advantage



(13)

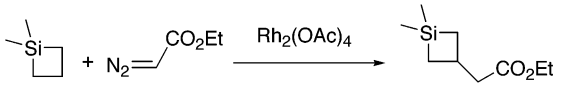
134
98% yield



133
R= 2,4,6-$Me_3C_6H_2$

of the copper catalyst appears to be its extremely bulky nature, which causes carbenoid dimerization to be disfavored. It has not yet been determined if the added bulk will also result in greater regioselectivity in the C−H activation process.

One very interesting example of intermolecular C−H activation is the rhodium(II) acetate-catalyzed reaction with silacycles.[230] As can be seen in the example in eq 14, the reaction of **135** with ethyl diazoacetate is very efficient, resulting in the formation of **136** in 97% yield.



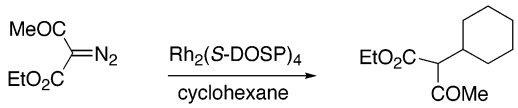
(14)

135 **136**
97% yield

In summary, asymmetric intermolecular C−H activation using the acceptor-substituted carbenoids has seen very limited advance. A suitable catalyst system needs to be developed so that the reactivity of these acceptor-substituted carbenoids is sufficiently tamed to allow controlled transformations to be achieved. To date, the only effective solution has been to modulate the reactivity of the carbenoid by changing the carbenoid structure.[44,45]

6.2. Acceptor/Acceptor-Substituted Carbenoids

Metal-catalyzed decomposition of disubstituted diazocarbonyls generates carbenoids that are more chemoselective than acceptor-substituted diazocarbonyls, although still highly reactive.[17,131] Very few examples have been reported on asymmetric C−H activation with acceptor/acceptor-substituted carbenoids.[134] One example is the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl diazoacetoacetate (**137**) with cyclohexane, which gave the C−H activation product **138** in 51% yield but with very low asymmetric induction.

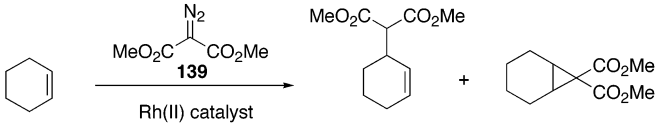


(15)

137 **138**
51% yield, 3% ee

The study of a few chiral catalysts for allylic C−H activation by acceptor/acceptor-substituted carbenoids has been conducted.[225] Once again, cyclopropanation is a major competing reaction, but the catalyst can significantly influence the chemoselectivity of the reaction. For instance, treatment of diazomalonate **139** with Hashimoto's phenylalanine catalyst Rh_2(*S*-PTPA)$_4$ in the presence of cyclohexene affords a 3:1 mixture of cyclopropane **141** and the C−H activation product **140** (Table 29). Pirrung's binaph-

Table 29. Cyclopropanation versus C−H Activation of Cyclohexene



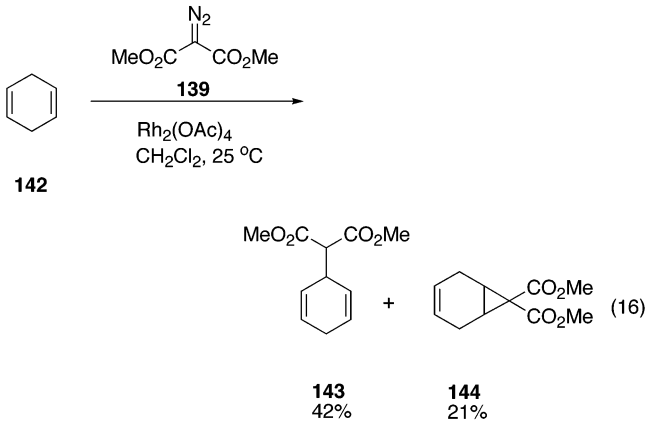
140 **141**

entry	catalyst	yield **140** + **141**, %	ratio **140**:**141**	ee **140**, %
1	$Rh_2(OAc)_4$	96	38:62	
2	Rh_2(*S*-PTPA)$_4$	86	24:76	24
3	Rh_2(*R*-BNP)$_4$	30	49:51	7

thyl phosphate catalyst, Rh_2(*R*-BNP)$_4$, gave an equal mixture of C−H activation and cyclopropanation products albeit in a greatly reduced yield.[225] The enantioinduction for the C−H activation product was poor for the reactions with either of the chiral catalysts.

Greater preference for C−H activation over cyclopropanation is displayed by acceptor/acceptor-substituted carbenoids when the site for insertion is highly activated.[225] For the doubly allylic methylene position of 1,4-diene **142** C−H activation product **143**

was favored over the cyclopropane **144** by a 2:1 ratio (eq 16). Even though the acceptor/acceptor-substituted carbenoids are more prone to C−H activation over cyclopropanation than acceptor-substituted carbenoids, highly enantioselective versions of this chemistry are not currently available.



6.3. Donor/Acceptor-Substituted Carbenoids

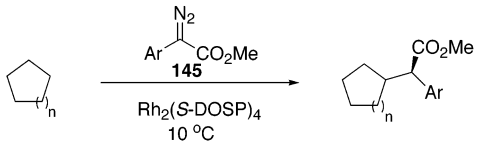
Donor/acceptor-substituted carbenoids have proven to be outstanding reagents for intermolecular C−H activation chemistry, displaying remarkable chemoselectivity and enantiocontrol.[44,45] Due to the enhanced stability of donor/acceptor-substituted carbenoids they are far less susceptible to dimer formation.[165] As a result, the C−H activation can be conducted with the trapping agent serving as the limiting reagent.[227,228,231] This is very rare for metal-catalyzed carbenoid transformations because, traditionally, intermolecular carbenoid reactions are conducted using an excess of substrate to limit unwanted side reactions such as carbene oligomerization.[17] The two most widely studied classes of donor/acceptor-substituted carbenoids have been those derived from aryldiazoacetates and vinyldiazoacetates.

6.3.a. Carbenoids Derived from Aryldiazoacetates

6.3.a.i. C−H Activation into Alkanes. The realization that asymmetric intermolecular C−H insertion reactions could be of practical synthetic use came about in 1997 when Davies and Hansen effected the decomposition of aryldiazoacetates **145** catalyzed by the prolinate catalyst $Rh_2(S\text{-DOSP})_4$ in the presence of a variety of cycloalkane solvents.[134] Conducting the reactions under refluxing conditions afforded C−H activation products in yields ranging from 53 to 96% and with 60−93% ee. Further enhancement in enantioselectivity (88−96% ee) without appreciable drop in yield was achieved by conducting the reactions at 10 °C in degassed solvent (Table 30).[165] The absolute configuration of the C−H activation products **146** was determined to be *R* for the $Rh_2(S\text{-DOSP})_4$-catalyzed reaction.

Crucial to the success of the intermolecular process is a delicate balance of electronic and steric effects.[44] In this regard the aryl substituent on the carbenoid carbon can have a subtle but important influence.[134,165] An electron-donating aromatic substituent on the carbenoid tends to result in lower yields of C−H activation products, presumably because the carbenoid would be less electrophilic. The size of the ester substituent at the carbenoid carbon is also very critical.[165] In the C−H activation of cyclohexane, changing from the methyl ester **147a** to the isopropyl ester **147b** to the *tert*-butyl ester **147c** caused the enantioselectivity to drop from 92% ee to 20% ee (Table 31). The drop in enantioselectivity with increasing size of the ester is a distinctive feature of $Rh_2(S\text{-DOSP})_4$-catalyzed reactions of donor/acceptor-substituted carbenoids because exactly the opposite effect is seen with carbenoids derived from other diazoacetate systems.[40,175]

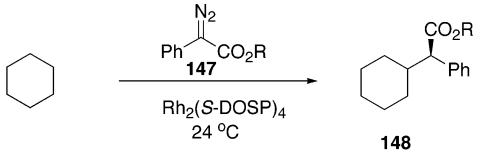
Table 30. C−H Activation of Cycloalkanes by Aryldiazoacetates



compd	*n*	Ar	yield, %	ee, %[a]
a	1	C_6H_5	72	96 (*R*)
b	1	*p*-ClC_6H_4	70	95 (*R*)
c	2	C_6H_5	80	95 (*R*)
d	2	*p*-BrC_6H_4	64	95 (*R*)
e	2	*p*-ClC_6H_4	76	94 (*R*)
f	2	*p*-$MeOC_6H_4$	23	88 (*R*)
g	2	*p*-$CF_3C_6H_4$	78	94 (*R*)
h	2	*o*-ClC_6H_4	81	90 (*R*)

[a] Configurational assignment in parentheses.

Table 31. Effect of Ester Substituent on the Enantioselectivity of Intermolecular C−H Activation



compd	R	yield, %	ee, %
a	CH_3	80	92
b	$CH(CH_3)_2$	39	86
c	$C(CH_3)_3$	45	20

The versatility of the intermolecular methodology has been well established through efficient and highly selective C−H activation of a range of alkane substrates.[165] The ability to functionalize such traditionally unreactive species in a highly regio- and stereoselective manner is a major advance. General trends regarding the activity of methine, methylene, and methyl C−H bonds toward C−H activation have been developed (Figure 6).[165] Tertiary sites are much more activated than primary sites, as evident for the formation of **149** as the sole C−H activation product in the reaction of 2,3-dimethylbutane with the corresponding metal−carbenoid. The reactions of adamantane and 2-methylbutane also gave preference to insertion at the methine site, affording **150** and **151**, respectively. The lack of C−H activation at the methylene sites in both of these cases was thought to be due to the steric influence of the adjacent

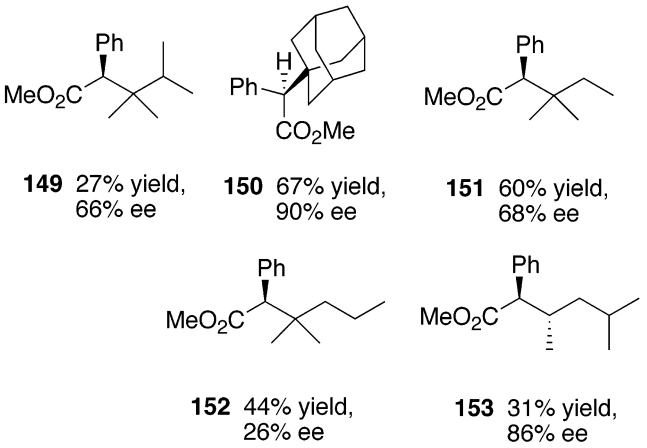
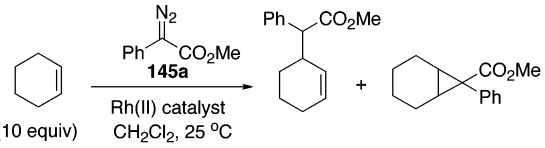


Figure 6. C–H activation product formed on reaction of methyl phenyldiazoacetates with various alkanes.

tertiary site. Indeed, when 2-methylpentane was exposed to the reaction conditions, insertion products **152** and **153** were formed in similar yields, indicating that, all things being equal, the reactivity of a methine position is comparable to that of a methylene position. Thus, the reactions were found to be remarkably chemoselective with the degree of reactivity following the sequence secondary ≈ tertiary ≫ primary C–H bonds. From these studies 2,2-dimethylbutane (2,2-DMB) presented itself as a suitably inert solvent for the C–H activation reactions.[165]

6.3.a.ii. Allylic C–H Activation. The propensity for olefins to undergo cyclopropanation when exposed to metal–carbenoids is well established, particularly for mono- or cis-substituted double bonds.[21] Olefins also influence adjacent C–H bonds, however, enhancing the C–H activation pathway. Müller and Tohill published an interesting study on the factors influencing the chemoselectivity between C–H activation versus cyclopropanation in intermolecular metallocarbenoid reactions.[225] The carbenoid derived from methyl phenyldiazoacetate (**145a**) is far more prone toward C–H activation than cyclopropanation, and this behavior is opposite that of the reactions of the acceptor and acceptor/acceptor-substituted carbenoids. Treatment of **145a** with a variety of chiral catalysts in the presence of cyclohexene afforded both the C–H activation product **154** and the cyclopropane **155** (Table 32). The pyrrolidinone catalyst Rh_2(*S*-MEPY)$_4$ demonstrated high chemoselectivity for the C–H activation product **154**, although the enantiocontrol was moderate (45% ee). The imidazolidinone catalyst Rh_2(*S*-PHOX)$_4$ and Hashimoto's carboxylate catalyst Rh_2(*S*-PTPA)$_4$ gave much poorer chemoselectivity but moderate enantioselectivity. Although the Rh_2(*S*-DOSP)$_4$-catalyzed reaction gave the best enantioselectivity (75% ee) for the C–H activation product **154**, the yield was poor (33%) when dichloromethane was used as solvent.[225] These conditions are not optimum for the Rh_2(*S*-DOSP)$_4$ catalyst because hydrocarbon solvents are required for the highest levels of asymmetric induction.[164,167] Indeed, when the reaction with Rh_2(*S*-DOSP)$_4$ was conducted in 2,2-dimethylbutane at −50 °C, the C–H activation product **154** under these optimized conditions was obtained in 58% yield with excellent enantioselectivity (93% ee) (Table 32, entry 6).[231] The poor diastereoselectivity obtained in these reactions is typical for intermolecular C–H activation reactions of simple alkenes.[231] Although the preference for insertion observed with some of the chiral dirhodium(II) species could not be fully rationalized, it is proposed that both steric and electronic factors have an influential role.[225]

Table 32. C–H Activation of Cyclohexene

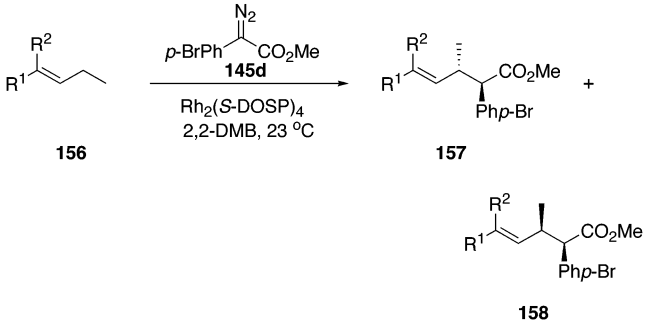


entry	catalyst	yield **154** + **155**, %	ratio **154**:**155**	de **154**, %	ee **154**, %[a]
1[b]	$Rh_2(OAc)_4$	50	75:25	24	
2[b]	Rh_2(*S*-PHOX)$_4$	52	66:34	14	4
3[b]	Rh_2(*S*-MEPY)$_4$	50	93:7	26	45 (*S*)
4[b]	Rh_2(*S*-PTPA)$_4$	45	50:50	6	53 (*S*)
5[b]	Rh_2(*S*-DOSP)$_4$	33	80:20	4	75 (*R*)
6[c,d]	Rh_2(*S*-DOSP)$_4$	73	79:21	0	93 (*R*)

[a] Configurational assignment in parentheses. [b] Reaction conducted by Müller group. [c] Reaction conducted by Davies group. [d] Reaction conducted in 2,2-dimethylbutane.

