Stereo- and Regiocontrol in the Formation of Lactams by Rhodium-Carbenoid C−H Insertion of α-Diazoacetamides

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Keywords: C−H insertion / Diazo compounds / Diazoacetamides / Lactams / Rhodium

The dirhodium(II)-catalysed intramolecular C–H insertion reaction of α-diazoacetamides is a powerful methodology for the preparation of highly valuable heterocyclic compounds such as lactams. In this Microreview we present lactam formation by intramolecular C–H insertion of α-diazoacetamides, focusing on the effects that have a profound impact on the reaction pathway.

Introduction

As part of the exciting field of activation of unfunctionalised C−H bonds, the use of dirhodium(II)-stabilised carbenes generated from α-diazo compounds is a powerful synthetic methodology for the preparation of highly valuable compounds.[1,2]

The pioneering work of Teyssié et al., Hubert et al. and Noels et al.[3] on the use of dirhodium catalysts to form metal carbenes that could be used in a selective and controlled way attracted the attention of the synthetic community. Since then a wide range of transformations in which these versatile intermediates are involved have rapidly found general applicability,[4−10] as shown in Scheme 1.

In recent years, the dirhodium(II)-catalysed intramolecular C−H insertion has emerged as a general strategy for the construction of numerous cyclic and heterocyclic compounds,[11,12] among which β- and γ-lactams are especially noteworthy since they are common scaffolds in numerous natural-products syntheses.[13−15] The success of this approach is related to the level of regio- and stereocontrol and, in some cases, to the high enantioselectivity of the C−H insertion process.[11,16]

An extensive literature is available on this subject, including several reviews emphasizing various aspects of this chemistry.[1,5,11,12,16] This Microreview aims to highlight lactam formation by intramolecular C−H insertion of α-

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MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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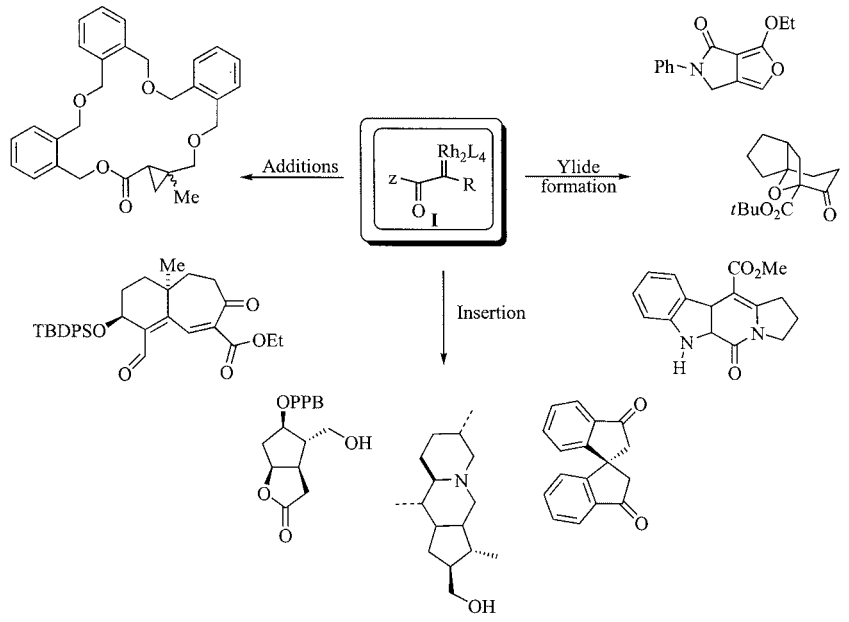
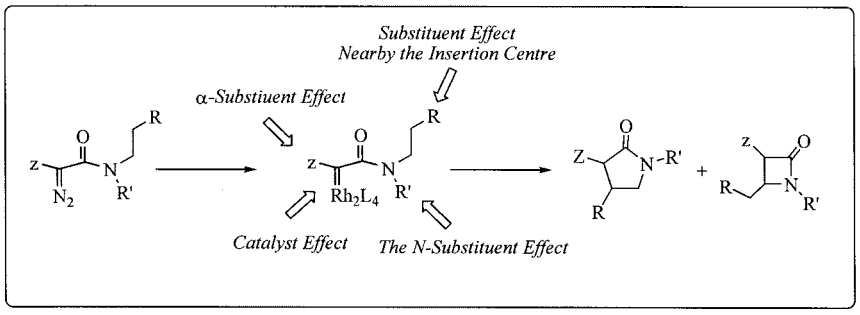


Scheme 1



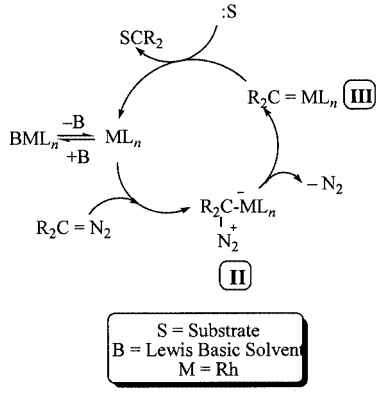
Scheme 2

diazoacetamides, within the dirhodium(II)-mediated carbene transformations, focusing on the effects that are recognized to have a profound impact on the reaction pathway, as illustrated in Scheme 2.

Mechanism of the C−H Insertion Reaction

Doyle et al. first proposed[5,17] what is now a widely accepted mechanism for the dirhodium(II)-catalysed transformations of diazo compounds, a catalytic cycle (Scheme 3) in which, after solvent decomplexation from the metal atom, a nucleophilic attack of the diazo compound on the electrophilic catalyst occurs, affording the intermediate ylide **II**, which upon nitrogen extrusion generates a metal-stabilized carbene **III**. Product formation takes place when the electrophilic carbene is transferred to an electron-rich substrate, thus recovering the catalyst.

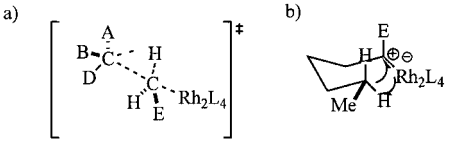
Although this catalytic cycle is generally accepted, the detailed mechanism of the transition-metal-catalyzed C−H bond activation and C−C bond formation has been the



Scheme 3

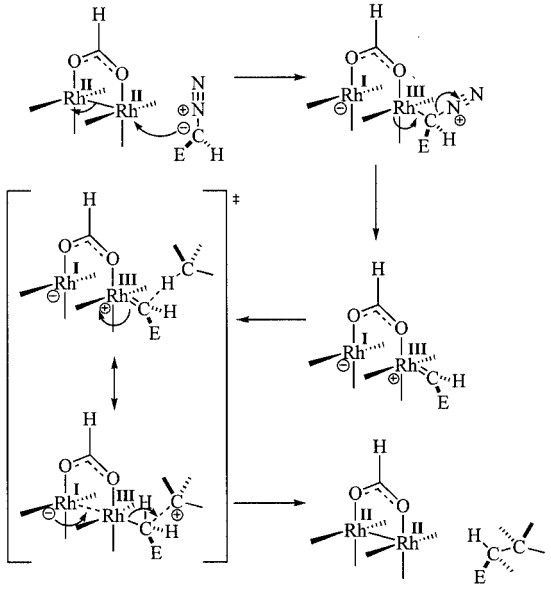
subject of considerable speculation. On the basis of the existing literature, various models of the C−H bond activation transition state have been proposed. In Scheme 4a, the transition state of the C−H bond activation proposed by Doyle et al.[18] is depicted. In this case, overlapping of

the carbene's p-orbital with the σ-orbital of the reacting C−H bond initiates the process; C−C and C−H bond formation take place while the catalyst dissociates from the substrate. Scheme 4b shows the proposal by Tabers et al. in which the alignment of the C−Rh bond with the target C−H bond is hypothesised.[19]



Scheme 4

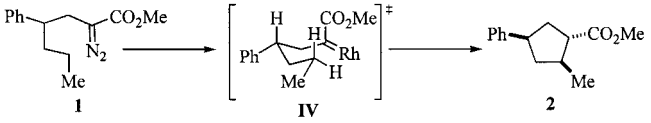
In a recent work, Nakamura et al.[20] have proposed a more accurate transition state model, based on high-level computational analysis, where the diazo species reacts with the dirhodium complex cleaving the Rh−Rh bond (Scheme 5). Nitrogen loss, resulting from rhodium back-donation, generates the electrophilic metal-carbene. Finally, product formation takes place when the hydride is transferred from the alkane to the carbene atom, and a C−C bond is formed while the Rh−Rh bond is regenerated.



