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An overview on the applications of 'Doyle catalysts' in asymmetric cyclopropanation, cyclopropenation and C–H insertion reactions

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Abstract. The chiral dirhodium(II) carboxamidates are a unique class of chiral catalysts useful for asymmetric inter- and intramolecular cyclopropanation, cyclopropenation and C–H insertion reactions with excellent enantioselectivities. The broad applications of these catalysts in organic syntheses are briefly reviewed.

Keywords. Doyle catalysts; asymmetric cyclopropanation; cyclopropenation; chiral catalysis; C–H insertions; chiral methyl phenidate.

1. Introduction

Johnson Matthey has recently obtained a worldwide exclusive licence to manufacture and sell a unique class of chiral dirhodium(II) carboxamidate catalysts called 'Doyle catalysts'. These homogeneous catalysts are capable of producing chiral cyclopropanes, cyclopropenes and C–H insertion products of very high enantioselectivity by diazo decomposition reactions. The purpose of this article is to provide a brief overview on the applications of dirhodium(II) carboxamidates for asymmetric cyclopropanation, cyclopropenation and C–H insertion reactions.

2. Metal catalyzed diazo decomposition

Cyclopropanation and C–H insertion reactions involve C–C bond formation which occurs efficiently by metal catalyzed decomposition [1] of diazo compounds. During the early part of this discovery both Cu(I) and Cu(II) have been successfully utilized in the presence of various ligands such as Schiff bases, semicorrins, aza-semicorrins and C_2-symmetric *bis*-oxazolines for intermolecular cyclopropanation reactions. Nozaki, Aratani, Corey, Pfaltz, Evans and Masumune have contributed significantly towards the development of this area. As of now Merck uses Aratani catalyst (**1**, figure 1) to produce *cilastatin* (scheme 1) commercially. Complexes of Ru(II) with C_2-symmetric 2,2′-*bis*(2-oxazolin-2-yl)pyridine (Pybox) have been efficiently demonstrated by Nishiyama for the highly enantioselective intermolecular cyclopropanation reaction. Other metals such as Co and Pd have also been used for diazo decomposition but with limited success. Reviews by Doyle [1], Davies [2] and Singh [3] give a detailed account of the applications of chiral metal complexes in diazo decomposition reactions.

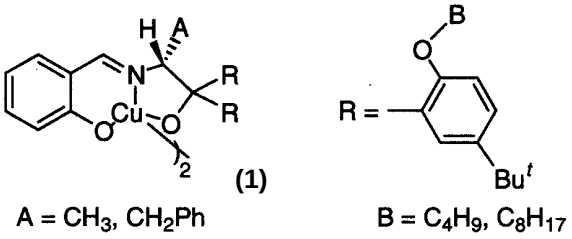
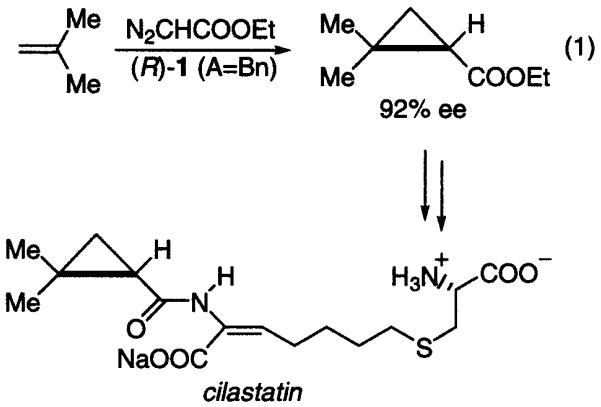


Figure 1. Aratani's copper catalyst used in the manufacture of *cilastatin*.



Scheme 1. Commercial production of *cilastatin* using Aratani's chiral copper catalyst.

The use of dirhodium(II) acetate as catalysts in diazo decomposition was observed initially by Teyssie [4]. Brunner [5], McKervey [6] and Hashimoto with Ikegami [7] independently developed the chiral dirhodium(II) carboxylates by exchanging the acetate with suitable chiral carboxylates, and explored their applications in diazo decomposition. Davies' fairly recent work [2,8] on similar systems has added a new dimension to this area, with a lot of exciting chemistry. About a decade ago, Doyle and coworkers [1,9] developed a unique series of chiral dirhodium(II) catalysts by replacing acetates in $Rh_2(OAc)_4$ with chiral carboxamidate ligands, and explored their applications in intramolecular cyclopropanation, cyclopropenation and C–H insertion reactions achieving very high enantioselectivities.