Davies recognized that allylic C–H activation of alkenes via metal-catalyzed diazoacetate decomposition offered an approach to γ,δ-unsaturated esters containing two stereocenters, systems classically synthesized through a Claisen rearrangement.[231] Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of aryldiazoacetate **145d** with *trans*-3-hexene (**156a**) afforded the desired γ,δ-unsaturated ester products **157a** and **158a** with excellent enantioinduction (Table 33). No

Table 33. Allylic C–H Activation of Acyclic Systems



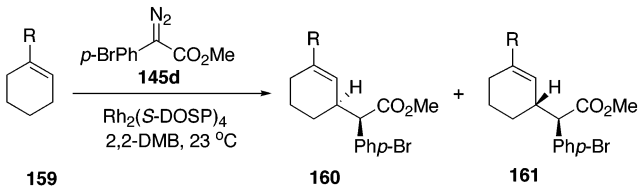
compd	R^1	R^2	yield, %	de, %	ee **157**, %	ee **158**, %
a	C_2H_5	H	56	12	92	80
b	CH_3	CH_3	67	50	86	66
c	C_6H_5	C_6H_5	33	70	96	30

cyclopropanation product was observed, as is typical for the reaction of aryldiazoacetates with trans-disubstituted or more highly substituted alkenes.[21,231] The poor level of diastereocontrol obtained was attributed to the inability of the chiral carbenoid to differentiate between the methylene substituents at the allylic site. An appreciable increase in diastereoselectivity was observed for trisubstituted olefins **156b** and **156c**, owing to the considerable size differentiation between the two methylene substituents.[44,231] Despite the fact that the olefin **156b** has three allylic sites, C–H activation occurs largely at the methylene

position to give **157b** and **158b**. Only a trace (4%) of C−H insertion into the allylic methyl group occurred, indicating the greater preference for C−H activation at secondary rather than primary positions.

Similar trends illustrating the highly regioselective reactions of donor/acceptor carbenoids have also been observed in cyclic substrates such as 1-substituted cyclohexenes (Table 34).[231] Despite the presence of

Table 34. C−H Activation of 1-Substituted Cyclohexene 159



159 160 161

compd	R	yield, %	ratio **160**:**161**	ee **160**, %	ee **161**, %
a	Me	53	17:83	94	98
b	Et[a]	46	25:75	90	94
c	^{i}Pr	65	36:64	90	93
d	^{t}Bu	46	62:38	91	81
e	Ph	65	23:77	90	95
f	Cl	58	65:35	96	91

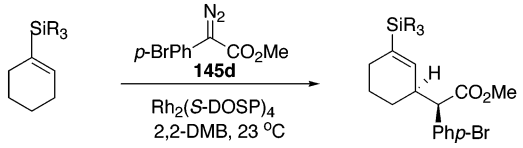
[a] Also isolated 2% yield of a product from C−H activation at the pendant ethyl group.

two or three allylic sites in each substrate **159**, only a single C−H insertion regioisomer (**160** + **161**) was produced owing to the effects of steric and electronic factors. From the table it is apparent that methylene sites are favored for intermolecular C−H activation, presumably because methylene C−H bonds are sufficiently weaker than methyl C−H bonds and are more accessible to the bulky rhodium−carbenoid complex than C−H bonds at methine sites.[44] 1-Ethylcyclohexene (**159b**) is therefore an intriguing substrate as it possesses three allylic methylene sites. However, the resultant C−H activation reaction is highly regioselective for the methylene C−H bond distal to the ethyl side chain, C−H insertion occurring only at the least crowded allylic methylene site.[231] The ethyl side chain is perhaps less sterically encumbered as it is less conformationally restrained, and so a trace amount (2% yield) of C−H activation at the pendant ethyl group was also observed. In each example in Table 34 excellent enantioselectivity was obtained, but the diastereoselectivity was moderate.

To maximize the diastereoselectivity for the allylic C−H activation of cyclohexenes, it was proposed that considerable size differentiation between the two allylic substituents would be required.[231] Vinylsilane groups are ideal substituents because not only does the silyl group induce the desired size differentiation but also it sterically protects the double bond from cyclopropanation. A steady improvement was seen with the trimethylsilyl derivative **162a** compared to cyclohexene, whereas the *tert*-butyldiphenyl silyl (TBDPS) derivative **162b** was exceptional. With **162b**, the C−H activation product **163b** was produced in 88% de and 95% ee (Table 35).

Hetaryldiazoacetates have recently been utilized in C−H activation reactions, demonstrating the

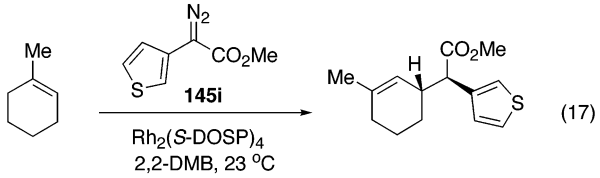
Table 35. Effect of Silylvinyl Groups on Stereoselectivity of C−H Activation



162 163

compd	SiR_3	yield, %	de, %	ee, %
a	TMS	48	40	88
b	TBDPS	64	88	95

variety of functionality that can be used in donor/acceptor-substituted carbenoid systems.[232] Although methyl thiophen-3-yldiazoacetate (**145i**) was unable to effect C−H activation in simple alkanes such as cyclohexane, the enhanced reactivity of the allylic methylene site in 1-methyl-1-cyclohexene **159a** was sufficient to trap the rhodium−carbenoid intermediate, affording γ,δ-unsaturated ester **164** in 40% yield, 50% de, and 94% ee (eq 17).[232]

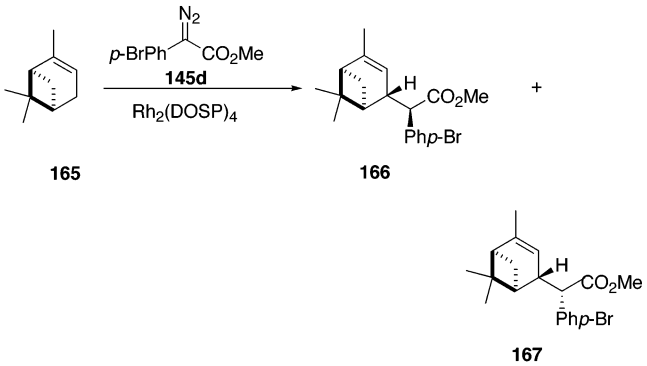


159a

164
40% yield,
50% de, 94% ee

Impressive levels of double-stereodifferentiation and kinetic resolution can also be obtained in allylic C−H activation reactions.[231] An elegant example involves carbenoid-induced C−H insertion of the terpenoid (α)-pinene (Table 36). The matched reaction of (+)-(α)-pinene [(+)-**165**] and aryldiazoacetate **145d** (2 equiv) with Rh_2(*S*-DOSP)$_4$ afforded C−H activation product **166** in 93% yield and 96% de. The

Table 36. Kinetic Resolution and Double-Stereoselection during the C−H Activation of (α)-Pinene



165 166 167

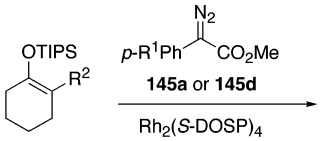
substrate **165**	catalyst	yield, %	ratio **166**:**167**	ee **166**, %
(+) (0.5 equiv)[a]	Rh_2(*S*-DOSP)$_4$	93	98:2	
(+) (0.5 equiv)[a]	Rh_2(*R*-DOSP)$_4$	62	24:76	
(±) (10 equiv)[b]	Rh_2(*S*-DOSP)$_4$	52	88:12	99

[a] Reaction conducted at 23 °C. [b] Reaction conducted at 0 °C.

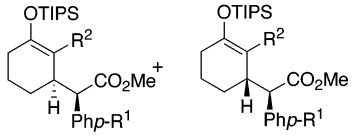
corresponding mismatched reaction of (+)-(α)-pinene [(+)-**165**] with Rh_2(*R*-DOSP)$_4$ gave a combined yield of 62% yield with 52% de in favor of **167**. Conducting the Rh_2(*S*-DOSP)$_4$ reaction with (±)-(α)-pinene [(±)-**165**] (10 equiv) resulted in the formation of **166** and **167** in an 88:12 ratio and a combined yield of 52%. The combined influence of kinetic resolution and enantiomer differentiation afforded the major diastereomer **166** in 99% ee.

Allylic C−H activation of silyl enol ethers generates silyl-protected 1,5-dicarbonyls, products typically derived from asymmetric Michael reactions.[228] The ability to effect efficient C−H activation adjacent to vinylic ethers is most remarkable as the highly electron rich double bond in the presence of most other carbenoid systems would readily undergo cyclopropanation.[21] With the stabilized carbenoids generated from aryldiazoacetates **145a** and **145d**, however, highly chemo- and regioselective C−H activation reactions of TIPS enol ether **130a** (R^2 = H) were accomplished, even at temperatures as low as −30 °C. In each case a single regioisomer was formed as a mixture of diastereomers (**168** and **169**) in 86−90% yield and with up to 96% ee (Table 37, entries 1 and

Table 37. Allylic C−H Activation of Cyclic Silyl Enol Ethers



130



168 **169**

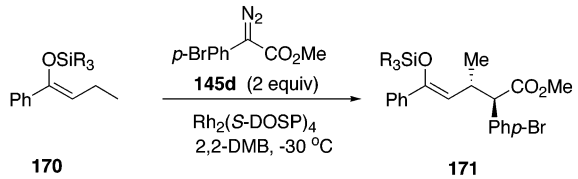
product	R^1	R^2	yield, %	ratio **168**:**169**	ee **168**, %	ee **169**, %
a[a]	H	H	90	70:30	96	86
b[a]	Br	H	86	65:35	94	84
c[b]	Br	Me	81	81:19	89	88

[a] Reaction conducted at −30 °C. [b] Reaction conducted at 0 °C.

2).[228] A vast improvement in the diastereoselectivity was observed when the tetrasubstituted TIPS enol ether **130c** (R^2 = Me) was exposed to the metal−carbenoid derived from aryldiazoacetate **145d** (entry 3).[228] The methyl substituent was of sufficient size to aid differentiation between the enantiotopic C−H bonds at the allylic methylene position in **130c** (R^2 = Me). Despite the increase in bulk adjacent to the site of C−H insertion, the presence of the methyl group did not upset the site selectivity of the reaction, and only a very slight loss in yield and asymmetric induction occurred.