Scheme 5

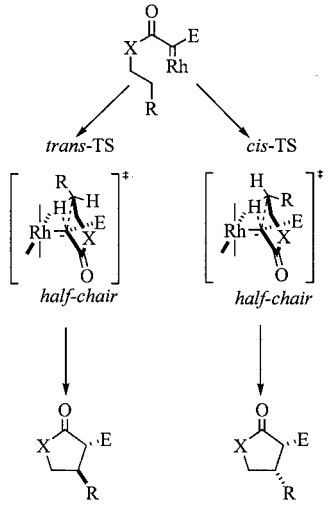
Apart from these general considerations, intramolecular C−H insertion has some particular features. The most widely recognised are the stereoselective outcome of the insertion process and the overwhelming preference for five-membered-ring formation.[11,12]

In an attempt to understand and predict the diastereoselectivity of the Rh-mediated intramolecular C−H insertion, Taber et al. have proposed an extremely useful chair-like model for the transition-state conformation in which all the substituents are in the most stable pseudoequatorial positions (Scheme 6).[19,21]



Scheme 6

Recently, Nakamura et al.[22] have presented a more detailed study where the transition state conformations for the five-membered-ring formation were evaluated. The observed preference for the *trans* stereoselectivity was considered to be a consequence of different energies between *cis* and *trans* transition states. The origin of this energy gap was attributed to the position occupied by the insertion centre substituent, which, in the *trans* half-chair transition-state conformation, occupies the sterically more stable equatorial position, while in the *cis* half-chair transition-state conformation it is positioned in the axial position and thereby suffers from 1,3-diaxial repulsion, as illustrated in Scheme 7.

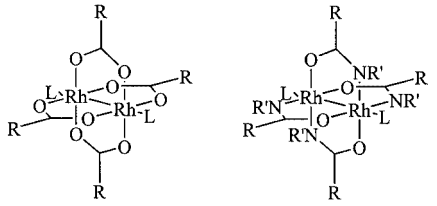


Scheme 7

Early studies[18,19] of intramolecular C−H insertion established a high preference for the five-membered-ring formation and a reactivity order of tertiary > secondary >> primary C−H bond. These observations can be understood considering the transition state model proposed by Nakamura et al.,[22] in which the transferred hydrogen takes part in a favourable six-membered cyclic structure, and that further stabilization is added when substituents such as an alkyl group are attached at the insertion centre. Despite these selectivity preferences, there are some noteworthy exceptions. There is general agreement that electron-donating substituents activate adjacent C−H bonds and electron-withdrawing substituents, even two atoms away from the insertion centre, deactivate C−H insertion in these reactions.[23] Sterically constrained systems can also drastically influence the selectivity of the reaction, limiting the predictability of product formation.[24]

The Catalyst Effect

A wide range of transition-metal complexes have been used for α-diazocarbonyl cyclisation but only the metal-carbenes generated from the reaction of diazo compounds with dirhodium(II) catalysts have shown general usefulness (Scheme 8).[16]

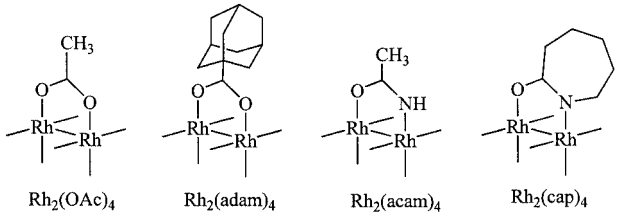


3 **4**

Scheme 8

The dirhodium(II) catalyst possesses a well-defined D_{2h} symmetry with four bridging ligands complexed to the dinuclear rhodium atoms and two axial ligands[25] that form a much weaker bond with the electrophilic centre.[26] These ligands are usually absent when the catalytic reactions take place, leaving one vacant axial coordination site on each rhodium atom for carbene attachment.[27]

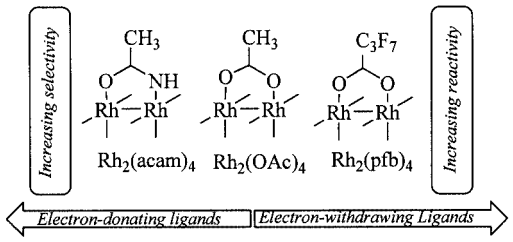
One of the most widely used catalysts for the achiral reactions is dirhodium(II) acetate, which can be obtained commercially or prepared by heating $RhCl_3 \cdot 3H_2O$ with sodium acetate and glacial acetic acid in ethanol under reflux. Dimers containing carboxylate ligands can be easily prepared by treating $RhCl_3 \cdot 3H_2O$ with the appropriate carboxylic salt.[28] Ligand exchange from dirhodium(II) acetate with various acetates or acetamides is an alternative method to prepare these dimers,[29] providing access to a broad range of catalysts (Scheme 9).[30]



$Rh_2(OAc)_4$ **5** $Rh_2(adam)_4$ **6** $Rh_2(acam)_4$ **7** $Rh_2(cap)_4$ **8**

Scheme 9

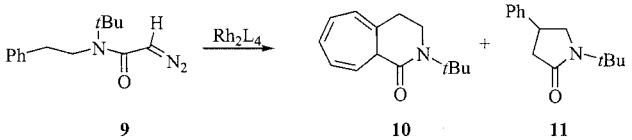
The dirhodium(II) carboxylates and the rhodium(II) carboxamides are especially important for their different electrophilic profiles. Electron-withdrawing ligands such as the carboxylates augment the catalyst's electrophilic character, increasing the reactivity towards diazo decomposition. Catalysts with electron-donating bridged ligands are often recognized as more selective, but on the other hand higher reactivity is required from the diazo compound in order to form the reactive metal-carbene (Scheme 10).[18,31,32]



Scheme 10

Rhodium(II) acetamide [$Rh_2(acam)_4$], and rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$], are representative examples of these electronically diverse catalysts.

In order to explore the chemeoselectivity of different catalysts, Padwa et al.[33] have performed a series of reactions in which the carbon−hydrogen insertion versus aromatic cycloaddition was explored. By tuning of the catalyst's electrophilic character, it was possible to observe different modes of reactivity. Carbenes generated from α-diazoacetamide **9** with more electrophilic catalysts underwent preferentially aromatic cycloaddition, while the use of catalysts with electron-donating ligands such as $Rh_2(cap)_4$ resulted in the formation of a more selective metal-carbene towards C−H insertion (Scheme 11).

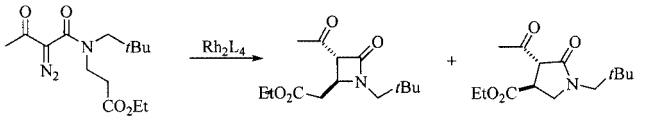


9 **10** **11**

	yield [%]	relative yield [%]	
		10	**11**
$Rh_2(OAc)_4$	85	68	32
$Rh_2(pfb)_4$	80	95	5
$Rh_2(cap)_4$	82	3	97
$Rh_2(acam)_4$	80	23	77

Scheme 11

Similar results were reported by Doyle et al. (Scheme 12),[34] in a competition study between ylide generation and C−H insertion on the cyclisation of substrate **12**; the C−H insertion reaction was the preferred reaction pathway when using $Rh_2(acam)_4$, whereas the more electrophilic metal-carbene generated with $Rh_2(pfb)_4$ underwent preferentially carbonyl ylide generation, yielding **15** as the major product.



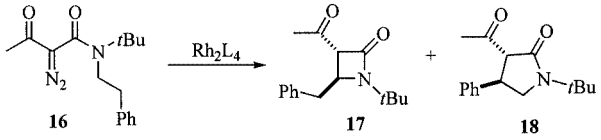
12 **13** **14**

	isolated yield [%]	relative yield [%]		
		13	**14**	**15**
$Rh_2(pfb)_4$	95	20	4	76
$Rh_2(OAc)_4$	90	50	12	38
$Rh_2(acam)_4$	93	56	16	28

15

Scheme 12

The influence of the catalyst ligand on the regioselectivity was underlined by the cyclisation of α-diazoacetoacetamide **16** (Scheme 13).[33] In this case, electronically diverse dirhodium(II) catalysts had a less dramatic effect on the competition for β- or γ-lactam formation. Nevertheless, metal-carbenes generated with a less electron-withdrawing catalyst such as $Rh_2(acam)_4$ tended to be more selective towards five-membered-ring formation.