3. Cyclopropanation

Cyclopropanation is a class of reaction, where a propane molecule is formed in a cyclic fashion by the addition of a carbene, 'R_2C:' to an olefinic bond. Diazo compounds undergo N_2 elimination by electrophilic addition to a transition metal complex with the formation of a carbene, which is being stabilized by the metal (scheme 2). The presence of an electron rich substrate (e.g. olefin) abstracts the carbene from the metal and regenerates the catalyst, thereby completing the catalytic cycle [1,10]. Chiral dirhodium(II)

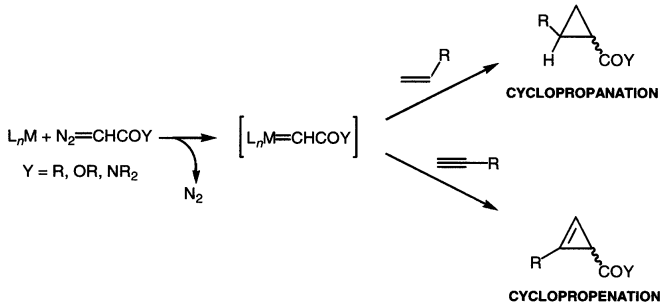
complexes are capable of producing enantiopure cyclopropanes by both intermolecular or intramolecular reactions. The selection of the catalyst and the choice of the diazo compounds seem to be important in favouring the inter- or intramolecular cyclopropane products. The mechanism of cyclopropenation is basically the same as that of cyclopropanation, where the electron-rich substrate is an alkyne.

The dirhodium(II) tetraprolinate originally developed by McKervey [6], the subsequent exploration of their applications in various systems by Davies [2,8], and the phthalimidocarboxylate developed by Hashimoto and Ikegami [7] are the first two prominent types of chiral dirhodium(II) carboxylates utilized for diazo decomposition reactions. However, these catalysts are most effective for intermolecular cyclopropanation reactions or C–H insertions. On the other hand, the dirhodium(II) carboxamidate catalysts [1,9] developed by Doyle, are best suited for intramolecular cyclopropanation reactions. Since the focus of this overview is on dirhodium carboxamidate based systems, discussion on intermolecular reactions is omitted.

3.1 *Intramolecular cyclopropanation reaction*

Doyle *et al* developed a series [1] of dirhodium(II) complexes containing chiral carboxamidates by varying the electronic, steric and ring size effects of the carboxamidate ligands. These are commonly known as 'Doyle catalysts' (figure 2).

These ligands are derived from common amino acids such as methyl 2-oxopyrolidine-5-carboxylic acid, methyl 2-oxooxazolidine-5-carboxylic acid, methyl N-(3-phenyl-propanoyl)-2-oxoimidazoline-4-carboxylic acid and isobutyl 2-oxoazetidine-4-carboxylic acid. Examples of Doyle catalysts include both *R* and *S* versions of $Rh_2(MEPY)_4$, $Rh_2(MEOX)_4$, $Rh_2(MPPIM)_4$ and $Rh_2(IBAZ)_4$ (figure 2).



Scheme 2. General mechanism for cyclopropanation and -propenation.

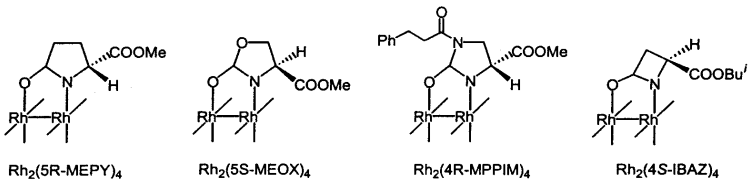


Figure 2. Examples of 'Doyle catalysts'.