The Rh_2(*S*-DOSP)$_4$-catalyzed C−H activations of the acyclic silyl enol ethers **170** are very interesting reactions because in addition to the high asymmetric induction (71−84% ee) the products **171** are formed with excellent diastereocontrol (>90% de, Table 38).[228] The most likely factor that causes this high

Table 38. Asymmetric C−H Activation of Acyclic Silyl Enol Ethers



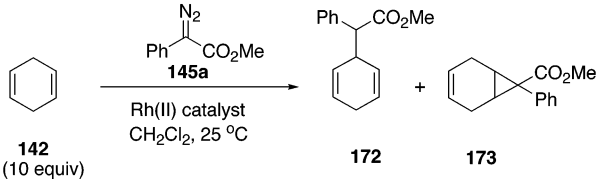
170 **171**

compd	SiR_3	yield, %	de, %	ee, %
a	TIPS	66	>90	71
b	TBDPS	65	>90	84

diastereoselectivity is the large difference in the size of the methylene substituents [i.e., C=C(OSiR_3)Ph vs Me]. The highest yields in these reactions were obtained when the trapping agent was the limiting agent, which is rarely the case in the reactions of the other classes of carbenoids.[17]

When two double bonds exist in a 1,4-relationship, the presence of the proximal olefin is known to further enhance the allylic position toward C−H activation.[225,233] The reaction of methyl phenyldiazoacetate (**145a**) with 1,4-cyclohexadiene (**142**) displayed remarkable selectivity for C−H activation to form **172** with a range of chiral rhodium(II) catalysts (Table 39). Indeed, none of the corresponding cyclo-

Table 39. C−H Activation of 1,4-Cyclohexadiene



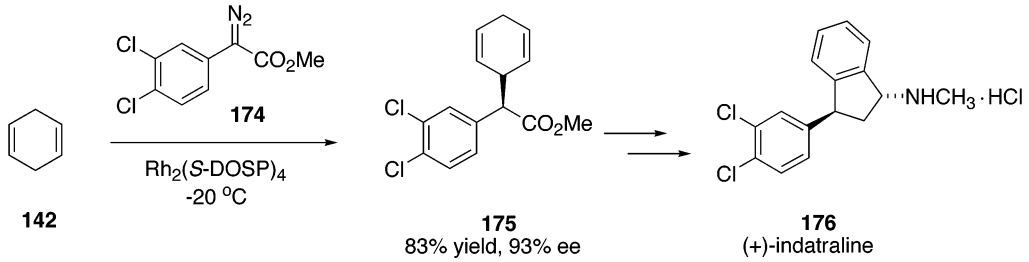
142 (10 equiv) **172** **173**

entry	catalyst	yield **172**, %	ratio **172**:**173**	ee **172**, %[a]
1[b]	Rh_2(*S*-DOSP)$_4$	98	>98:2	65 (*R*)
2[b,c]	Rh_2(*S*-DOSP)$_4$	50	>98:2	71 (*R*)
3[b,d]	Rh_2(*S*-DOSP)$_4$	37	>98:2	72 (*R*)
4[e,f]	Rh_2(*S*-DOSP)$_4$	80[g]	>98:2	91 (*R*)
5[b]	Rh_2(*S*-TBSP)$_4$	98	>98:2	74 (*R*)
6[b,d]	Rh_2(*S*-TBSP)$_4$	86	>98:2	33 (*R*)
7[b]	Rh_2(*S*-MEPY)$_4$	98	>98:2	4
8[b]	Rh_2(*S*-PTPA)$_4$	98	>98:2	40 (*S*)

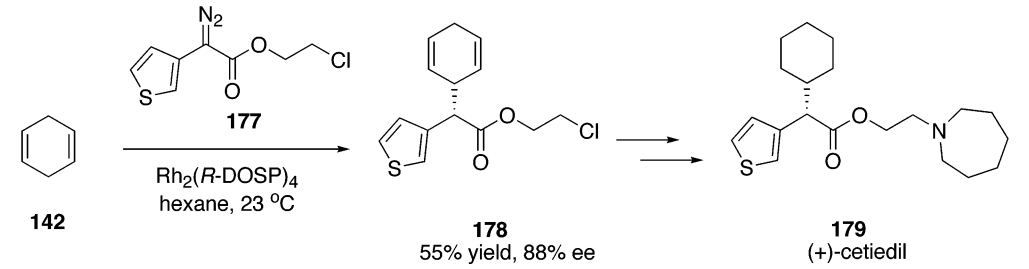
[a] Configurational assignment in parentheses. [b] Reaction conducted by Müller group. [c] Reaction conducted in pentane. [d] Reaction conducted in trifluorotoluene. [e] Reaction conducted in hexane at −50 °C. [f] Reaction conducted by Davies group. [g] Yield of C−H activation product following reduction of **172**.

propane product **173** was apparent in the crude reaction mixture. This result is in sharp contrast to the corresponding reactions with acceptor- or acceptor/acceptor-substituted carbenoids, where the cyclopropanation product was a significant component of the reaction mixture (for example, eq 16).[225,233] The tetraprolinate catalyst Rh_2(*S*-DOSP)$_4$ is by far the best catalyst for this reaction, achieving the formation of **172** in 91% ee when the reaction was conducted in hexane at −50 °C.[233] Doyle's carboxamide

Scheme 6



Scheme 7

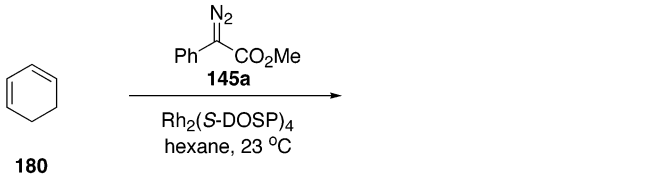


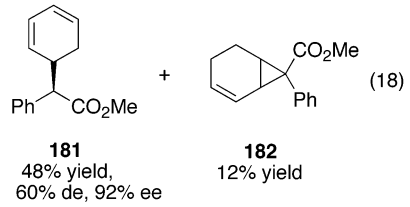
catalyst, Rh_2(*S*-MEPY)$_4$, gave only a 4% ee, whereas Hashimoto's Rh_2(*S*-PTPA)$_4$ gave 40% ee.[225]

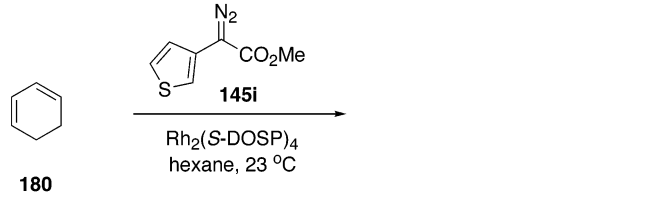
A range of aryldiazoacetates have been successfully used in the Rh_2(*S*-DOSP)$_4$-catalyzed reaction, with 1,4-cyclohexadiene affording activation products in 64−84% yield with 92−95% ee.[233] Davies has exploited this C−H activation to efficiently construct a number of pharmaceutically relevant targets. The potent monoamine re-uptake inhibitor (+)-indatraline (**176**) was readily constructed, the key transformation being the Rh_2(*S*-DOSP)$_4$-catalyzed allylic C−H activation of 1,4-cyclohexadiene (**142**) by the rhodium−carbenoid derived from 3,4-dichlorophenyldiazoacetate **174** (Scheme 6).[234] The C−H activation product **175** was obtained in 83% yield and 93% ee when the reaction was conducted at −20 °C.

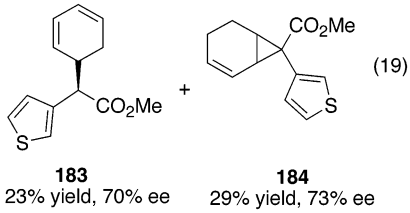
The synthetic utility of the hetaryldiazoacetate, methyl thiophen-3-yldiazoacetate **177**, in C−H activation chemistry was demonstrated in the enantioselective synthesis of the antiepileptic compound (+)-cetiedil (**179**, Scheme 7).[232] The reaction of **177** with 1,4-cyclohexadiene followed by reduction of the resultant diene unit enabled rapid access to the cetiedil core. The key C−H activation step, catalyzed by Rh_2(*R*-DOSP)$_4$, afforded γ,δ-unsaturated ester **178** in 55% yield and 88% ee. The ability to successfully effect the C−H activation reaction in the presence of the electrophilic alkyl chloride and nucleophilic thiophene ring illustrates the compatibility of the chemistry with various functional groups.

The reaction of methyl phenyldiazoacetate (**145a**) with the related 1,3-cyclohexadiene system **180** was found to be less selective than 1,4-cyclohexadiene, affording a 4:1 mixture of C−H activation product **181** (48% yield, 60% de, 92% ee) to cyclopropanation product **182** (eq 18).[233] A turnaround in chemoselectivity was observed for the reaction with methyl thiophen-3-yldiazoacetate (**145i**) in which formation of the cyclopropane product **184** was favored by a ratio of 1.3:1 over C−H activation (eq 19).[232] 1,3-Cycloheptadiene proved to be an even less favorable substrate for allylic C−H activation, predominantly





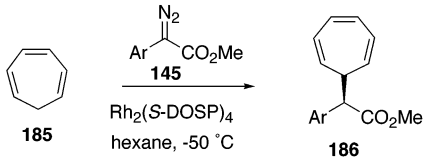




forming the cyclopropanation product in 57% yield, with less than 5% of the desired C−H activation product being observed.[227]

1,3,5-Cycloheptatriene (**185**) also underwent highly site selective allylic C−H activation to form **186** with a wide variety of aryldiazoacetates in 53−64% yield and 91−95% ee (Table 40).[227] In this system, no cyclopropanation was observed even though this is the dominant reaction with ethyl diazoacetate.[227] The strong preference displayed by the donor/acceptor-substituted carbenoids toward allylic C−H activation

Table 40. C−H Activation of 1,3,5-Cycloheptatriene

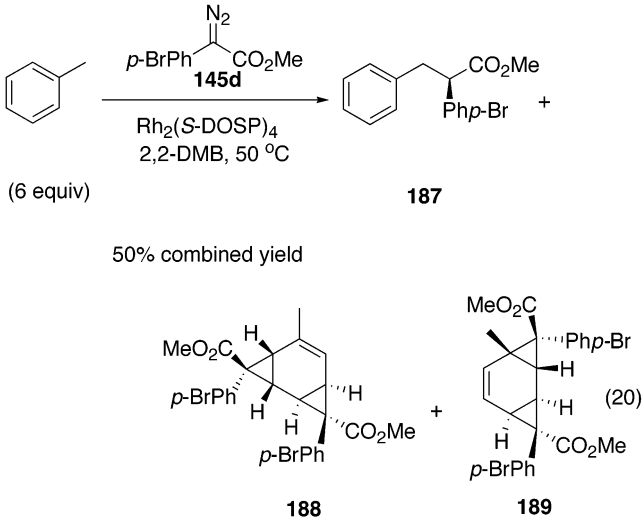


product	Ar	yield, %	ee,[a] %
a	C_6H_5	55	95
b	*p*-ClC_6H_4	64	95
c	*p*-MeC_6H_4	60	94
d	2-naphthyl	53	91

[a] Absolute configuration determined as (*R*).

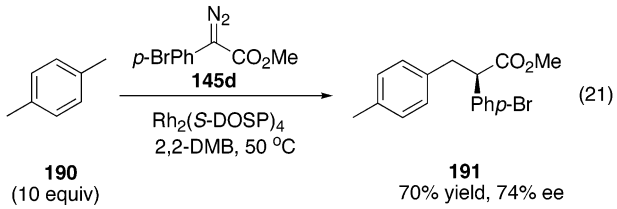
in 1,4-cyclohexadiene and 1,3,5-cycloheptatriene and the distinct lack of vigor for the C−H insertion pathway in 1,3-cyclohexadiene and 1,3-cycloheptadiene are most intriguing. It would appear that a simple allylic system is not sufficient to fully override the competing cyclopropanation pathway of cis double bonds. Only doubly allylic methylene sites are sufficiently activated to establish C−H activation as a more attractive pathway. Positive charge buildup on the carbon is considered to occur during the C−H activation process and is more pronounced in the reactions of the donor/acceptor-substituted carbenoids than other carbenoids because they are more stabilized and would react through a later transition state.[44,45,135] Cycloheptatriene may be an exceptional substrate for C−H activation as positive charge buildup in this reaction would have favorable aromatic stabilization.[227]

6.3.a.iii. Benzylic C−H Activation. Until quite recently it has generally been accepted for both inter- and intramolecular processes that insertion into primary C−H bonds is not very favorable.[17,44] However, when the Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of *p*-bromophenyldiazoacetate **145d** was conducted in toluene, a 14% yield of **187**, the product arising from insertion into the methyl position, was obtained (eq 20).[235] The major products were the regioisomers **188** and **189** derived from double cyclopropanation of the aromatic ring.



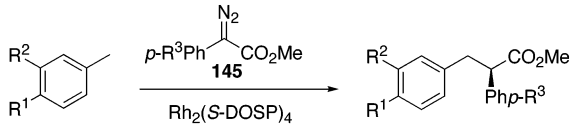
187 : (**188+189**)= 28:72

The bis-cyclopropanation pathway could be avoided by protecting the aromatic ring with a para-substituent to sterically encumber the benzene ring.[236] Thus, treatment of *p*-xylene (**190**) with aryldiazoacetate **145d** under the standard reaction conditions afforded C−H activation product **191** in 70% yield and 74% ee (eq 21).