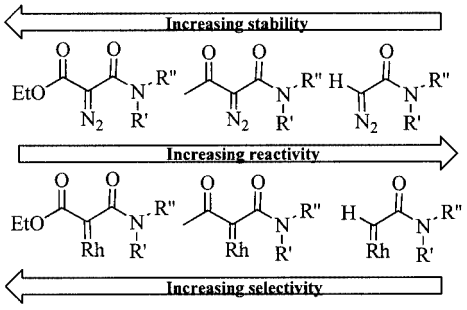
	isolated yield [%]	relative yield [%]	
$Rh_2(pfb)_4$	85	56	44
$Rh_2(OAc)_4$	94	49	51
$Rh_2(acam)_4$	90	30	70

Scheme 13

The α-Diazoacetamide Framework Effect

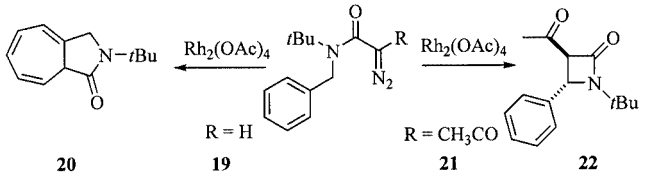
The α-Substituent

As already mentioned, the metal-carbene electrophilicity is one of the most important features determining the chemo- and regioselectivity of the insertion process. Apart from the catalyst, changing the substituents on the carbene carbon atom is an alternative way to alter the electronic character of the intermediate. Typically, less electron-withdrawing groups tend to make diazo compounds more unreactive towards metal-carbene formation, although once formed the intermediate exhibits an increased stability and selectivity (Scheme 14).[35]



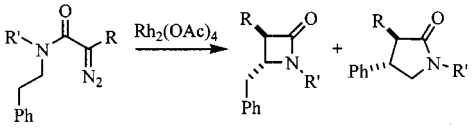
Scheme 14

A classical example of the α-substituent influence on chemoselectivity is presented in Scheme 15. Treatment of *N*-benzyl-*N*-*tert*-butyldiazoacetoacetamide (**21**) with dirhodium(II) acetate in refluxing benzene afforded exclusively the *trans*-β-lactam **22** in 98% yield,[36] whereas carbene addition to the aromatic ring was the only product observed when the deacylated substrate **19** was treated with $Rh_2(OAc)_4$ in dichloromethane at room temperature.



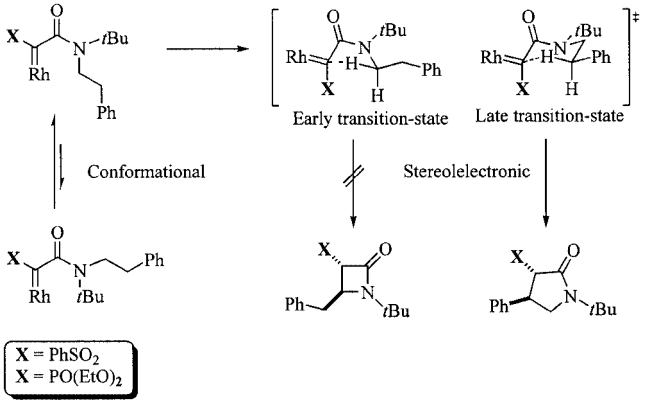
Scheme 15

Studies conducted on a series of diazoacetamides with different substituents on the carbene carbon atom underlined the α-substituent influence on the regioselectivity.[33,37−39a] As depicted in Scheme 16, higher selectivity towards γ-lactam formation was obtained when less electron-withdrawing substituents are attached to the carbene carbon atom. Nonetheless, as Jung et al.[38] and Afonso et al.[39a] have reported on the basis of the existing literature,[18−22] the enhanced regioselectivity observed for both α-diazoacetamides **25** and **26** resulted from the combination of conformational and stereoelectronic effects (Scheme 17), among which the carbene electrophilicity is of pivotal importance, presumably because the C−H insertion proceeds via a later transition state[18] as a consequence of the extra stabilization added by the phenylsulfonyl and phosphoryl moieties, which are not as electron-withdrawing as their carbonyl counterpart in α-diazoacetamide **23**.



Entry	Substrate	R	R'	Yield [%]	β/γ
2	**23**[33]	$COCH_3$	*t*Bu	94	49/51
3	**24**[37]	CO_2CH_3	PMP	76	1/99
4	**25**[38]	$PhSO_2$	*t*Bu	95	-/95
5	**26**[39a]	$PO(EtO)_2$	*t*Bu	95	-/95

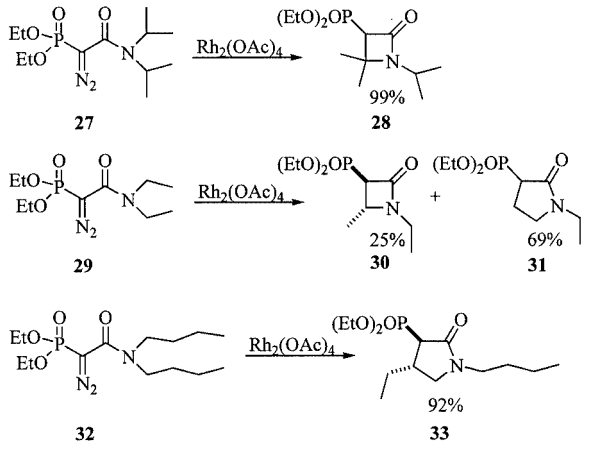
Scheme 16



Scheme 17

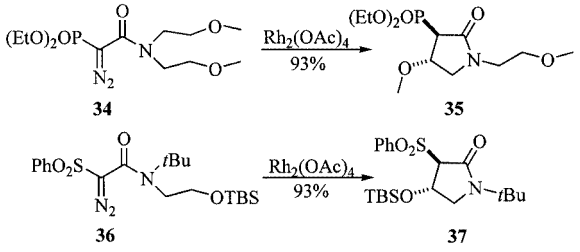
The Insertion Centre

In cases where the structure of the α-diazoacetamide allows both β- and γ-lactam formation, a mixture of both isomers often arises from the C−H insertion process. Despite the overwhelming preference for the five-membered-ring formation, the insertion-centre nature can drastically influence the reaction regioselectivity. This electronic effect was highlighted in the following sequence of cyclisations with symmetrical α-phosphono-α-diazoacetamides in chlorinated solvents[39a] (Scheme 18) and in an ionic liquid.[39b] The nitrogen atom and the methyl group activate the adjacent C−H bond, directing the cyclisation of α-diazoacetamide **27** towards exclusive β-lactam formation. However, when this activation was reduced, as in the case of the α-diazoacetamide **29**, a preference for the γ-lactam formation was observed, becoming the only product isolated from the cyclisation of α-diazoacetamide **32**.



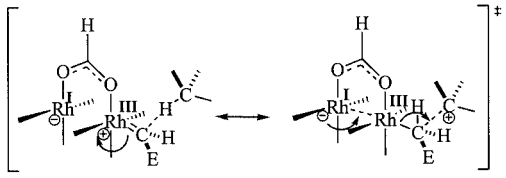
Scheme 18

A rationalization for this electronic effect was presented by Taber et al.[40] According to them, the alkyl and electron-donating groups (Scheme 19) alter the electron density of the C−H bond, making it more susceptible to an attack by the electrophilic rhodium-carbene.[23a]



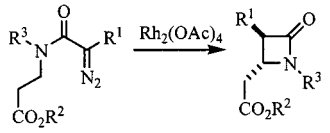
Scheme 19

A more detailed explanation can be envisioned from the C−H insertion model proposed by Nakamura et al.,[20,22] in which a hydride is transferred from the alkane where the insertion takes place to the electrophilic carbene atom. In this way, the positively charged alkane carbon atom will be stabilized by a resonance contribution by adjacent electron-donating groups, as shown in Scheme 20.