Diazo decomposition of several examples of trisubstituted and *cis*-disubstituted allylic diacetates in the presence of $Rh_2(MEPY)_4$ catalyst has been used to synthesize cyclopropane fused lactones [11] in excellent yields with high enantiomeric excess (*ee*) (> 94%). Similar reactions when carried out using the *trans* isomers gave moderate *ee* (65–85%). However, the use of $Rh_2(MPPIM)_4$ catalyst resulted in 95–96% *ee* (scheme 3), emphasizing the importance of steric bulk and positioning of the ligand on enantioselectivity control. A comparative study [12] (table 1) using Doyle catalysts with that of Evans' Cu(I) *bis*-oxazoline [13] and Nishiyama's Ru(II) pybox [14] indicates that dirhodium(II) carboxamidates are far superior in producing enantiopure products. Results obtained from diazo N-allylacetamides [9d] are identical to that of the diazoacetate system in terms of yield and enantioselectivity.

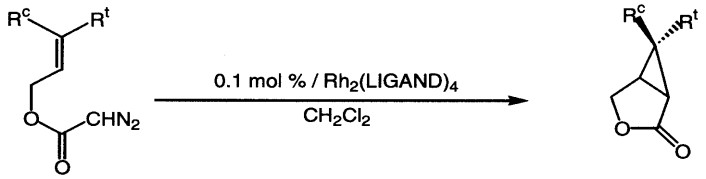
Doyle [15,16a] recently extended asymmetric intramolecular cyclopropanation for the formation of several interesting macrocyclic lactones.

Poulter [17] very efficiently used $Rh_2(5R\text{-MEPY})_4$ to produce optically pure presqualene diphosphate, an intermediate in the biosynthesis of squalene from farnesyl diphosphate. The key step in this synthesis is the stereoselective intramolecular cyclopropanation of farnesyl diazoacetate to the (–)-lactone using the Doyle catalyst (scheme 4).

Martin has been using *R* and *S* versions of $Rh_2(MEPY)_4$ to make conformationally restricted peptide isosteres as renin [18] and collagenease [19] inhibitors. Recently he extended this methodology to make cyclopropane-derived peptidomimics (scheme 5), which are novel analogues of enkephalin [20].

3.2 *Intramolecular cyclopropenation reaction*

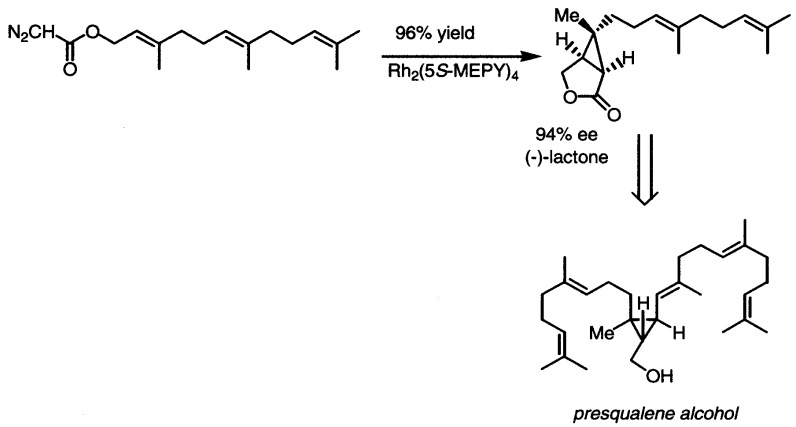
Intramolecular cyclopropenation [16a] has also been successfully attempted recently with excellent enantioselectivity (scheme 5). Based on the limited study, $Rh_2(4S\text{-IBAZ})_4$



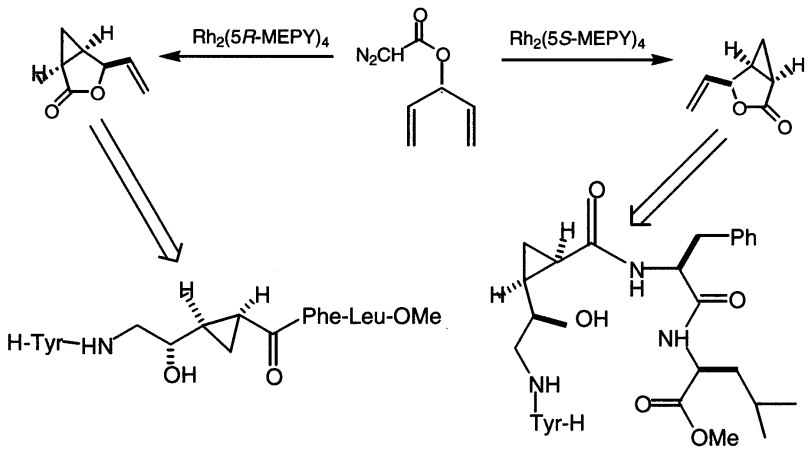
Scheme 3. Intramolecular cyclopropanation of substituted allylic diazoacetates.