Successful C−H activation of primary benzylic positions has been accomplished on a range of substrates to form 2,3-diarylpropanoates **193** (Table 41).[236] A notable trend is the higher yields and

Table 41. C−H Activation at Primary Benzylic Sites



product	R^1	R^2	R^3	temp, °C	yield, %	ee, %
a	OMe	H	Br	50	71	74
a	OMe	H	Br	0	69	83
b	OMe	H	H	50	67	71
b	OMe	H	H	0	14[a]	
c	OMe	H	OMe	50	35	67
d	OTBS	OMe	Br	50	80	77
e	OTBS	OMe	H	50	80	75
f	OTBS	OMe	OMe	50	30	67

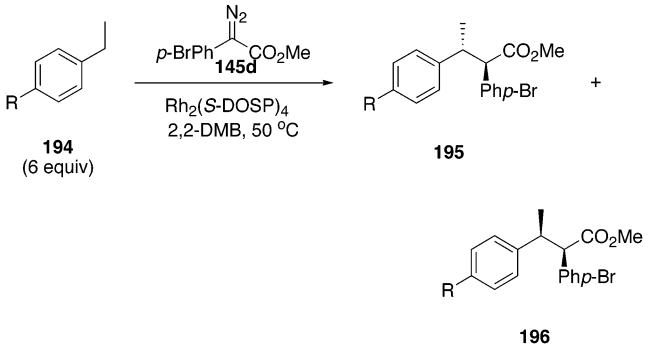
[a] ^{1}H NMR yield of crude reaction mixture with internal standard.

enantioselectivities obtained for aryldiazoacetates possessing electron-withdrawing groups than those possessing electron-donating groups. It appears that those carbenoids which possess slightly more electrophilic character tend to undergo more effective C−H activations. As methyl C−H bonds are stronger, less nucleophilic, and therefore less activated than methine or methylene C−H bonds, it stands to reason that only sufficiently electrophilic carbenoids can achieve effective insertion into a benzylic methyl C−H bond. In addition, it is notable that the more electron-rich substrates appear to undergo C−H activation with greater ease (compare entries 1, 3, and 5 with entries 6−8). It is likely that electron donation from the highly electron-rich arene ring helps to stabilize the charge buildup at the benzylic position during the C−H activation process.[236]

C−H activation at a secondary benzylic site is favored over a primary benzylic site.[235] Benzylic C−H activation was readily accomplished on ethylbenzene (**194**) with only a trace (<10%) of bis-cyclopropanation occurring. Studies conducted on a range of ethylbenzene derivatives revealed that the presence of an electron-donating para-substitutent on the substrate gave enhanced activation at the benzylic

site, resulting in higher yields for the C−H activation products **195** and **196** (Table 42). Interestingly, the

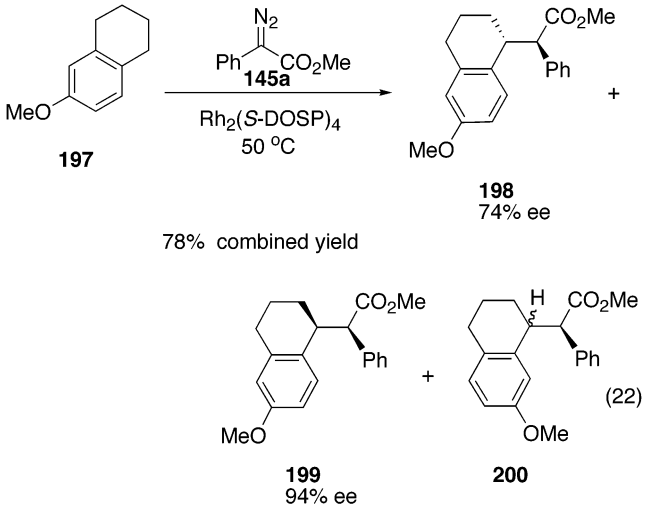
Table 42. C−H Activation at Secondary Benzylic Sites



compd	R	yield **195** + **196**, %	ratio **195**:**196**	ee **195**, %	ee **196**, %
a	MeO	86	68:32	89	76
b	Et	71	75:25	89	70
c	Me	64	82:18	89	74
d	H	49	84:16	86	
e	Br	38	73:27	88	58
f	OAc	77	78:22	86	53
g	$MeCO_2$	56	80:20	83	58

electronic nature of the para-substituent had little influence on the level of asymmetric induction. The diastereoselectivity was modest, which is a common feature of intermolecular C−H activation at secondary benzylic positions.

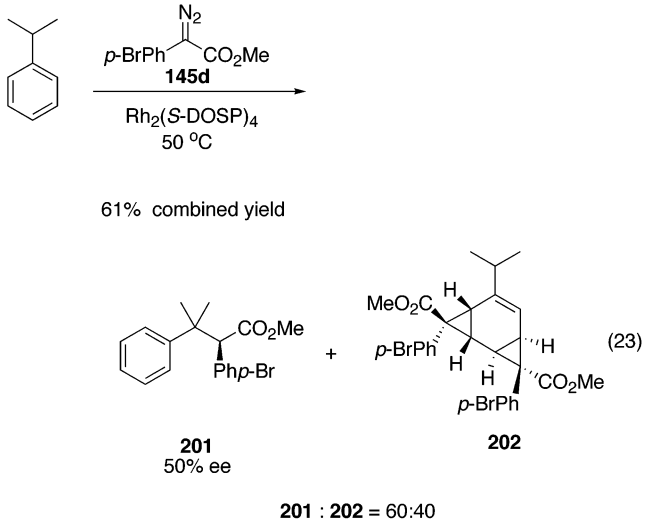
The reaction can also be conducted on bicyclic systems. A noteworthy example that further demonstrates the influence of an electron-donating para-substituent is the reaction of phenyldiazoacetate **145a** with tetrahydronaphthalene **197** (eq 22).[235] The



198:**199**:**200** = 19 : 79 : 2

reaction proved to be highly regioselective for the benzylic position para to the methoxy substituent to form the diastereomeric mixture **198** and **199**. Only a trace (2%) of insertion occurred at the less activated benzylic position meta to the methoxy group to form **200**.

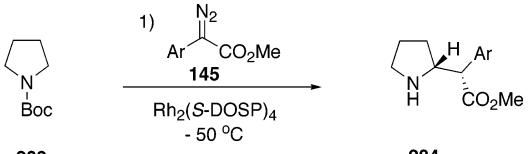
Benzylic methine C−H activation occurs in lower yield and with lower enantiocontrol than witnessed in the ethylbenzene series. The reaction of aryldiazoacetate **145d** with isopropylbenzene gave a 60:40 mixture of the C−H activation product **201** and the bis-cyclopropane **202** (eq 23).[235] The low yield of



201 was attributed to the tertiary site being too sterically encumbered to allow for effective C−H insertion, thus enabling competing double-cyclopropanation to occur. Competition studies revealed that C−H activation at ethylbenzene was 20 times more favorable than C−H activation into toluene and 5 times more favorable than C−H activation into isopropylbenzene, demonstrating that as a result of both steric and electronic effects, methylene sites are most favored for benzylic intermolecular C−H activation.[235]

6.3.a.iv. C−H Activation α to Nitrogen. Donor/acceptor-substituted carbenoids are also capable of very efficient intermolecular C−H activation α to nitrogen.[156,232,237−239] This reaction offers a novel strategic approach for the synthesis of chiral β-amino acids, products typically available via asymmetric Mannich reactions. Davies and co-workers have extensively studied a wide range of cyclic and acyclic amines.[232,237−239] Simple five-membered cyclic amines were found to be excellent substrates for C−H activation chemistry (Table 43).[232,237] The reaction displays remarkable diastereo- and enantioselectivity with a range of aryldiazoacetates. In all cases only

Table 43. C−H Activation of *N*-Boc-pyrrolidine

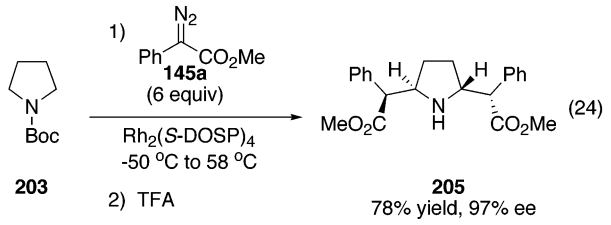


product	Ar	yield, %	de, %	ee, %
a	C_6H_5	72	92	94
b	p-ClC_6H_4	70	94	94
c	p-MeC_6H_4	67	93	93
d	2-naphthyl	49	93	93
e	3-thiophenyl[a]	64	91	67

[a] Reaction conducted at 23 °C.

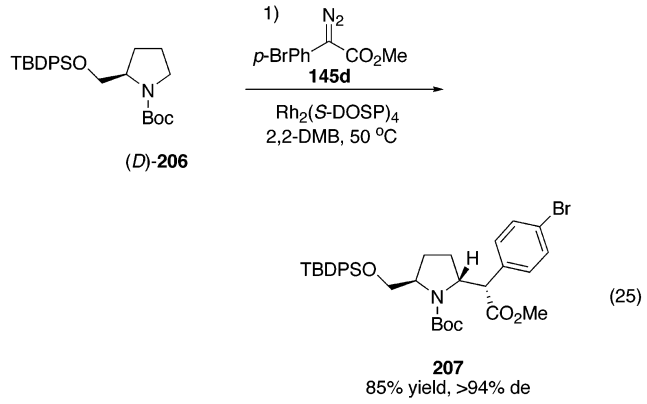
the product **204** arising from C−H activation adjacent to the nitrogen functionality was observed, without any occurrence of double insertion.

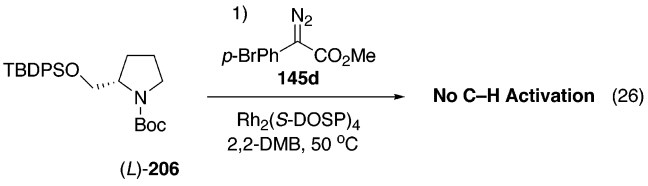
The ability to effect double C−H activation in a controlled manner was also investigated as it enabled the rapid synthesis of novel C_2 symmetric amines (eq 24). C−H activation at both methylene sites adjacent



to nitrogen was accomplished on *N*-Boc-pyrrolidine (**203**) by controlled addition of 6 equiv of phenyldiazoacetate **145a** to form **205** containing four stereocenters essentially as a single diastereomer.[237,239] The higher enantioselectivity obtained in the formation of **205** compared to that in the initial C−H activation step (97% ee cf. 94% ee) was as a result of double-diastereoselection occurring in the second step.

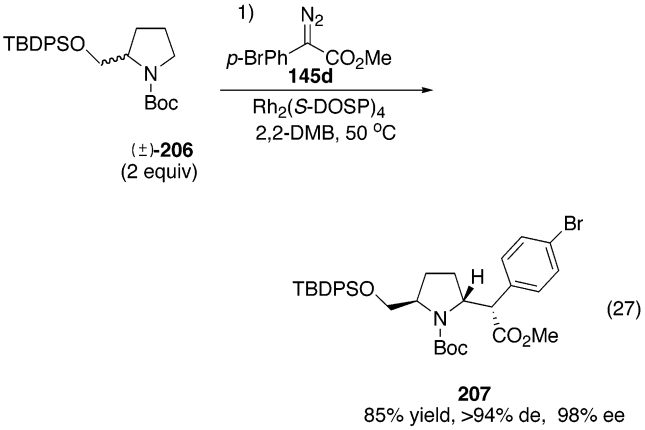
Expanding the study to 2-substituted *N*-Boc-pyrrolidines not only highlighted the remarkable site selectivity attainable using donor/acceptor-substituted carbenoids but also exploited impressive double-stereodifferentiation and kinetic resolution to control the formation of up to four stereocenters.[239] With siloxy ether (D)-**206** for instance, despite the neighboring heteroatom influence present on two methylene sites and a methine position, only the methylene group at the 5-position was accessible to the rhodium−carbenoid, presumably due to steric hindrance by the bulky siloxy substituent (eq 25). The Rh_2(*S*-DOSP)$_4$-



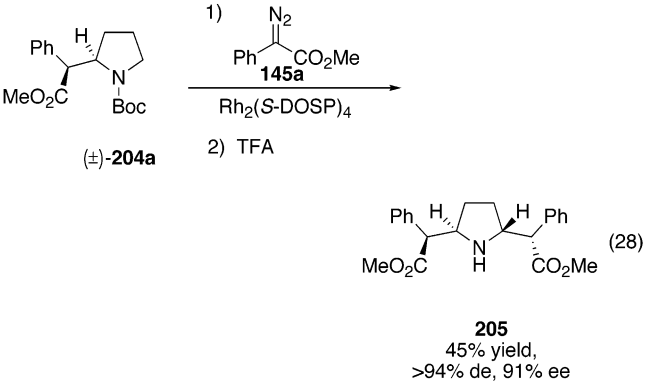


catalyzed reactions displayed impressive double-stereodifferentiation, with the (D)-**206** matched reaction affording the C−H activation product **207** as a single diastereomer in 85% yield. In sharp contrast, the mismatched reaction with (L)-**206** failed to give any C−H activation product (eq 26); carbene dimers and O−H insertion with adventitious water were the only observable products.[239]

On the basis of the above results it is clear that 2-substituted pyrrolidines are very promising substrates for kinetic resolution reactions.[239] Indeed, conducting the reaction on the racemate (±)-**206** gave **207** as a single diastereomer with 98% ee (eq 27) owing to a combination of inherent kinetic resolution and enantiomer product differentiation by the catalyst.

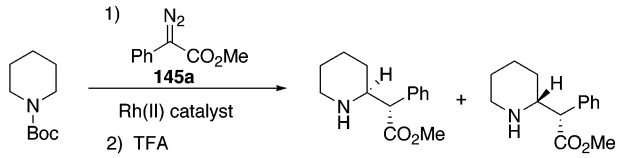


Impressive levels of stereoselectivity were obtained for a number of 2-substituted *N*-Boc-pyrrolidine substrates, establishing the generality of the approach.[239] A particularly worthy example involves the Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of methyl phenyldiazoacetate **145a** in the presence of racemic (±)-**204a**, which gave the C_2 symmetric **205** in 91% ee (eq 28).



Although C−H activation of five-membered cyclic amines is relatively facile, six-membered cyclic amines displayed significantly less reactivity toward C−H activation. Independently, Davies[237] and Winkler[156] recognized that asymmetric C−H activation of the carbenoid derived from methyl phenyldiazoacetate (**145a**) in the presence of *N*-Boc-piperidine (**208**) enabled very direct access to *threo*-methylphenidate (**209**) (Ritalin). The poor stereoselectivity observed with the piperidine system meant that a variety of catalysts were examined (Table 44). Excellent asymmetric induction was achieved with the bridged prolinate catalyst Rh_2(*S*-biDOSP)$_2$ (86% ee for **209**),[237] whereas the carboxamidate Rh_2(5*R*-MEPY)$_4$ showed

Table 44. Effect of Catalyst on the C−H Activation of *N*-Boc-piperidine



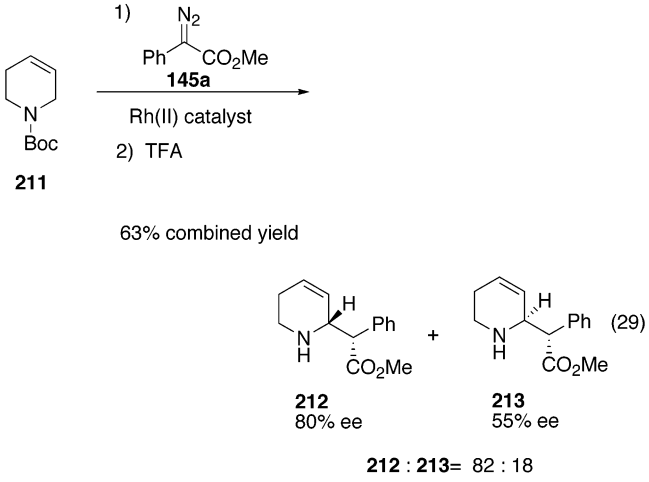
208 **209** **210**

entry	catalyst	temp, °C	yield, %	ratio **209**:**210**	ee **209**, %[a]	ee **210**, %[a]
1[b]	Rh_2(*S*-DOSP)$_4$	25	86	50:50	25 (2*S*)	79 (2*S*)
2[b]	Rh_2(*S*-biDOSP)$_2$	25	73	71:29	86 (2*R*)	65 (2*R*)
3[c]	Rh_2(*S*-TBSP)$_4$	50	—[d]	52:48	30	—[d]
4[c]	Rh_2(5*R*-MEPY)$_4$	50	44	97:3	69 (2*R*)	—[d]
5[c]	Rh_2(4*S*-IBAZ)$_4$	50	—[d]	92:8	26	—[d]
6[c]	Rh_2(4*S*-MPPIM)$_4$	90	—[d]	55:45	16	—[d]

[a] Configurational assignment in parentheses. [b] Reaction conducted by Davies group. [c] Reaction conducted by Winkler group. [d] Result not reported in the publication.