Scheme 20

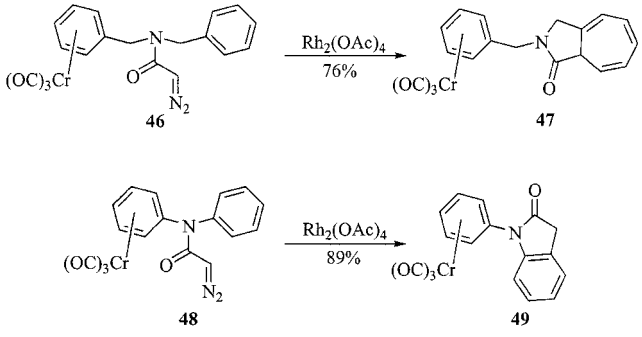
A clear example of electronic regioselectivity control by an electron-withdrawing group is presented in Scheme 21. The ester substituent directs the cyclisation towards β-lactam formation by deactivating the α-methylene group.[23b]



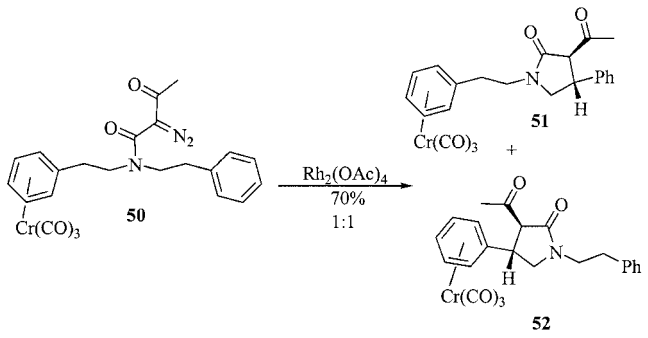
Substrate	R^1	R^2	R^3	Isolated yield [%]	Product
38[34]	$COCH_3$	Et	*t*Bu	96	**39**
40[37]	CO_2CH_3	*t*Bu	PMP	53	**41**
42[38]	$PhSO_2$	Et	*t*Bu	>99	**43**
44[39a]	$PO(EtO)_2$	Me	*t*Bu	94	**45**

Scheme 21

Interesting findings were recently reported by Merlic et al.[41] on the reactivity of complexed arenes with tricarbonylchromium. These complexed systems were found to be protected from Buchner reaction and aromatic C−H insertion, as presented in Scheme 22. This deactivation was explained by the electron-withdrawing nature of the tricarbonylchromium moiety. Nevertheless, this effect has no influence in the competing C−H insertion reaction onto the benzylic positions. Cyclisation of substrate **50** yielded a 1:1 mixture of both γ-lactams **51** and **52** (Scheme 23).



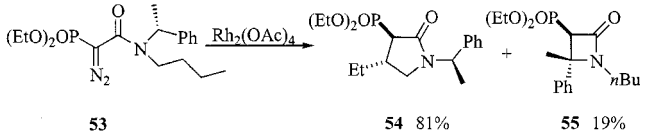
Scheme 22



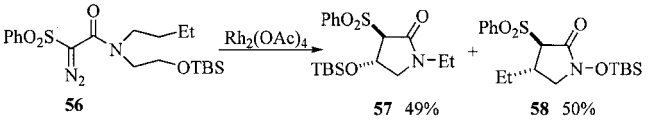
Scheme 23

The N-Substituent

In some cases, the conformational effect exerts a more profound influence on the chemo-, regio- and stereoselectivity of the C−H insertion process than the electronic factors. For example, cyclisation of α-diazoacetamide **53** furnishes a 19:81 mixture of β- and γ-lactam (Scheme 24), despite the fact that β-lactam **55** results from the insertion into a more activated C−H bond.[39a] The electronic activation was also not sufficient to allow the exclusive formation of γ-lactam **57**[38] from substrate **56**, as represented in Scheme 25.

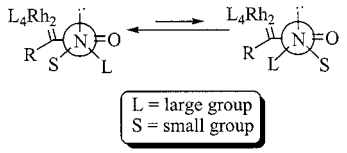


Scheme 24



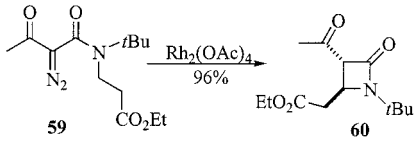
Scheme 25

The crucial role of the conformational effect has been explained by Doyle et al.[34] in terms of conformational preferences about the amide N−C(O) bond of the metal-carbene intermediate. According to them, the overlap of the non-bonded nitrogen electrons with the carbonyl π-system fixes the conformation in such a way that the larger *N*-substituent is placed *syn* to the sterically less demanding amide carbonyl group, while the smaller *N*-substituent is located in close proximity to the reactive carbene centre, facilitating the C−H insertion as represented in Scheme 26. When such conformational bias is absent, the regioselectivity is lost and a mixture of products is obtained as a result of insertion into the C−H bond of both *N*-substituents.



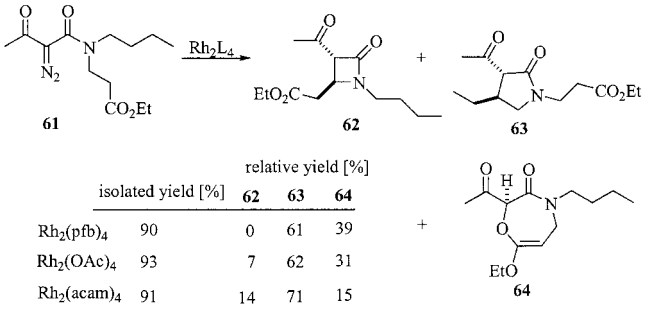
Scheme 26

Doyle et al. evaluated the conformational effect by careful design of *N*,*N*-disubstituted α-diazocetoacetamides.[34] The observation of exclusive *trans*-β-lactam formation with substrate **59** resulted from the deactivating influence of the ester substituent on the α-methylene group and the activation from the heteroatom adjacent to the β-methylene group (Scheme 27).



Scheme 27

When the *tert*-butyl group was replaced by the neopentyl group in substrate **12**, to allow insertion at the activated methylene group, three products were formed but none resulting from insertion into this activated position (Scheme 12). On the other hand, the comparable sizes of *n*-butyl and β-propionate *N*-substituents in the metal-carbene derived from the α-diazoacetamide **61** yielded a mixture of products resulting from the insertion into the C−H bond of both *N*-substituents (Scheme 28).[34]

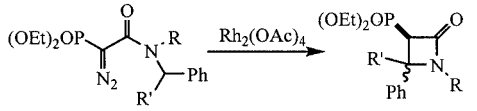


	isolated yield [%]	relative yield [%] 62	63	64
$Rh_2(pfb)_4$	90	0	61	39
$Rh_2(OAc)_4$	93	7	62	31
$Rh_2(acam)_4$	91	14	71	15

Scheme 28

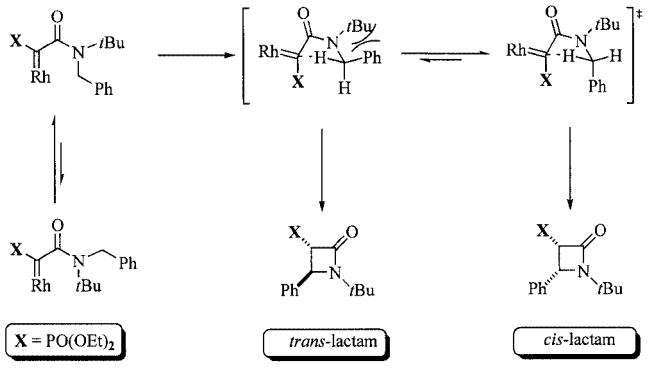
In further evidence of the steric influence exerted by the *N*-substituent on the stereoselectivity, Afonso et al.[39a] performed a series of reactions in which the *tert*-butyl group controls the stereoselectivity of β-lactam formation (Scheme 29). Catalytic cyclisation of the symmetric diazoacetamide **65** afforded 95% of the *trans* diastereomer, whereas in substrate **69** the *cis* diastereomer was obtained in 88% yield, probably as a consequence of the steric effect exerted by the bulky *tert*-butyl group, as shown in Scheme 30. Cyclisation of diazoacetamide **67** furnished a 60:40 (*cis*/*trans*) mixture of both isomers resulting from the

interaction of the *tert*-butyl group with both methyl and phenyl groups.



Substrate	R	R'	Crude *cis* [%]	Crude *trans* [%]	Yield [%]	Product
65	CH_2Ph	H	5	95	81(*trans*)	**66**
67	*t*Bu	Me	60	40	75(*trans*)	**68**
69	*t*Bu	H	88	12	89(*trans*)	**70**

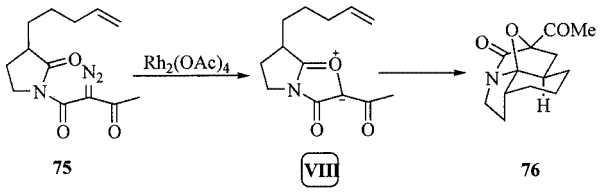
Scheme 29



Scheme 30

The *N*-substituent not only influences the regio- and stereoselectivity of the C−H insertion but the reaction itself can be tuned. Doyle et al.[42] have shown that, depending on the *N*-substituent, α-diazoacetamides can undergo carbonyl ylide generation resulting from the carbene interaction with the unshared electron pairs of the carbonyl functionality instead of the carbon−hydrogen insertion of the alkyl substituent, as illustrated in Scheme 31. For example, the imides **71** and **72** readily react with $Rh_2(OAc)_4$ to form a metal-carbene, which adopts preferentially a conformation where the dipole repulsion is minimized. The ylide intermediate **VII** reacts in the presence of DMAD to afford cycloadducts **73** and **74** in 82% and 86% yield, respectively.