Table 1. Comparison of Doyle catalysts with Cu(I) and Ru(II) catalysts.

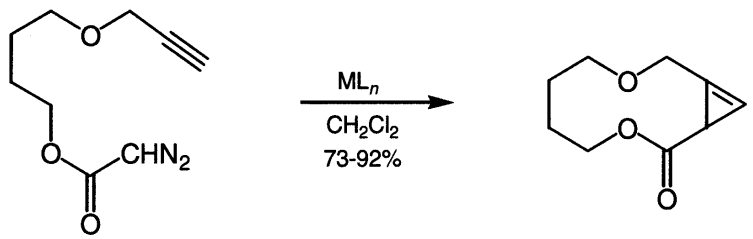
R^t	R^c	$Rh_2(5S\text{-MEPY})_4$ Doyle	$Rh_2(4S\text{-MPPIM})_4$ Doyle	Cu(I)-*bis* oxazoline Evans	(pybox)$RuCl_2$(ethene) Nishiyama
H	H	95 *ee*		20 *ee*	
Me	Me	98 *ee*		–13 *ee*	–76 *ee*
Ph	H	68 *ee*	96 *ee*	4 *ee*	– 86 *ee*
^{n}Pr	H	85 *ee*	95 *ee*	– 29 *ee*	78 *ee*
H	Ph	94 *ee*			–24 *ee*
H	^{n}Pr	94 *ee*		–37 *ee*	21 *ee*
		72–93% yield		58–82%	54–91% yield



Scheme 4. Stereoselective intramolecular cyclopropanation of fernesyl diazoacetate.



Scheme 5. Synthesis of cyclopropane-based peptidomimics using Rh_2 (5*S*-MEPY)$_4$.



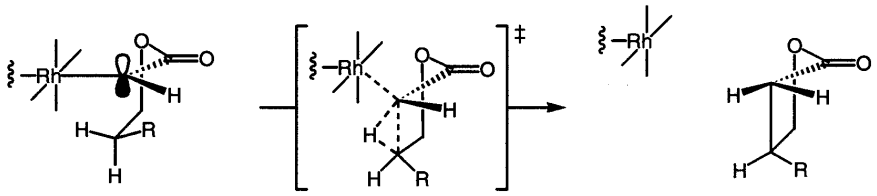
Rh_2(4*S*-IBAZ)$_4$	98%(*ee*)
Rh_2(5*S*-MEPY)$_4$	78%(*ee*)
$CuPF_6$/bis-oxazoline	83%(*ee*)

Scheme 6. Enantioselective cyclopropenation reaction Rh_2 (4*S*-IBAZ)$_4$ catalyst.

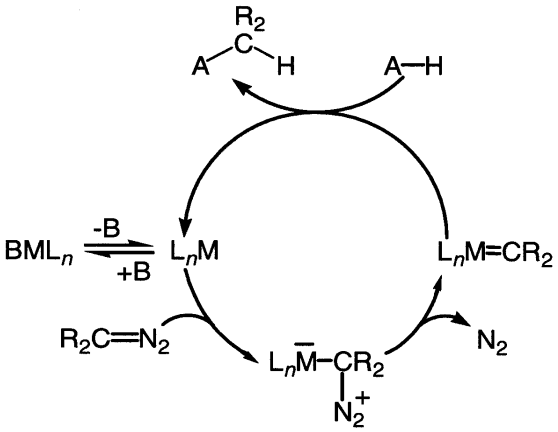
catalyst seems to be the catalyst of choice, and for the system containing both olefinic and acetylenic multiple bonds, the conversion appears to be catalyst-dependent. However, more work has to be done to understand the mechanism on selectivity. Evans' Cu-*bis*oxazoline catalyst gave poor selectivity [16a] for the same systems, under identical conditions. Earlier studies show that $Rh_2(MEPY)_4$ catalyst is useful for asymmetric intermolecular cyclopropenation [16b,c] as well.