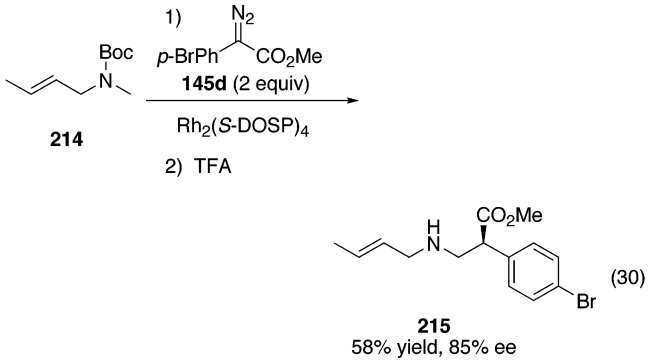
the greatest preference toward the desired threo isomer **209** (94% de).[156] It is likely that the ineffectiveness of the piperidine ring toward C−H activation was due to conformational constraints as the ring would be in a well-defined chair conformation.

A change in diastereoselectivity for the Rh_2(*S*-DOSP)$_4$-catalyzed reaction was obtained for the reaction of the aryldiazoacetate **145a** with *N*-Boc-tetrahydropyridine (**211**) (eq 29).[237] In this case the



erythro diastereomer **212** predominated following a trend opposite to that of *N*-Boc-piperidine but the same as that of *N*-Boc-pyrrolidine.[237]

Extending the chemistry to acyclic amines uncovered a remarkable and rather unexpected result.[238] Attempted Rh_2(*S*-DOSP)$_4$-catalyzed C−H activation at the allylic methylene position of Boc-protected *N*-methylcrotylamine (**214**) proved to be unsuccessful and instead gave **215** arising from C−H insertion at the *N*-methyl position (eq 30).[238] This result was found to be general for a range of *N*-Boc-methylamine systems with yields in the range of 46−67% and 31−96% ee following Boc-deprotection.[238] The high regioselectivity of the reaction is thought to occur as a result of the sterically encumbered rhodium−carbenoid being unable to access the activated allylic site and so instead attacking the less activated yet



more sterically accessible *N*-methyl position. The activating influence of the neighboring nitrogen is thought to assist with normally unfavorable methyl C−H insertion.[238]

The C−H activation α to nitrogen is an effective method for the synthesis of β^2-substituted amino acids and may have utility for the synthesis of β-peptides.[238] The potential of this approach has been illustrated by the synthesis of the dipeptide **218** (Scheme 8). A Rh_2(*S*-DOSP)$_4$-catalyzed C−H activation of the Cbz-protected *N*-benzyl-*N*-methylamine **216** gave the β-amino acid derivative **217** in 77% yield and 93% ee, which could then be appropriately deprotected and coupled to form **218**.[238]

6.3.a.v. C−H Activation α to Oxygen. In analogy to the nitrogen-containing systems, intermolecular C−H activation α to ether oxygens is also a very favorable process.[134,165,240,241] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of tetrahydrofuran with a range of aryldiazoacetates results in highly regioselective insertion at the 2-position of tetrahydrofuran, affording **219** with excellent enantioselectivity (95−98% ee), although with only moderate diastereoselectivity (Table 45).[134,165] The remarkable chemoselectivity displayed by donor/acceptor-substituted carbenoids is evident from the fact that although only 2 equiv of tetrahydrofuran was present in a vast excess of hexane as solvent, the insertion product **219** was still obtained in good yield (upto 74%).

The C−H activation reaction has been extended to acyclic systems in the form of siloxy ethers.[240,241] The presence of a silicon group on the ether oxygen delivers exceptional diastereocontrol, enabling selective formation of *syn*-β-hydroxy esters, products classically generated through the asymmetric aldol reaction. The reaction of a variety of di- and tetraalkoxysilanes **220** with methyl phenyldiazoacetate (**145a**) at ambient temperatures catalyzed by Rh_2(*R*-DOSP)$_4$ afforded the corresponding C−H activation products **221** with excellent enantiocontrol and with strong preference for the syn diastereomer in all cases (>90% de).[241] The selectivity of the reaction was most impressive, with insertion occurring exclusively at the oxygen-bound methylene carbon and with only a single insertion occurring on each substrate despite the presence of up to four oxygen-activated methylene sites. Entries 4 and 5 of Table 46 demonstrate that excellent stereoselectivity can still be achieved when alternative substituents are attached to the silicon center. These latter two results indicate the wide utility of the chemistry as novel oxygen-protecting groups are formed. Further studies revealed

Scheme 8

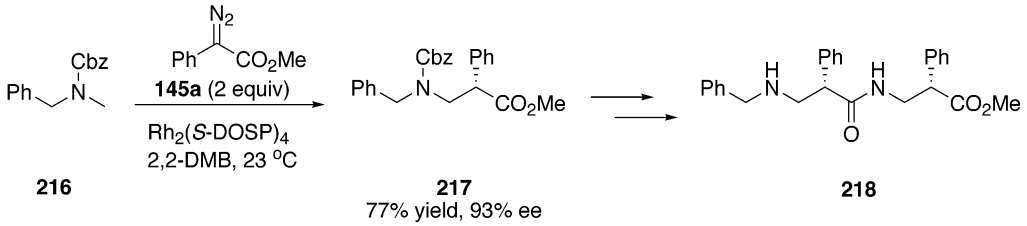
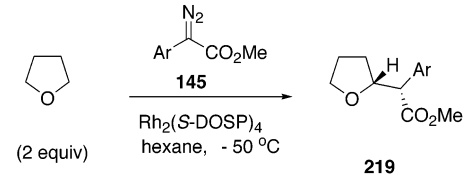
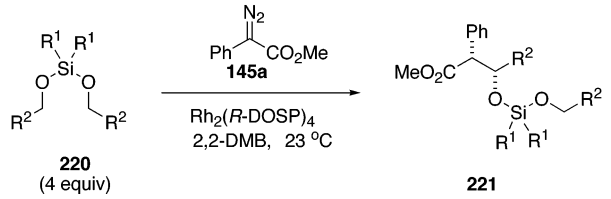


Table 45. C–H Activation of Tetrahydrofuran



product	Ar	yield, %	de, %	ee, %
a	C_6H_5	67	47	97
b	*p*-ClC_6H_4	74	41	98
c	*p*-MeC_6H_4	60	60	97
d	*p*-$MeOC_6H_4$	56	55	96
e	2-$C_{10}H_7$	62	23	95

Table 46. C–H Activation of Di- and Tetraalkoxysilanes



compd	R^1	R^2	yield, %	de, %	ee, %
a	OC_2H_5	CH_3	70	>90	95
b	$O^nC_3H_7$	C_2H_5	52	>90	92
c	$O^nC_4H_9$	$^nC_3H_7$	58	>90	93
d	CH_3	CH_3	51	>90	93
e	C_6H_5	CH_3	52	>90	94

that the chemistry worked most efficiently with methylene C–H activation rather than methyl or methine C–H insertion.[241] This highlights the general trend that occurs in Rh_2(DOSP)$_4$-catalyzed donor/acceptor-substituted carbenoid activation chemistry due to a compromise between steric and electronic effects.[44,45]

The spectacular chemoselectivity available through the pairing of a donor/acceptor-substituted diazocarbonyl with the Rh_2(DOSP)$_4$ complex has also been demonstrated in the reactions of allylic siloxyethers.[240] Monosubstituted double bonds are known to be very amenable to cyclopropanation with donor/acceptor carbenoids.[21] For instance, in the Rh_2(OOct)$_4$-catalyzed reaction of aryldiazoacetate **145b** with TBS-protected allyl silyl ether (**222a**) the cyclopropanation pathway was preferred over the C–H insertion reaction by a ratio of 2.5:1. However, in the corresponding Rh_2(DOSP)$_4$-catalyzed reaction shown in eq 31, the C–H activation pathway dominated, affording **223a** in an excellent 98% de.[240]

The highest yields and diastereoselectivity in the C–H activation reactions were obtained with trans-substituted allylic silyl ethers, which, due to the sterically encumbered rhodium prolinate/arylcarbenoid complex, were not susceptible to cyclopropanation.[164] The Rh_2(*R*-DOSP)$_4$-catalyzed decomposition of aryldiazoacetate **145b** with a range of *trans*-allylic silyl ethers **222** afforded the C–H activation products **223** with excellent diastereoselectivity for the syn product and in good yields and enantioselectivity (Table 47).[241]

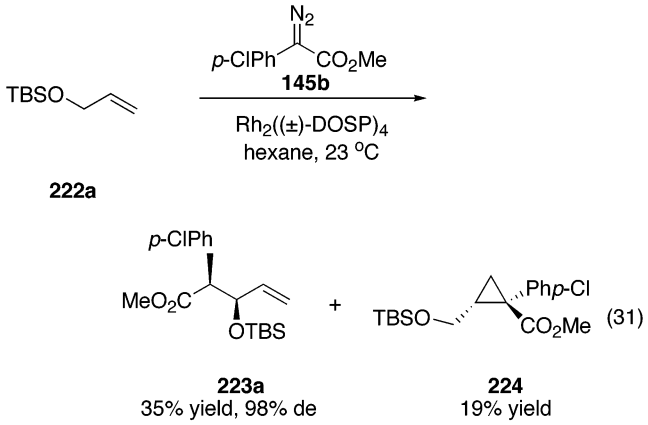
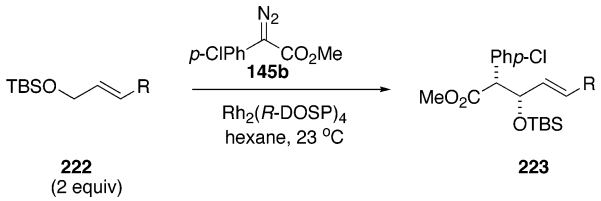


Table 47. C–H Activation of *trans*-Allylic Silyl Ethers



compd	R	yield, %	de, %	ee,[a] %
a	H	35	98	90
b	CH_3	70	96	80
c	$CH{=}CHCH_3$	71	98	74
d	C_6H_5	70	97	85

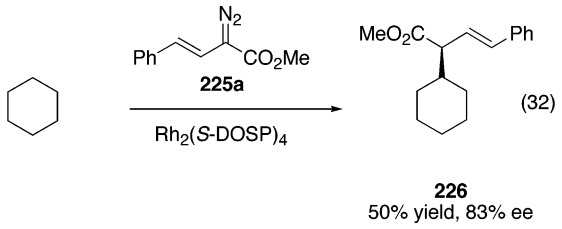
[a] Absolute configuration assigned as (2*R*,3*S*).

6.3.b. Carbenoids Derived from Vinyldiazoacetates

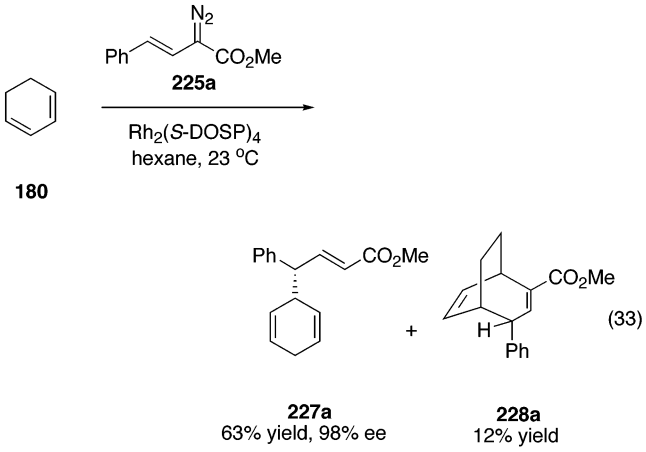
The ability to conduct efficient intermolecular C–H activation reactions with vinylcarbenoids illustrates the generality of the donor/acceptor-substituted carbenoid effect and adds to the diversity and widespread synthetic utility of the chemistry.[44,45] Studies into vinylcarbenoid structure have revealed that *cis*-vinyldiazoacetates and unsubstituted vinyldiazoacetates (along with their analogous ketone derivatives) are poor substrates for intermolecular C–H activation, at least with alkanes, favoring instead oligomerization pathways.[224] *trans*-Vinyldiazoacetates, however, are much better substrates and, when used

in conjunction with the tetraprolinate catalyst Rh_2(*S*-DOSP)$_4$, can effect highly efficient asymmetric C−H activation reactions.[44,45,134,227,233,236,241]

6.3.b.i. C−H Activation of Alkanes. The first example of a C−H activation reaction using vinyldiazoacetates involved an intermolecular insertion into cyclohexane of the carbenoid derived from the vinyldiazoacetate **225a** (eq 32).[134] In the Rh_2(*S*-DOSP)$_4$-catalyzed reaction the resulting insertion product **226** was formed in 50% yield and 83% ee, illustrating that high asymmetric induction can be achieved with donor/acceptor-substituted carbenoids derived from vinyldiazoacetates.