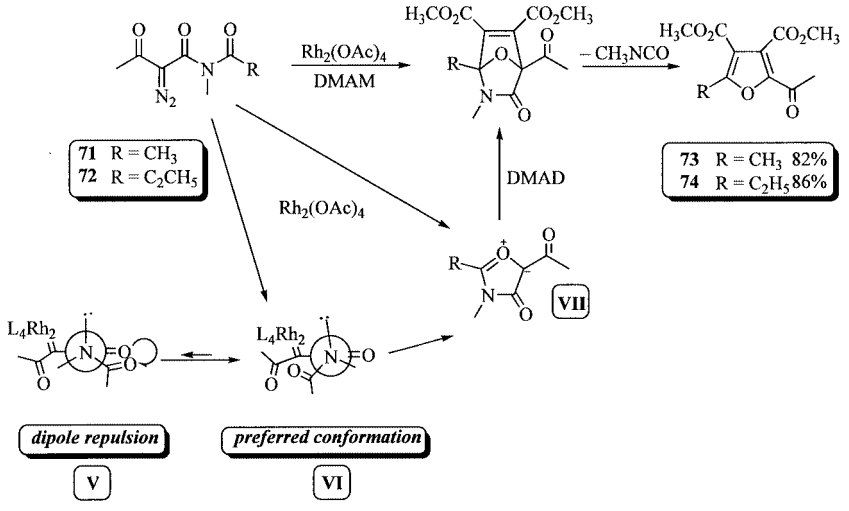
This strategy has been elegantly used in the synthesis of highly functionalised nitrogen heterocycles, such as the cycloadduct **76**, which was easily prepared by treating diazoacetamide **75** with $Rh_2(OAc)_4$ at 80 °C followed by intramolecular 1,3-dipolar cycloadition of the intermediate isomünchone **VIII** (Scheme 32).[43]



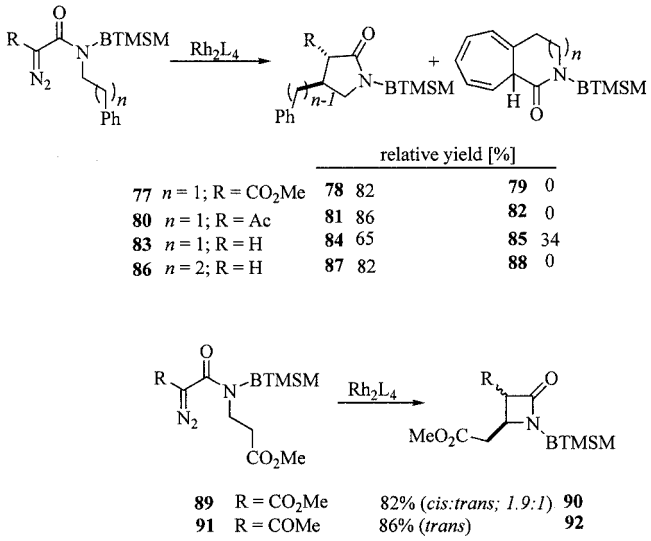
Scheme 32

The synthetic utility of the carbon−hydrogen insertion reaction with α-diazoacetamides also depends on the *N*-substituent which, in this case, has to be regarded as an *N*-protecting group. For this propose the *N*-substituent has to fulfil the requirements of being easily introduced into the molecule, of controlling the regioselectivity during the C−H insertion, and of being easily removed at the end of the synthesis.

In a recent work, the *N*,*N*-bis[(trimethylsilyl)methyl] (*N*-BTMSM) group was proposed by Wee et al. as an *N*-protecting group.[44] The evaluation of this *N*-substituent was done in the series of reactions depicted in Scheme 33. The C−H insertion reactions proceed in good overall yields of γ-lactam formation without insertion into the C−H bond of the *N*-BTMSM group. The preferential reaction at the *N*-alkyl substituent suggests a strong bias of the conformation about the N−C(O) bond, placing the *N*-BTMSM group *syn* to the sterically less demanding amide carbonyl group.

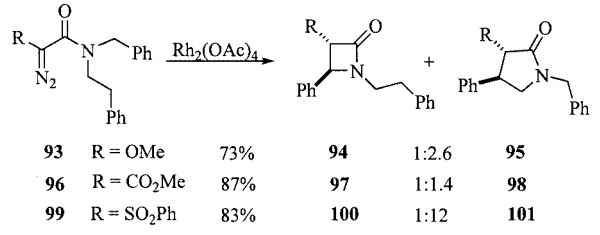


Scheme 31



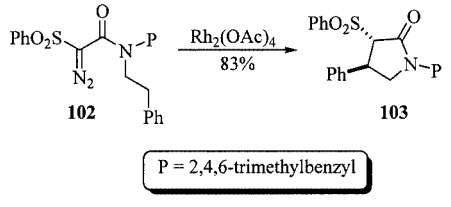
Scheme 33

Jung et al.[45] have presented a study in which *N*-benzyl moieties were used as amide protecting groups, as presented in Scheme 34. The insertion reaction was carried out on α-diazoacetamides with different α-substituents but only in the case of α-diazo-α-(phenylsulfonyl)acetamide (**99**) was a high preference for γ-lactam formation observed.



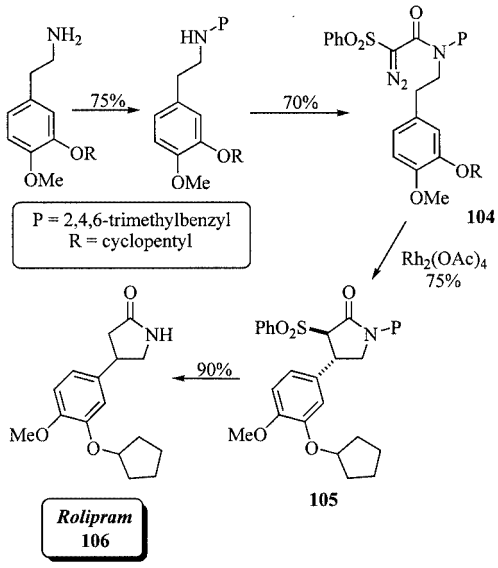
Scheme 34

To improve the regioselectivity, sterically hindered and electronically diverse benzyl groups were tested. The optimal *N*-protecting group was found to be the 2,4,6-trimethylbenzyl moiety, affording exclusively the *trans* γ-lactam **103** in 83% yield (Scheme 35).



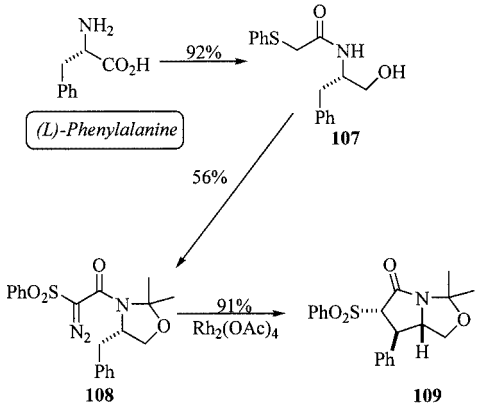
Scheme 35

This methodology was readily used in the total synthesis of racemic rolipram (**106**),[45] known to be a selective inhibitor of phosphodiesterase (PDE) type IV and an anti-inflammatory agent (Scheme 36).



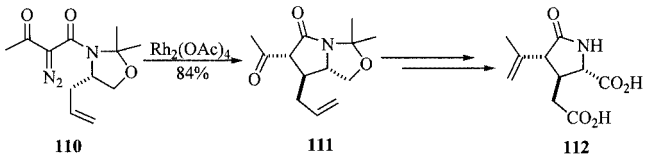
Scheme 36

The construction of α-diazoacetamides where the nitrogen atom is protected as a cyclic compound is another synthetic useful strategy in order to control the regio- and stereoselectivity of the insertion. An efficient synthesis of chiral γ-lactams was developed using α-diazo-α-(phenylsulfonyl)acetamides derived from α-amino acids.[46] As shown in Scheme 37 the precursor **108** was prepared by a ring-closure reaction with 2,2-dimethoxypropane. The regio- and stereochemical outcomes of the cyclisation were attributed to conformational preferences resulting from the presence of the *gem*-dimethyl group.