4. C–H insertion reactions

Insertion of a carbene into an unactivated C–H bond is a fairly well known reaction in organic chemistry for C–C bond [1] formation. When the same reaction occurs through metal catalyzed diazo decomposition, enantio- and stereoselectivity can be achieved. Chiral dirhodium(II) catalysts are capable of producing C–H inserted inter- and intramolecular products in excellent selectivity. Scheme 7 illustrates the commonly accepted mechanism, where the *p* orbital of the metal carbene overlaps with the s orbital of the C–H, leading to C–C and C–H bond formation of the carbene carbon. This leads to the regeneration of the Rh_2L_4 catalyst. The catalyst cycle is depicted in scheme 8.



Scheme 7. Mechanism showing the orbital involvement in C–H insertion reactions.



Scheme 8. Catalyst cycle for C–H insertions.

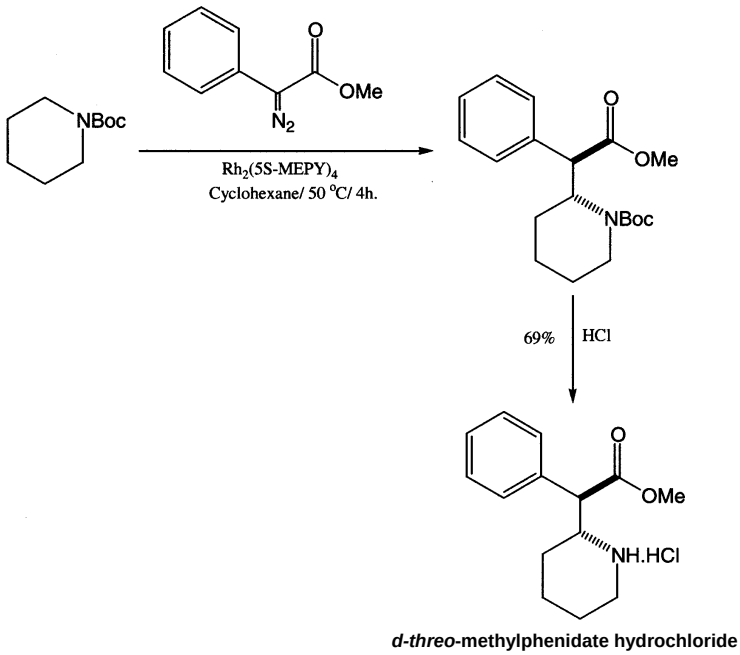
4.1 *Intermolecular C–H insertions*

The dirhodium(II) carboxylate catalysts developed by McKervey and Davies have been known to produce intermolecular cyclopropanation products [1,2,6] with excellent enantiomeric excess, in comparison to the dirhodium(II) carboxamidate systems. However, recent studies indicated that dirhodium(II) carboxamidates could be used for intermolecular reactions as well.

One of the most promising reactions in this area is the synthesis of chiral methylphenidate. The racemic form (ritalin^{TM}) of this material is currently prescribed in the United States mainly for children with attention deficit disorder. Johnson Matthey's Pharmaceutical Business is also a leading supplier of the bulk material. However, the *d-threo* isomer is 13 times more active than its mirror image.

Considering the two recent lengthy (eight and nine steps) syntheses [21], the two-step Rh mediated asymmetric synthesis (scheme 9) described by Winkler [22] using Doyle's Rh_2(*S*-MEPY)$_4$ catalyst should be of considerable importance. This process involves an asymmetric C–H insertion reaction at the a-position of the N-Boc piperidine with methylyphenyl diazoacetate, in the presence of a Rh catalyst, followed by the deprotection of the Boc. Davies also tried the same reaction [23] using his Rh_2(*S*-DOSP)$_4$ catalyst with some success.

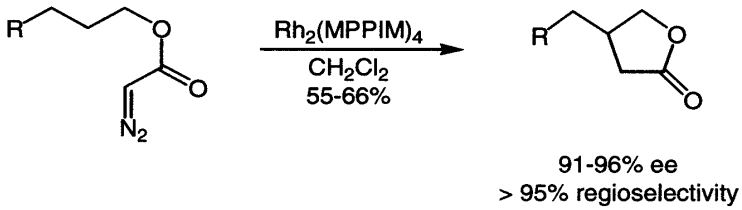
Doyle's Rh_2(*S*-MEPY)$_4$ catalyst gave 69% ee for the *d-threo*-isomer with very good selectivity (*de* = 95), while Rh_2(*S*-DOSP)$_4$ gave only 25% *ee* with moderate diastereomeric ratio. Winkler was able to improve the *ee* to 95% by two recrystallizations, while Davies' new Rh_2(*S*-biDOSP)$_2$ catalyst [24] gave 86% *ee* with 52% yield of the pure diastereomer. However, for the four-membered amine, pyrrolidine Davies' Rh_2(S-DOSP)$_4$ gave outstanding enantio- and diastereoselectivity.