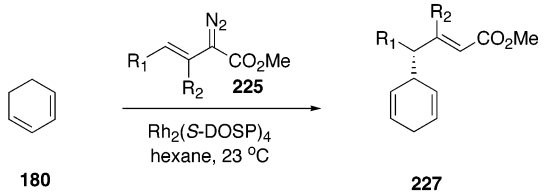


6.3.b.ii. Allylic C−H Activation. The Rh_2(*S*-DOSP)$_4$-mediated reactions of vinylcarbenoids with allylic substrates resulted in very unusual chemistry.[233] For instance, the reaction of 1,3-cyclohexadiene (**180**) with vinyldiazoacetate **225a** did not afford the expected C−H activation product. Instead, an unprecedented carbenoid reaction occurred to give the 1,4-cyclohexadiene **227a** (eq 33). A second product, **228a**, arising from the well-established tandem cyclopropanation/Cope rearrangement was also obtained in various amounts depending on catalyst selection.[132,242−246] Rh_2(*S*-DOSP)$_4$ was the best catalyst for limiting the cyclopropanation/Cope pathway, favoring **227a** over **228a** by a ratio of 5.3:1.0.[233]



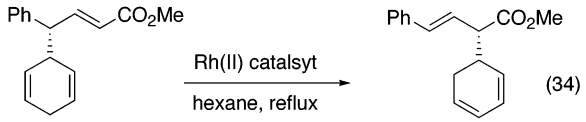
The reaction was compatible with a range of vinyldiazoacetates **225** (Table 48), although ortho-substituents on the aromatic ring of arylvinyldiazoacetates tended to reduce the chemo- and stereoselectivity of the reaction, giving preference to the cyclopropanation/Cope rearrangement pathway (entries 5 and 6).[233] In addition, dienyldiazoacetate **225g** and cyclic vinyldiazoacetate **225h** also afforded the 1,4-cyclohexadiene **227** in good yield and with excellent enantioinduction, indicating the breadth of the chemistry.[233]

Table 48. Reaction of Vinyldiazoacetates with 1,3-Cyclohexadiene



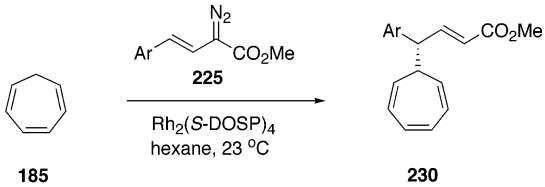
compd	R_1	R_2	yield, %	ee, %
a	C_6H_5	H	63	96
b	*p*-$MeOC_6H_4$	H	58	99
c	3,4-$Cl_2C_6H_3$	H	59	99
d	2-naphthyl	H	50	99
e	*o*-$MeOC_6H_4$	H	17	86
f	1-naphthyl	H	22	84
g	(*E*)-CH=CHC_6H_5	H	60	99
h	$-(CH_2)_4-$		73	97

The means by which 1,4-cyclohexadiene **227** was formed is most intriguing. Although the most obvious route would involve allylic C−H activation of 1,3-cyclohexadiene (**180**) followed by a Cope rearrangement, this was not the case.[233] Heating **227a** in refluxing hexane resulted in the reverse Cope rearrangement to the direct C−H activation product **229** (eq 34). Thus, the thermodynamically favored product is the one from direct allylic C−H activation of **180**, and so if formed under the reaction conditions, it would be unable to rearrange to **227a**. The mechanism of the reaction is thought to be a combined C−H insertion/Cope rearrangement rather than a two-step process, or, alternatively, the vinylcarbenoid may react as a 2π-system in a reaction analogous to an ene reaction.[233]



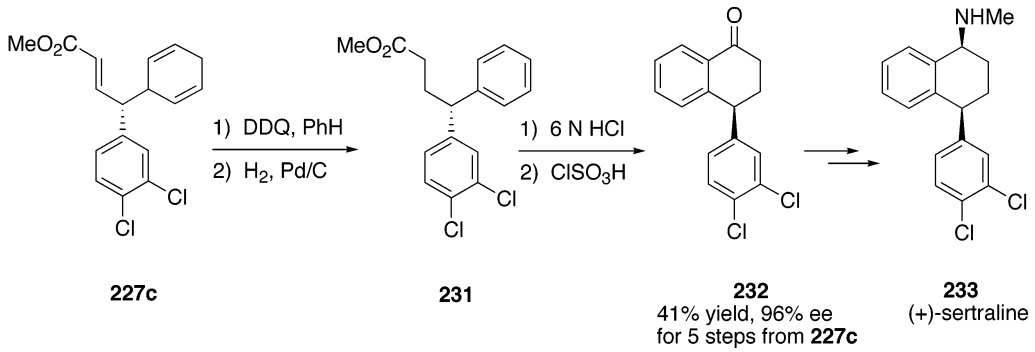
Interestingly, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl phenylvinyldiazoacetate (**225a**) with 1,3-cycloheptadiene gave <5% of C−H insertion products, favoring instead the tandem cyclopropanation/Cope rearrangement pathway.[227] However, with cycloheptatriene (**185**), only trace amounts (<5%) of cyclopropanation products were formed, the preferred reaction being the combined C−H insertion/Cope rearrangement to give the α,β-unsaturated ester **230** in 56−67% yield (Table 49).[227]

Table 49. Reaction of Vinyldiazoacetates with 1,3,5-Cycloheptatriene



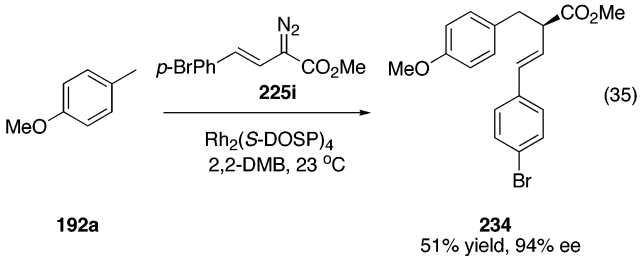
product	Ar	yield, %	ee, %
a	C_6H_5	56	99
b	*p*-BrC_6H_4	67	99

Scheme 9



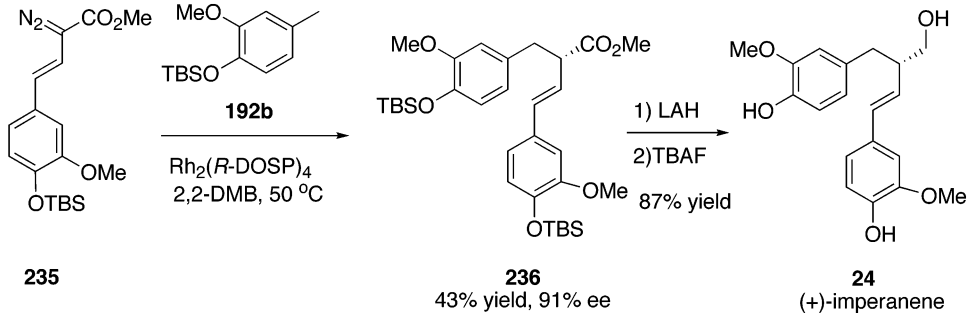
Davies and co-workers have also demonstrated the practical utility of this methodology by a short formal synthesis of the antidepressant (+)-sertraline (**233**, Scheme 9).[233] The combined C−H activation/Cope rearrangement product **227c** is formed in 99% ee, and through conventional steps it can be converted to the tetralone **232**, which has been previously converted to (+)-sertraline (**233**).

6.3.b.iii. Benzylic C−H Activation. To effect efficient C−H activation on primary C−H bonds requires substrates that harbor an activated methyl group while discouraging approaches to competitive sites.[17,235,238] *p*-Methoxytoluene (**192a**) is an excellent candidate as the *p*-methoxy unit electronically activates the benzylic position while blocking any approach to the benzene ring, thereby preventing cyclopropanation.[236] As with aryldiazoacetates, vinyldiazoacetates are capable of undergoing carbene-induced C−H insertion at primary benzylic sites.[236] The Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of *p*-bromophenylvinyldiazoacetate **225i** in the presence of *p*-methoxytoluene (**192a**) gave the C−H activation product **234** in 51% yield and 94% ee (eq 35).

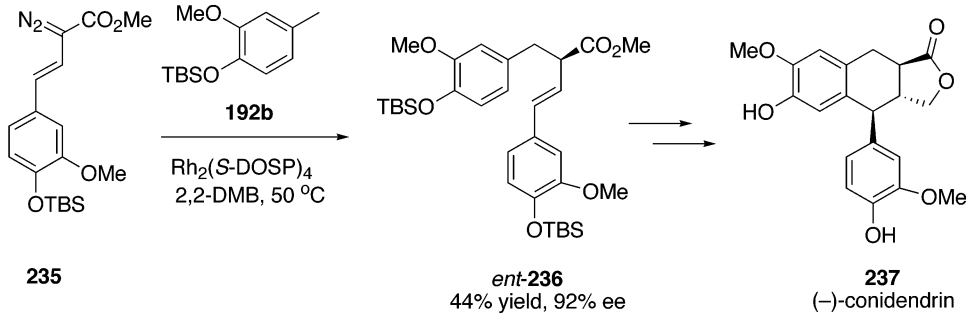


Benzylic C−H activation using vinylcarbenoids has been employed as the key transformation to generate a common intermediate in the synthesis of both (+)-imperanene (**24**) and (−)-α-conidendrin (**237**).[236] The total synthesis of (+)-imperanene was accomplished in a mere three steps commencing with the Rh_2(*R*-DOSP)$_4$-catalyzed decomposition of arylvinyldiazoacetate **235** in the presence of **192b** at 50 °C to generate **236** in 43% yield and 91% ee (Scheme 10). Despite the high electron density present in arene **192b**, the steric interference of the OTBS and OMe substituents totally inhibited cyclopropanation of the aryl

Scheme 10



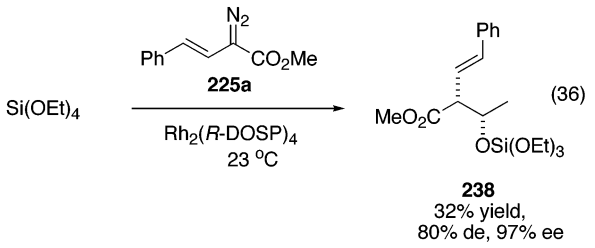
Scheme 11



ring. Reduction of the ester moiety of **236** and cleavage of the silyl protecting group afforded (+)-imperanene (**24**). This approach compliments the previous synthesis of (+)-imperanene (**24**), which involved an intramolecular C−H activation as the key step.[191]

The total synthesis of (−)-α-conidendrin (**237**) was achieved in only four steps via C−H activation followed by a tandem Prins reaction/electrophilic substitution (Scheme 11).[236] The same C−H activation was the key asymmetric step, but using the opposite enantiomeric form of the chiral catalyst, Rh_2(*S*-DOSP)$_4$, to give *ent*-**236** in comparable yield and enantioinduction (44% yield, 92% ee). The tandem Prins reaction/electrophilic substitution cascade set up the remaining stereocenters, enabling a very rapid access to **237**.

6.3.b.iv. C−H Activation α to Oxygen. The C−H activation α to oxygen with vinylcarbenoids has not been extensively explored. The only published report to date is the reaction of phenylvinyldiazoacetate **225a** with tetraethoxysilane (eq 36).[241] The reported



(36)

yield of the product **238** was low (32%), but the enantioselectivity was spectacular (97% ee). Further studies are needed to determine how general the scope of this type of chemistry is as the resulting products could be readily modified to more elaborate structures.

It would appear that a critical requirement for successful intermolecular C−H activation reactions is the use of donor/acceptor-substituted carbenoids.[44,45] Only donor/acceptor carbenoids are sufficiently stabilized to display the chemo- and regioselectivity required to effect synthetically useful reactions. Although dependent on the nature of the substrate, the level of stereocontrol is also strongly influenced by the choice of chiral catalyst.[44,45] A number of chiral catalysts have been examined,[156,165,225,233,237,240] but Rh_2(*S*-DOSP)$_4$ is currently the only catalyst that has been shown to achieve efficient and selective intermolecular C−H activation in a broad array of reactions with aryl and vinyldiazoacetates.[44,45] It would seem that the presence of the prolinate ligand provides the correct level of electron withdrawal from the carbenoid to produce a sufficiently reactive yet stabilized carbenoid. The typically high levels of diastereoselectivity and exceptional levels of enantiocontrol witnessed in Rh_2(*S*-DOSP)$_4$-catalyzed reactions of donor/acceptor-substituted carbenoids are believed to be due to the highly demanding approach that is required for the substrate to take to reach the carbenoid center. Indeed, studies by Pirrung suggested that Rh_2(*S*-DOSP)$_4$-catalyzed C−H insertion reactions occur at half the rate of the achiral-catalyzed [namely, Rh_2(Piv)$_4$ or Rh_2(OOct)$_4$] process as a result of ligand-decelerated catalysis, due to steric encumbrance of one of the enantiotopic pathways.[129] A more demanding approach would be consistent with a reaction that proceeds through a later transition state and is therefore more selective.[129]

The use of donor/acceptor-substituted carbenoid systems in conjunction with the dirhodium tetraprolinate catalyst Rh_2(*S*-DOSP)$_4$ has enabled intermolecular asymmetric C−H activation to become a highly practical process.[44,45] Several new strategic approaches to some of the classic reactions of organic synthesis have been devised through C−H activation; these include the Claisen rearrangement,[231,232] the Michael reaction,[228] the Mannich reaction,[156,232,237−239] and the aldol reaction.[240,241] Figure 7 illustrates the widespread applicability that C−H activation chemistry offers in organic synthesis.