Scheme 37

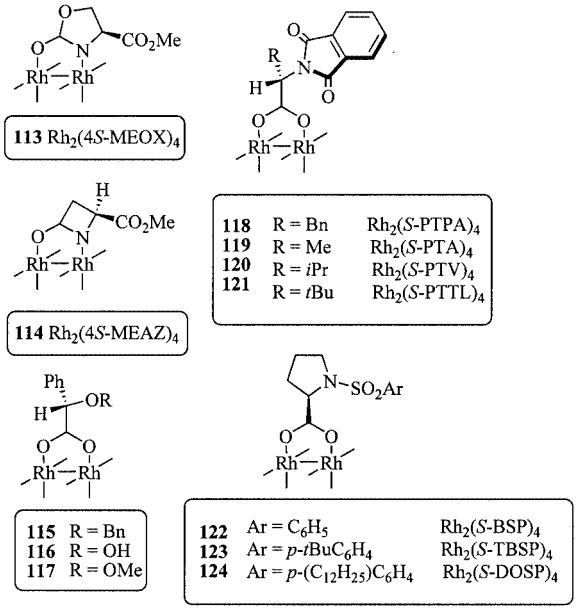
A similar strategy was used by Hashimoto et al.[47] for the preparation of the allokainic acid **112**, as shown in Scheme 38.



Scheme 38

Enantioselective C−H Insertion with α-Diazoacetamides

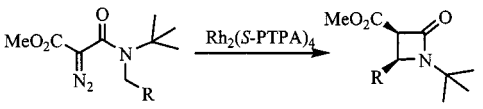
The dirhodium(II)-catalysed asymmetric C−H insertion has been recognised as a powerful procedure for the preparation of many interesting compounds.[35,48,49] This fact is favoured by the range of chiral dirhodium(II) catalysts described in the literature.[29,50−53] Some representative examples are illustrated in Scheme 39.



Scheme 39

The enantioselective version of the dirhodium(II)-catalysed C−H insertion reaction of α-diazoacetamides is still an open issue, manly because in this particular reaction all the considerations presented in the previous section have to be taken together with the additional challenge of finding the right chiral dirhodium catalyst for each family of α-diazoacetamides.

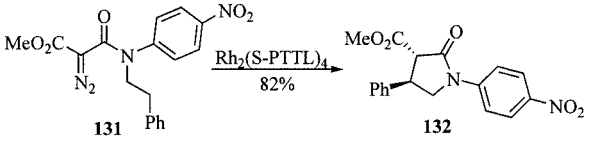
In a study conducted on the *N*-*tert*-butyl-α-diazoacetamides **125**, **127** and **129**, Hashimoto et al.[54] performed the enantioselective cyclisation using dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate] [Rh_2(*S*-PTPA)$_4$], as shown in Scheme 40. High yields of β-lactams were observed with all substituents, and the influence of the phenyl moiety resulted in the increase of the enantioselectivity. Interestingly, α-diazoacetamide **129** underwent C−H insertion reaction yielding the β-lactam instead of the expected γ-lactam product.



Entry	Substrate	R	Yield [%]	Product	*ee* [%]
1	**125**	Ph	94	**126**	74
2	**127**	CH_2CO_2Me	98	**128**	56
3	**129**	$CH_2CH_2CH_3$	97	**130**	60

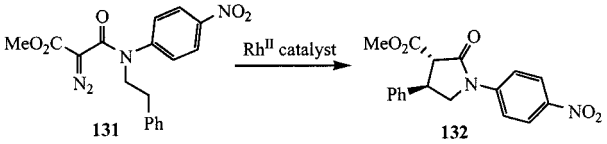
Scheme 40

In order to direct the C−H insertion reaction towards the construction of 4-substituted 2-pyrrolidinones, Hashimoto et al. conducted a series of reactions with α-(methoxycarbonyl)-α-diazoacetanilides. Inspired by earlier findings by Wee et al.,[37] Hashimoto et al.[55] discovered that the *p*-nitrophenyl group could effectively work as an *N*-protecting group, yielding the γ-lactam **132** as the major product (Scheme 41).



Scheme 41

Based on this diazo framework, several chiral dirhodium(II) carboxylates were screened, as shown in Scheme 42. Among the dirhodium(II) carboxylates incorporating *N*-phthaloyl-(*S*)-amino acids tested, Rh_2(*S*-PTTL)$_4$, derived from *tert*-leucine, proved to be the most efficient, yielding the γ-lactam **132** in 80% yield with 74% *ee* (Entry 4). The bulky catalyst Rh_2(*S*-TBSP)$_4$, developed by Davies et al., afforded the same product in 87% yield but with a reduced degree of enantioselectivity (only 6% *ee*, Entry 5).

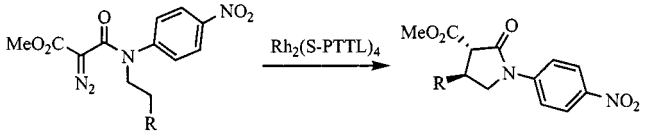


Entry	Rh^{II} catalyst	Yield [%]	*ee* [%]
1	Rh_2(*S*-PTPA)$_4$	82	47
2	Rh_2(*S*-PTA)$_4$	83	47
3	Rh_2(*S*-PTV)$_4$	82	26
4	Rh_2(*S*-PTTL)$_4$	80	74
5	Rh_2(*S*-TBSP)$_4$	87	6

Scheme 42

In order to test the effectiveness of this catalyst[55] and its influence on the enantioselectivity, the chemical properties of the insertion centre were altered (Scheme 43). A drastic

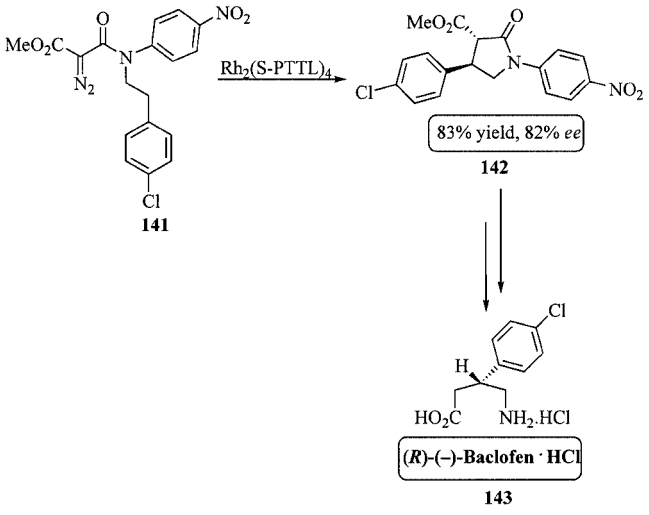
decrease in the enantioselectivity was observed when the aryl group was replaced by an alkyl group in the insertion centre. Different electron-donating or electron-withdrawing substituents on the benzene ring had little influence on the enantioselectivity, although a slight increase was observed with the *p*-$MeOC_6H_4$ group.



Entry	Substrate	R	Yield [%]	Product	*ee* [%]
1	**131**	Ph	80	**132**	74
2	**133**	*p*-$MeOC_6H_4$	72	**134**	81
3	**135**	*p*-$NO_2C_6H_4$	81	**136**	73
4	**137**	Me	82	**138**	33
5	**139**	Et	84	**140**	34

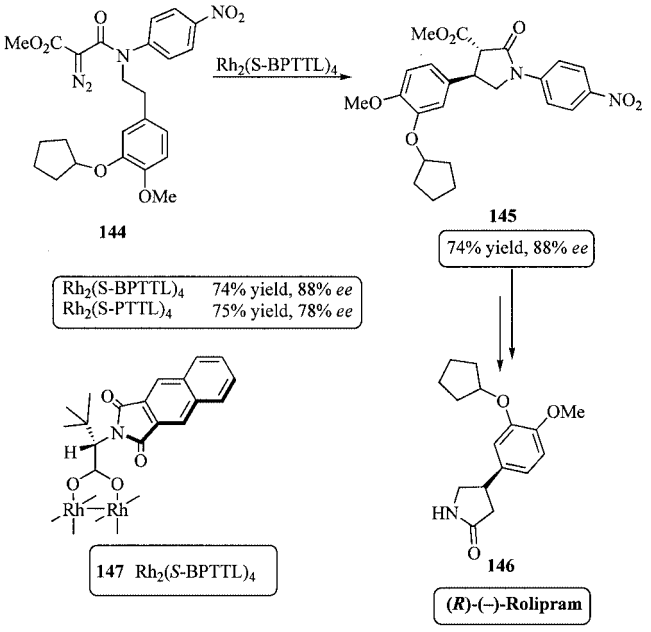
Scheme 43

The success with the cyclisation of α-diazoacetanilides with Rh_2(*S*-PTTL)$_4$ was readily applied to the synthesis of (*R*)-(−)-baclofen (**143**), which is a $GABA_B$ receptor antagonist,[55] as shown in Scheme 44.