Scheme 9. Chiral methylphenidate synthesis using Doyle's Rh_2(*S*-MEPY)$_4$ catalyst.

4.2 *Intramolecular C–H insertions*

Dirhodium(II) carboxamidate catalysts have proven to be extremely effective [25] for intramolecular C–H insertion reactions of diazoacetates (scheme 10). Doyle used this approach initially to construct several examples of enantiopure g-lactones, by the diazo decomposition reaction of alkoxy substituted diazoacetates with the aid of Rh_2(*S*-MEPY)$_4$ and Rh_2(*S*-MEOX)$_4$ catalysts [1]. Similar C–H insertion reactions [26] conducted with acyclic



Scheme 10. Regio- and stereoselective C–H insertion reaction, leading to g-lactones.

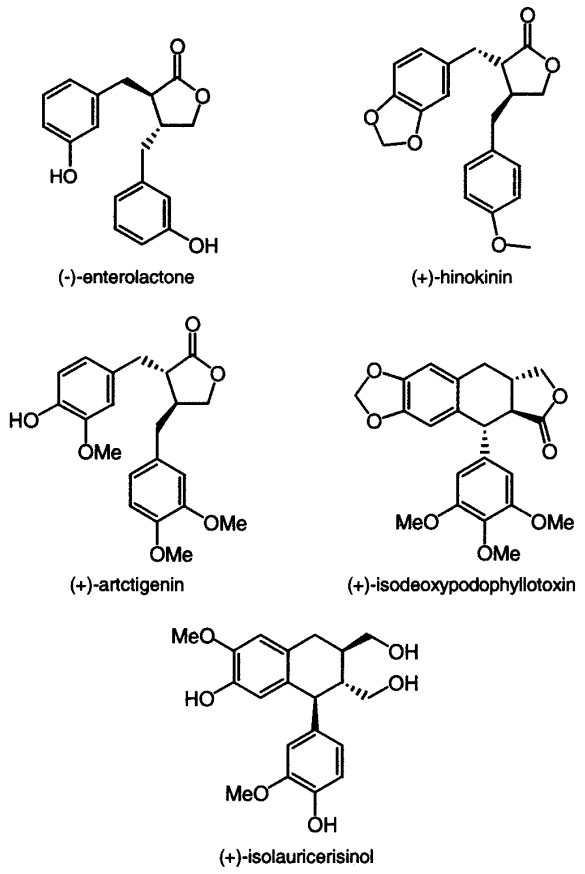
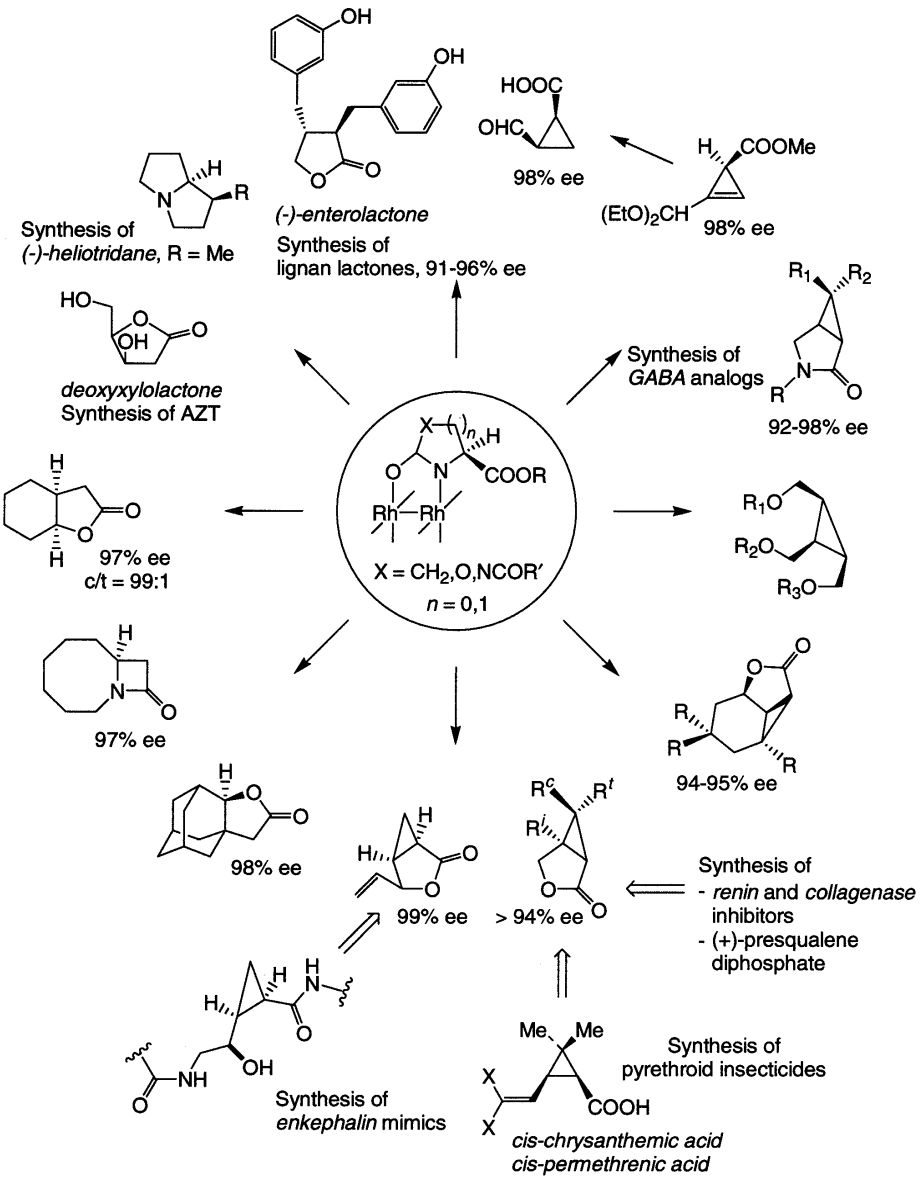