As illustrated throughout this section, donor/acceptor carbenoid-induced C−H activation chemistry displays remarkable chemo- and regioselectivity. Competition experiments conducted by Davies and co-workers provide an idea of the relative reactivity between various substrates (Figure 8).[165] The studies reveal that the site selectivity relies on the influence of both steric and electronic factors. The degree of reactivity generally follows the sequence secondary ≈ tertiary ≫ primary C−H bonds. With C−H insertion chemistry the most reactive C−H bonds are those that can stabilize a buildup of positive charge during the transition state. Thus, insertion into the more nucleophilic tertiary C−H bond is preferred electronically, and so insertion into primary bonds is least favorable. This is in direct contradiction to C−H activation via oxidative addition in which the primary C−H bond undergoes oxidative addition most easily.[3] As steric factors can become severe for insertion into a tertiary C−H bond, secondary sites tend to be preferred over tertiary sites. In addition, a small ester substituent on the diazocarbonyl and the use of a hydrocarbon solvent are critical for high levels of asymmetric induction in the Rh_2(DOSP)$_4$-catalyzed process.[165] In general, selective C−H activation at methylene sites has been the most widely observed transformation.[44,45] Insertion into primary sites is rarely observed unless the system is strongly activated electronically.[235, 236, 238]

7. Models for Asymmetric Induction

C−H activation via diazocarbonyl reagents is generally assumed to involve a metallocarbenoid intermediate and proceed through a catalytic cycle consisting of metal-catalyzed extrusion of nitrogen from the diazo compound, followed by simultaneous C−H activation and C−C bond formation.[17,18,20,46,52,247] The rate-determining step is believed to be nitrogen extrusion, although with less reactive substrates insertion into the C−H bond may be rate-limiting.[129,135,248,249] At present there exist several theories on the reaction mechanism[58,100,107,112,129,135,165,208−210,248,250,251] ranging from Taber's four-centered hypothesis[107,250] and Doyle's

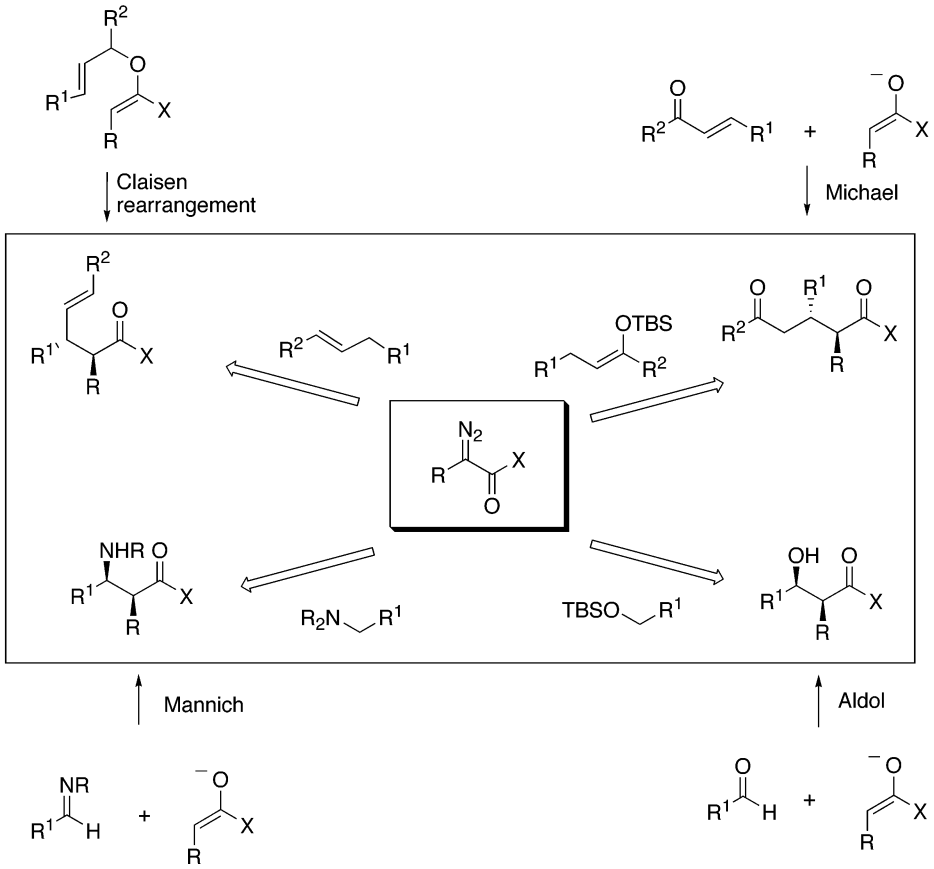


Figure 7. C−H activation as a surrogate of classic reactions of organic synthesis.

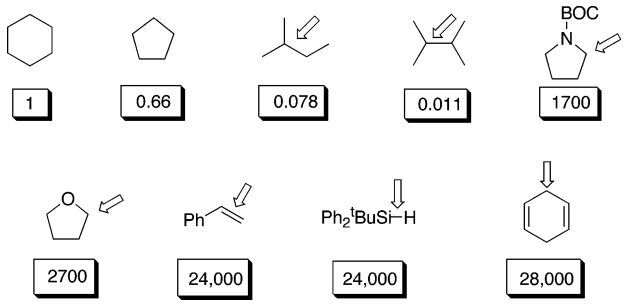


Figure 8. Relative reactivity of methyl phenyldiazoacetate (**145a**) toward different substrates in the presence of Rh_2(*S*-DOSP)$_4$.

three-centered concerted bond formation process[58] through Davies's concerted yet nonsynchronous process[165] to Pirrung's stepwise approach.[100]

Nakamura recently suggested, on the basis of high-level computational modeling studies of the reaction of rhodium−carbenoids with methane, that the carbonyl group and the Rh−C bond were orthogonal and therefore not in conjugation with one another.[135] If this were the case, then the two faces of the carbenoid complex would not be equivalent, a feature that has not been addressed by any of the mechanistic models presented to date. Furthermore, the C−H bond undergoing insertion is proposed to be in the same plane as the rhodium−carbene carbon bond.

Our aim here is not a detailed discussion of the reaction mechanism, which is obviously still not fully understood, but to introduce simple predictive models for the observed relative and absolute stereochemistry from C−H activation processes. These models will also explain why certain chiral catalysts are highly effective with certain diazocarbonyl species but give poor selectivity with others. These are oversimplified models designed to assist in the prediction of stereochemistry. A more in-depth and detailed analysis of the catalytic systems and transition state structures presented by Doyle,[17,39] Hashimoto,[40,222] and Davies[43,165] can be found in the relevant texts.

From the studies to date into various diazocarbonyl systems it is apparent that dirhodium(II) catalysts provide the highest levels of asymmetric induction but also that no one class of chiral rhodium(II) complex is effective for all C−H activation reactions. The sterically most encumbered of the catalysts are the rhodium amide catalysts [for example, Rh_2(5*S*-MEPY)$_4$], and these are exceptional catalysts for asymmetric induction in intramolecular C−H activation of acceptor-substituted carbenoids derived from diazoacetates and diazoacetamides.[17] This is the least functionalized and one of the most reactive classes of carbenoids, and so a sterically demanding catalyst is required to orientate the carbenoid to ensure high regio- and stereoselectivity.[17] Hashimoto's dirhodium tetracarboxylate catalysts possessing *N*-phthalimide amino acid ligands, such as Rh_2(*S*-PTPA)$_4$, are excellent for asymmetric induction in the intramolecular C−H activation of acceptor/acceptor-substituted carbenoids[40,172−174] and on occasion with donor/acceptor-substituted carbenoids.[171] The ortho-metalated arylphosphine dirhodium complexes **19** are reasonably effective for intramolecular C−H activation of acceptor-substituted carbenoids derived from diazo-

ketones.[35] Finally, the dirhodium tetracarboxylates are exceptional at intermolecular C−H activation of donor/acceptor-substituted carbenoids[44,45] [e.g., Rh_2-(*S*-DOSP)$_4$] and reasonably efficient in certain intramolecular C−H activation of donor/acceptor-substituted carbenoids[223] [e.g., Rh_2(*S*-biTISP)$_2$, Rh_2(*S*-DOSP)$_4$, and Rh_2(*S*-PTTL)$_4$] and carbenoids derived from α-methyl-α-diazoketones [e.g., Rh_2(*S*-BSP)$_4$].[130]

One of the most interesting features of all four classes of catalysts is that they behave as if they are of higher symmetry than the individual ligands. The central core of the dirhodium lantern structure has D_{4h} symmetry, and, depending on how the ligands orient themselves, the resulting complex may also have high symmetry.[30,51] In the case of the dirhodium carboxamidates, the ligands are arranged with the nitrogen of two amides bound to one rhodium and the nitrogen of the other two caboxamides binding to the other rhodium in an "up-up-down-down" manner, generating a complex of C_2 symmetry.[39] The arylphosphine complex also exists in a C_2 symmetric arrangement,[35] whereas Hashimoto's catalyst, which could have conformational mobility, does in fact exist, at least in the crystalline form, in a conformation that mimics a C_2 symmetric arrangement.[222] The dirhodium tetraprolinates have been proposed to have the sulfonyl groups arranged in an "up-down-up-down" arrangement, and if this were indeed the case the complex would exist in a D_2 symmetric arrangement.[43] The existence of all the most effective chiral dirhodium complexes in a C_2 symmetric arrangement or higher is very beneficial for asymmetric induction because this would mean the two faces of the catalysts are the same.[30,43]

Due to the challenges associated with the transition state models of these reactions, predictive models will be discussed only for the three types of C−H activation catalysts that result in >90% ee. On the basis of their structure, the catalyst systems can be viewed simply as the models A−C shown in Figure 9. In Doyle's catalysts,[39] two identical large blocking groups are present on adjacent quadrants, and so the model can be simplified to the structure in model A. In Rh_2(5*R*-MEPY)$_4$ for example, the "sidearms" of the blocking group would represent the methyl ester substituents. The overall effect makes two adjacent quadrants very crowded, whereas the other two are more accessible.[17] Hashimoto's catalyst (model B) would globally have similar features to Doyle's catalyst as it is also C_2 symmetric.[222] The blocking groups are not as pronounced because the complexes are dirhodium tetracarboxylates and the ligand influence is further removed from the carbenoid binding site.[17,43] In the case of the prolinate catalyst (model C) the chiral influence is very different due to the D_2 symmetric arrangement of these complexes.[43] The blocking groups represent the arylsulfonates, and they are arranged in opposite quadrants. In the case of the tetraprolinates, this is considered to be the preferred solution phase conformation of the ligands, whereas in the bridged prolinates the ligands are locked in this arrangement.[43]

Using these simple models as reasonable depictions of the gross ligand influence of these catalysts, a good

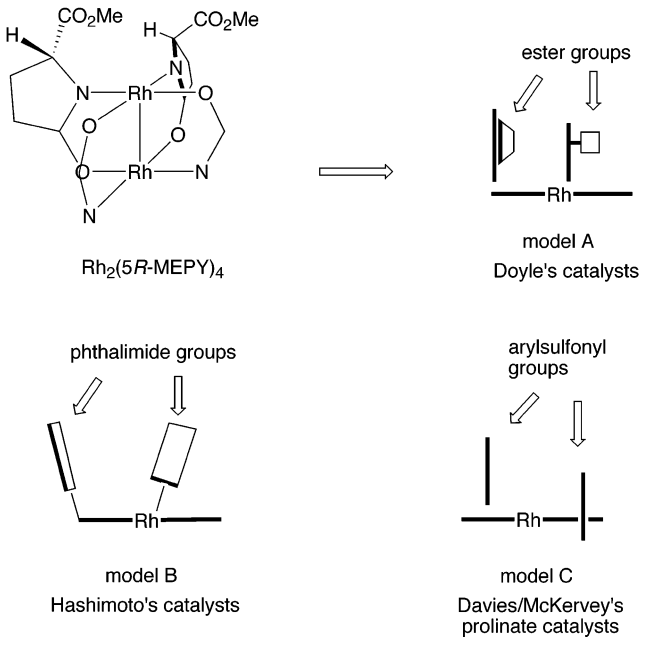


Figure 9. Simple models of the various dirhodium chiral catalysts.

predictive model for the asymmetric induction observed in each system is possible. With the C_2 symmetric complexes, the conformation of the carbenoid intermediate is assumed to follow certain requisites in line with the hypothesis proposed by Doyle[58] and Taber.[107] In the model systems, the C−H bond undergoing insertion is positioned parallel to the Rh−C bond and the carbonyl substituents adjacent to the carbene carbon lie anti to the face of the rhodium catalyst. The orientation of the carbenoid relative to the catalyst system is crucial to the observed asymmetric induction. Hashimoto's catalysts are especially effective for acceptor/acceptor-substituted carbenoids as the binding pocket is not so crowded and so disubstituted carbenoids can readily fit. The bulky phthaloyl groups are thought to control the carbenoid orientation and thus the asymmetric induction.[222] In this system, large differentiation in size between the two acceptor substituents is required to achieve high enantiocontrol.[213] In the case of the intramolecular C−H activation to form β-lactams, a bulky substituent on the amide nitrogen, such as a *tert*-butyl group, is needed.[174] To avoid any steric interactions between the *tert*-butyl group and the phthaloyl group on the left-hand side of model B, the carbenoid intermediate is forced to adopt the conformation illustrated in Figure 10.[174] C−H activation then occurs from the front face (away from the phthaloyl groups), between the Rh−C unit and the C−H^a bond as they lie in a parallel relationship. The R substituent points up and away from the catalyst face and the phthaloyl groups; hence, the insertion reaction is highly selective for the *trans*-β-lactam product **93**.[174]

In the case of the acceptor/acceptor-substituted carbenoids derived from α-diazo-β-ketoesters a very large ester group is preferable for high asymmetric induction[213] as this would ensure that the ester group adopts the less crowded position (Figure 11). The

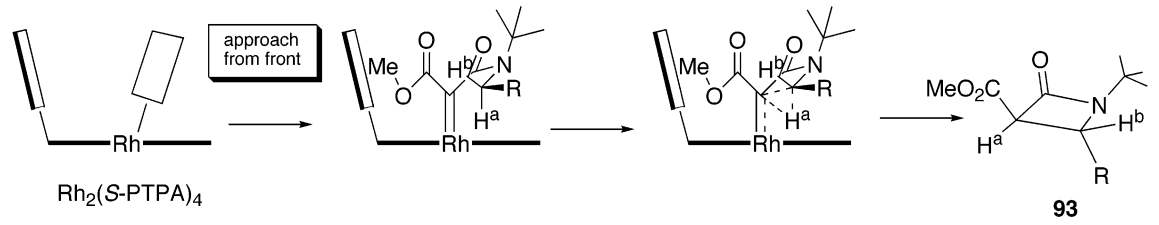


Figure 10. Model for asymmetric induction in β-lactam formation with Hashimoto's catalyst.