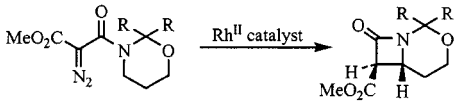
Scheme 44

The same methodology was implemented in the enantioselective synthesis of (*R*)-(−)-rolipran.[56] In this case, again the Rh_2(*S*-PTTL)$_4$ proved to be an efficient catalyst, yielding the pyrrolidinone **145**, a precursor of (*R*)-(−)-rolipran, in 75% yield and 78% *ee*. Nonetheless, the catalyst of choice for this cyclisation is Rh_2(*S*-BPTTL)$_4$ (**147**), derived from the *N*-benzene-fused phthaloyl-(*S*)-*tert*-leucine, which furnished the pyrrolidinone **145** in 74% yield and 88% *ee*, as shown in Scheme 45.



Scheme 45

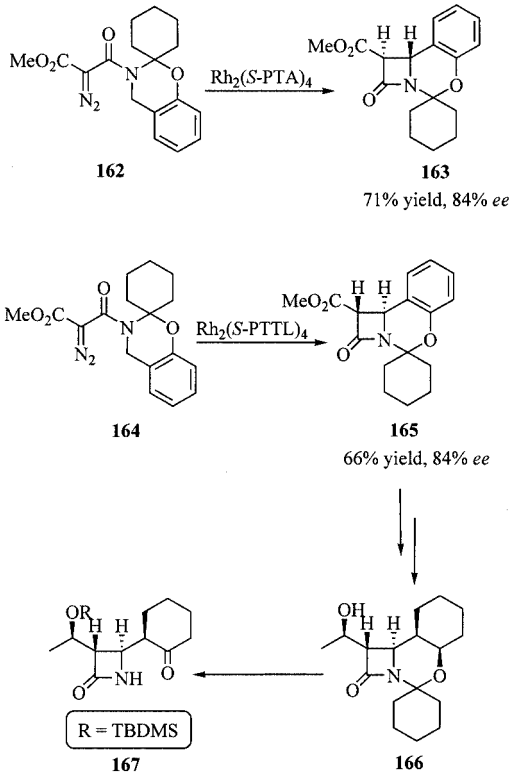
Hashimoto et al. used their findings in the enantioselective construction of 3-oxa-1-azabicyclo[4.2.0]octanes, which are key intermediates in the synthesis of 1-unsubstituted and 1β-methylcarbapenem antibiotics.[57] Following the original findings of Ponsford and Southgate,[58] who incorporated the amide nitrogen atom into a tetrahydro-1,3-oxazine system, Hashimoto et al. performed the cyclisation catalysed by dirhodium(II) carboxylates incorporating *N*-phthaloyl-(*S*)-amino acids; the results are illustrated in Scheme 46.



Entry	Substrate	R, R	Rh^{II} catalyst	Product	Yield [%]	*ee* [%]
1	**148**	-$(CH_2)_5$-	Rh_2(*S*-PTPA)$_4$	**149**	89	90
2	**150**	-$(CH_2)_5$-	Rh_2(*S*-PTV)$_4$	**151**	86	92
3	**152**	-$(CH_2)_5$-	Rh_2(*S*-PTPG)$_4$	**153**	85	92
4	**154**	-$(CH_2)_5$-	Rh_2(*S*-PTTL)$_4$	**155**	85	93
5	**156**	-$(CH_2)_5$-	Rh_2(*S*-PTA)$_4$	**157**	94	96
6	**158**	Me, Me	Rh_2(*S*-PTA)$_4$	**159**	89	93
7	**160**	Et, Et	Rh_2(*S*-PTA)$_4$	**161**	89	83

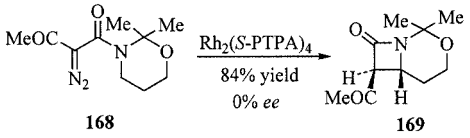
Scheme 46

The constrained framework of the α-diazoacetamide directed the insertion towards the exclusive β-lactam formation with exceptional degrees of enantioselectivities, with all catalysts tested. Nevertheless, the Rh_2(*S*-PTA)$_4$ catalyst exhibited the highest enantioselectivity (94% yield and 96% *ee*). Considering these observations, an enantioselective route to trinem antibiotics was proposed,[59] as depicted in Scheme 47.



Scheme 47

A striking evidence for the specificity of these catalysts on the cyclisation of α-diazoacetamides, with a methoxycarbonyl group as an α-substituent, was given by Hashimoto et al.[57] when the α-oxo-α-diazoacetamide analogue of **158** was subjected to the $Rh_2(S\text{-PTA})_4$-catalysed cyclisation, yielding the desired β-lactams **169**, but without any asymmetric induction, as represented in Scheme 48.

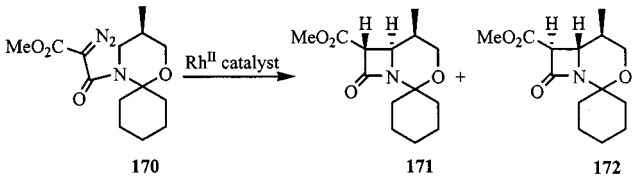


Scheme 48

Exploring the cyclisation of an optically active α-(methoxycarbonyl)-α-diazoacetamide catalysed by dirhodium(II) tetrakis[*N*-phthaloyl-(*R*)- and -(*S*)-phenylalaninate], Hashimoto et al. performed a double stereodifferentiation, providing an effective route to diastereoselection in the following system (Scheme 49).[60]

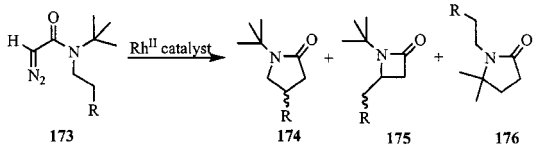
In their related studies, Doyle et al. developed an efficient procedure for the enantioselective synthesis of lactams.[61,62] Using dirhodium(II) catalysts with pyrrolidinones or oxazolidinones as bridging ligands, the lactams were obtained with moderate to high yields, as shown in Scheme 50.

The combination of an extremely reactive α-diazoacetamide with a chiral dirhodium(II) catalyst with electron-donating ligands resulted in an enhancement of the enantioselectivity. Even though different environments were tested



Entry	Rh^{II} catalyst	Yield, [%]	171/172
1	$Rh_2(OAc)_4$	75	25:75
2	$Rh_2(R\text{-PTPA})_4$	77	2:98
3	$Rh_2(S\text{- PTPA})_4$	47	85:15

Scheme 49

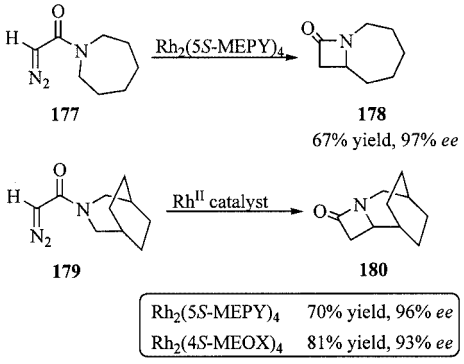


Entry	Diazo-acetamide	R	Rh^{II} catalyst	Yield [%]	174/175/176	174 *ee* [%]	175 *ee* [%]
1	**a**	Et	$Rh_2(5S\text{-MEPY})_4$	74	88:12:0	63	73
2	**a**		$Rh_2(4S\text{-BNOX})_4$	92	92:8:0	<2	0
3	**a**		$Rh_2(4S\text{-MEOX})_4$	82	91:9:0	71	80
4	**b**	*i*Pr	$Rh_2(5S\text{-MEPY})_4$	91	80:20:0	58	72
5	**b**		$Rh_2(4S\text{-MEOX})_4$	93	82:18:0	69	65
6	**c**	OEt	$Rh_2(5S\text{-MEPY})_4$	91	100:0:0	58	–
7	**c**		$Rh_2(4S\text{-MEOX})_4$	97	100:0:0	78	–
8	**d**	COOEt	$Rh_2(5R\text{-MEPY})_4$	64	2:9:89	-	44
9	**d**		$Rh_2(4S\text{-MEOX})_4$	54	2:25:73	-	46
10	**d**		$Rh_2(4S\text{-BNOX})_4$	60	12:88:<1	16	20

Scheme 50

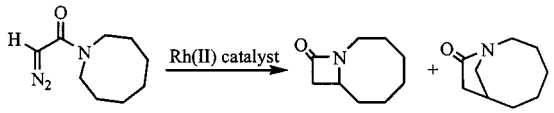
near the insertion centre, $Rh_2(4S\text{-MEOX})_4$ proved to be the catalyst of choice for this transformation.