Figure 3. Various lignan lactones prepared by the usage of Rh_2(4*S*-MPPIM)$_4$.



Scheme 11. Summary of the applications of Doyle catalysts in enantioselective organic syntheses.

diazoacetamides, gave a mixture of b- and g-lactams with modest enantiomeric excess. The ratio between b- and g-lactam seems to depend on the substitutents on the nitrogen. However, b-lactam (four-membered ring) formation was generally favoured in the case of cyclic diazoacetamides, although ring sizes play an important role in the selectivity[27]. The enantiomeric excess values are up to 97%.

The asymmetric C–H insertion technology has been extended very efficiently to construct a series of g-lactones with very good regio- and enantiocontrol.

The b-substituted-g-butrolactones serve as the major intermediates for a series of lignan lactones[28] (figure 3) with excellent yield and *ee*. Based on the several systems studied so far, it appears that $Rh_2(MPPIM)_4$ is the best catalyst of choice. The generality of C–H insertion reactions has been verified successfully for both *R*- and *S*-enantiomers. Recently, Doyle's group has accomplished[29] the syntheses of 2-deoxyxylono-1,4-lactone and 2-deoxyribono-1,4-lactone from 1,3-dioxan-5-yl diazoacetates, with *ee*'s up to 96%.

5. Conclusions

Chiral dirhodium(II) carboxamidate catalysts have been employed efficiently during the last decade for asymmetric cyclopropanation, cyclopropenation and C–H insertion reactions. Based on the limited study, it was believed that the chiral dirhodium(II) carboxamidate catalysts are generally good for intramolecular C–H insertions and cyclopropanations, while the analogous carboxylates are unique for intermolecular reactions. Winkler's chiral methylphenidate synthesis using Doyle catalyst demonstrated that it could be very efficiently used for intermolecular C–H insertions as well. In addition to cyclopropanation and C–H insertions, these catalysts are also capable of other chiral transformations. Scheme 11 summarizes the applications of Doyle catalysts for various organic transformations with outstanding enantio controls.

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