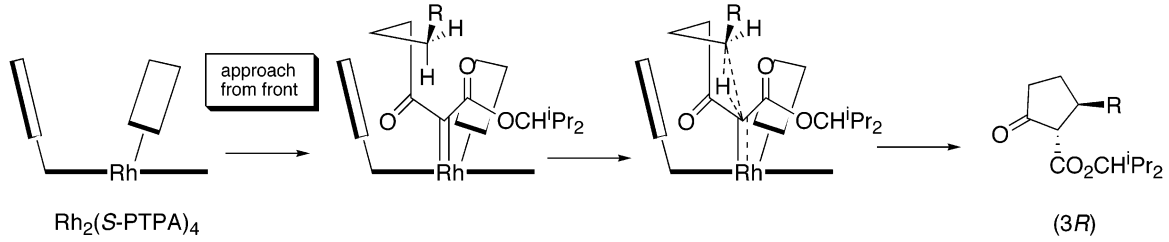


Figure 11. Model for asymmetric induction in cyclopentanone formation with Hashimoto's catalyst.

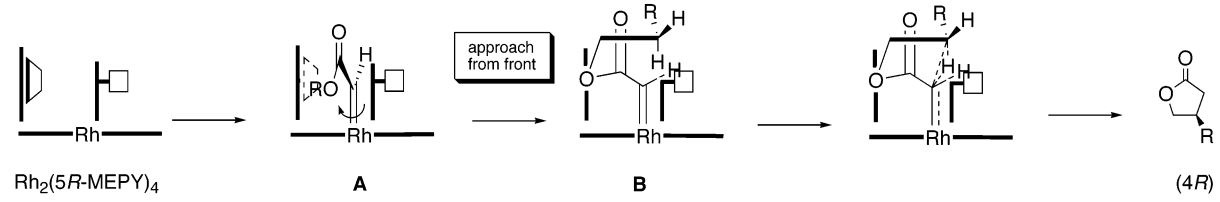


Figure 12. Model for asymmetric induction with Doyle's catalysts.

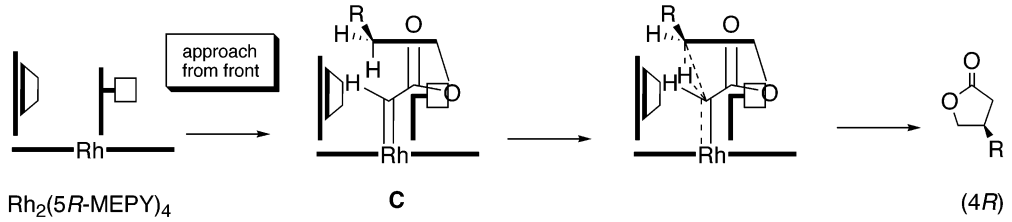


Figure 13. Alternative model for rhodium(II) carboxamidate system.

ketone carbonyl is positioned syn to the face of the catalyst to avoid repulsive interactions between the hydrogen atoms at the α-methylene position and the catalyst face.[206] Attack from the front face, with the R substituent oriented up and away from the catalyst face and the phthaloyl groups, would give the observed stereoselectivity.

Doyle's carboxamidate complexes are very effective at catalyzing the reactions of acceptor-substituted diazoacetate and diazoacetamide systems.[17] Doyle proposes that attack of the diazocarbonyl species generates a metallocarbenoid complex which adopts ground state arrangement **A** to minimize interactions with the pendent ester groups (Figure 12).[17] Rotation around the Rh−C axis as indicated in arrangement **A** leads to C−H activation through intermediate **B**, in which the C−H bond undergoing insertion approaches from the front face and is positioned parallel to the Rh−C bond.[34,138] The R group is thought to point up and back in order to avoid steric interactions with the other two ligands attached to the rhodium metal, such is the steric congestion around the metal core in the rhodium(II) carboxamidate complexes.[17] C−H activation leads to the observed asymmetric induction.

A major future challenge with the understanding of this chemistry is the need to define the exact trajectory of approach of the C−H bond to the carbenoid. Even though the C−H bond is parallel to the Rh−C carbenoid bond in both Hashimoto's and Doyle's models, the orientation of the other substituents is different, and this has an impact on the predicted asymmetric induction. For example, scrutinizing the C−H activation reaction of acceptor-substituted carbenoids in Doyle's carboxamidate complexes by adopting the principles used in Hashimoto's system[40,222] provides an alternative model that still successfully accounts for the observed enantioselectivity (Figure 13). In accord with Hashimoto's model, owing to the steric demand of the left-hand blocking group, only the hydrogen substituent of the carbenoid carbon would be sufficiently small to be accommodated in that position. The carbenoid would therefore adopt the orientation illustrated in arrangement **C** with the R group lying up and away from the catalyst face and the ester groups. Consequently, in this model compared to Figure 12, the opposite face of the carbenoid is available for C−H activation. C−H activation would occur from the front face to give the product identical to that obtained in Figure 12.

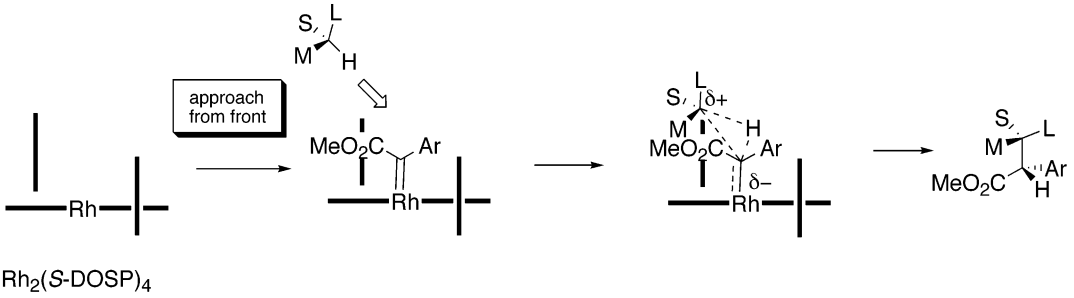


Figure 14. Predictive models for intermolecular C−H activation with dirhodium tetraprolinates.

The high asymmetric induction in the intermolecular C−H activation requires that the trajectory of approach of the substrate to the carbenoid must be very precise and demanding.[165] This may explain why only the highly stabilized donor/acceptor-substituted carbenoids are capable of high asymmetric induction in intermolecular C−H insertions. Even though the exact trajectory of attack of the carbenoid is not known, a model has been developed that is excellent at predicting the enantioselectivity and diastereoselectivity of a range of intermolecular reactions (Figure 14).[43−45,165] In this model, the substrate approaches from the front face, over the electron-withdrawing group, with the largest group (L) pointing away from the catalyst and the carbenoid and the medium-sized group (M) pointing away from the carbenoid.[43,165] Due to the D_2 symmetry of the catalyst the possible orientations of the carbenoid are considerably decreased, but there are still two distinct orientations, and these would lead to opposite asymmetric induction.[43] It appears that the carbenoid bound to the tetraprolinates such as Rh_2(*S*-DOSP)$_4$ and the bridged prolinates such as Rh_2(*S*-biTISP)$_2$ adopt different orientations because the asymmetric induction is opposite for the two classes of catalysts.[43] Even though this model is an excellent predictor of the stereochemistry in these reactions, it may need refinement in the future as the C−H bond undergoing insertion is not aligned parallel to the Rh−C bond.

These models are useful not only as predictive models but also to rationalize why different types of catalysts are required for each class of carbenoid. It is likely that all of these models will undergo further refinement as a better mechanistic picture of these reactions is acquired through the highly sophisticated computational modeling techniques that are becoming available.

8. Conclusions

This review has been arranged to highlight the impact of both catalyst design and carbenoid structure on catalytic asymmetric C−H activation. A general chiral catalyst effective for all carbenoid systems has not been found, but the reason for this is simply because the various carbenoid systems have very different chemical and structural characteristics. Consequently, the most effective chiral catalysts tend to operate best on a specific class of carbenoids.

The rhodium carboxamide catalysts developed by Doyle are exceptional catalysts for intermolecular C−H activation of diazoacetates and diazoacetamides.[17] The resulting acceptor-substituted carbenoids are very reactive, and the sterically demanding carboxamide ligands are ideal for locking the reacting conformation of the carbenoid. Furthermore, the carboxamidate ligands would make the rhodium complex less electrophilic than the dirhodium tetracarboxylates, and this would temper the reactivity of the carbenoids.[17] With a series of rhodium carboxamidate catalysts available, fine-tuning is possible to obtain the optimum catalyst for different substrates.[39] The bulky imidazolidinone catalysts, Rh_2(MPPIM)$_4$ and Rh_2(MACIM)$_4$, are the most effective for acyclic diazoacetates and cycloalkyl diazoacetates, respectively.[17] The oxazolidinone catalyst Rh_2(MEOX)$_4$ is an excellent choice for cyclic diazoacetamides[17] and in systems that require controlling a competition between C−H activation and cyclopropanation.[150] The azetidinone catalysts Rh_2(IBAZ)$_4$ and Rh_2(MEAZ)$_4$ are more reactive than the other carboxamide catalysts and perform reasonably well in intramolecular reactions of phenyldiazoacetates.[124]

Hashimoto's *N*-phthaloyl amino acid catalysts are especially effective for the intramolecular C−H activation chemistry of acceptor/acceptor-substituted carbenoids.[40] Very high regio- and enantioselectivity can be obtained for β-lactam formation using a bulky amide substituent.[174] Again, a family of catalysts is available for optimization of specific systems. The best enantioselectivities for five-membered ring formation are obtained when using some of the bulkiest catalysts in the series.[40] With regard to cyclopentanone formation, a bulky ester substituent is found to enhance enantioinduction.[40] For intramolecular C−H activations of phenyldiazoacetates at methylene sites the *tert*-leucinate-derived catalyst Rh_2(PTTL)$_4$ is especially effective.[171]

The rhodium prolinate catalysts introduced by McKervey[160] and then refined by Davies[43] have proven to be exceptional chiral catalysts for intermolecular C−H activation of donor/acceptor-substituted carbenoids.[44,45] The hydrocarbon soluble catalyst Rh_2(S-DOSP)$_4$ has proven to be very effective with a wide range of substrates.[44,45] The rhodium prolinates have also met with reasonable success in intramolecular C−H activations. They are the catalysts of choice for methyl-substituted diazoketones[130] and phenyldiazoacetates inserting into a methine site.[223]

The C−H activation chemistry is now maturing to the stage that practitioners of organic synthesis can consider this chemistry as a powerful strategic reac-

tion for total synthesis.[37,55] A successful C−H activation can avoid many functional group manipulations and greatly streamline a synthetic sequence. The recent progress made in intermolecular C−H activation significantly enhances the synthetic potential of this chemistry.[44,45]

Research in the field of carbenoid induced C−H activation is booming, especially with the realization that this approach to "C−H activation" is a very practical catalytic process.[44,45] In addition to further catalyst development a major area of future growth will be to expand the chemistry to a broader range of carbenoid systems.[44,45] The vast majority of studies to date have been conducted on diazocarbonyl systems, but several other electron-withdrawing groups could be used in this chemistry. The recent realization of the synthetic potential of the donor/acceptor-substituted carbenoids begs the question of what range of donor groups are compatible with this chemistry. The current developments in computational methods to study the mechanism of these C−H activation processes will have a major impact in ensuring that this chemistry becomes more rational and predictable. Considering the vast array of complex structures that are readily accessed, the field is wide open for the innovative application of this exciting chemistry.

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Several postdoctoral associates, graduate students, and undergraduate students in the Davies group have made major contributions to the chemistry described in this review. Without their dedication and ingenuity, this chemistry would not have reached its current level of broad synthetic utility. We gratefully acknowledge financial support of this work by the National Science Foundation (CHE 0092490). We thank The Royal Commission for the Great Exhibition of 1851 for a fellowship for R.E.J.B.

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