In order to enhance the regio- and enantiocontrol, the same approach was undertaken with α-diazoacetamides prepared from cyclic amines. The cyclisation of α-diazoacetamides **177** and **179** resulted in the formation of β-lactams **178** and **180** in high yields and with an exceptional degree of enantioselectivity (Scheme 51).[63]



Scheme 51

α-Diazoacetamide **181** yielded a mixture of β- and γ-lactams as a consequence of a higher flexibility of the cyclic amine (Scheme 52). When the reaction was performed in refluxing dichloromethane, the γ-lactam was the preferred product and was formed with excellent enantiocontrol. When the reaction was carried out in refluxing dichloroethane, the relative yield of β-lactam increased, although with low enantiocontrol. On the other hand, the γ-lactam product maintained the high enantioselectivity.



181 **182** **183**

Entry	Rh^{II} catalyst	Solvent	Yield [%]	**182/183**	*ee* [%] **182**	*ee* [%] **183**
1	Rh_2(5*S*-MEPY)$_4$	CH_2Cl_2,	77	40:60	31	97
2	Rh_2(5*S*-MEPY)$_4$	$C_2H_4Cl_2$	67	67:33	30	96
3	Rh_2(4*S*-MEOX)$_4$	CH_2Cl_2,	95	26:74	15	98
4	Rh_2(4*S*-MEOX)$_4$	$C_2H_4Cl_2$	68	49:51	8	96
5	Rh_2(4*S*-MACIM)$_4$	$C_2H_4Cl_2$	81	39:61	66	96

Scheme 52

This methodology was readily applied in the synthesis of 2-deoxylonolactam. α-Diazoacetamide **185** was prepared from **184** and subjected to catalysed cyclisation, yielding the desired γ-lactam **186** and products **187** and **188** resulting from insertion of the *N*-protecting group (Scheme 53).[64]

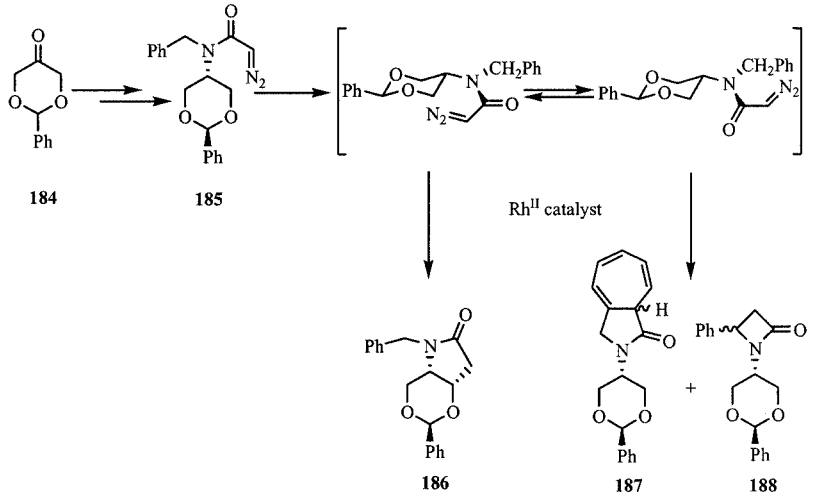
Taking advantages of the findings by Wee et al.[44] about the utility of the *N*-protecting group BTMSM, Doyle et al.[65] performed the cyclisation of α-diazoacetamide **189**, as illustrated in Scheme 54.

The bis(triethylsilyl)methyl (BTMSM) group proved to be an excellent *N*-protecting group directing the insertion towards the exclusive γ-lactam formation. The results reported in Scheme 54 underline significant differences in enantioselectivities resulting from the type and the configuration of the catalyst and also the temperature. Nevertheless, Rh_2(MEOX)$_4$ provided superior results over Rh_2(4*R*-MEOX)$_4$.

The somewhat surprising influence of the catalyst configuration on the degree of enantioselectivity was explained by Doyle et al. in terms of the relative access through competing diastereomeric conformations, as represented in Scheme 55.

The findings reported were finally applied to the enantioselective synthesis of the 2-deoxylonolactam **193**, as shown in Scheme 56.

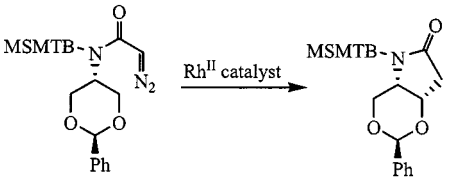
Due to the increasing success of the enantioselective C−H insertion reactions with several families of diazo compounds catalysed by chiral dirhodium(II) catalysts, chiral auxiliaries have been less used as a straightforward solution for asymmetric induction. Nevertheless, some useful applications in the field of lactam synthesis have been reported.



184 **185** **186** **187** **188**

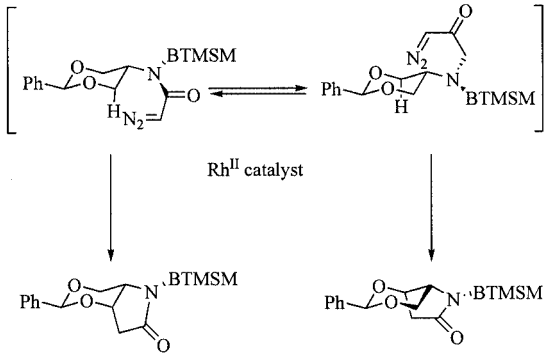
Entry	Rh^{II} catalyst	**186/187/188**	Yield [%] **186**	*ee* [%] **186**
1	$Rh_2(OAc)_4$	43:57:0	22	–
2	Rh_2(5*S*-MEPY)$_4$	95:5:0	75	85
3	Rh_2(4*S*-MEOX)$_4$	74:16:10	61	78
4	Rh_2(4*S*-IBAZ)$_4$	49:35:16	45	19
5	Rh_2(4*S*-MPPIM)$_4$	53:18:29	48	37
6	Rh_2(*S*-TBPRO)$_4$	22:78:0	9	56

Scheme 53

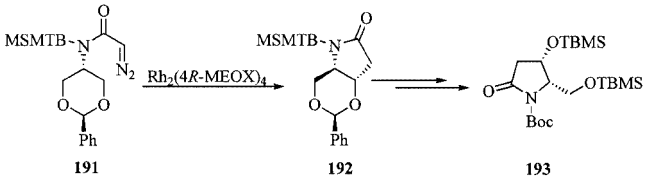


Entry	Rh^{II} catalyst	Cat. Config.	Room temperature Yield [%]	*ee* [%]	Reflux Yield [%]	*ee* [%]	Abs. config.
1	$Rh_2(MEPY)_4$	*R*	72	66	80	44	*S,S*
2		*S*	82	50	84	43	*R,R*
3	$Rh_2(MEOX)_4$	*R*	72	84	95	90	*S,S*
4		*S*	76	70	92	68	*R,R*
5	$Rh_2(MPPIM)_4$	*R*	-	-	62	1	
6		*S*	-	-	88	4	
4	$Rh_2(MEAZ)_4$	*R*	81	78	77	77	*S,S*
5		*S*	69	66	80	70	*R,R*
6	$Rh_2(PTTL)_4$	*S*	-	-	71	29	*R,R*

Scheme 54



Scheme 55

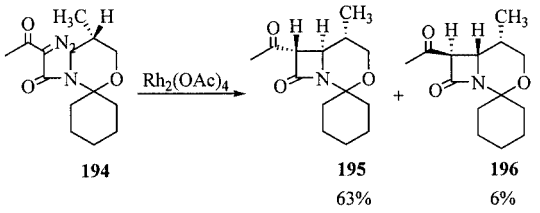


Scheme 56

Southgate et al.[66] have prepared optically active 1-methylcarbapenems starting from the α-diazoacetamide **194**, as illustrated in Scheme 57.

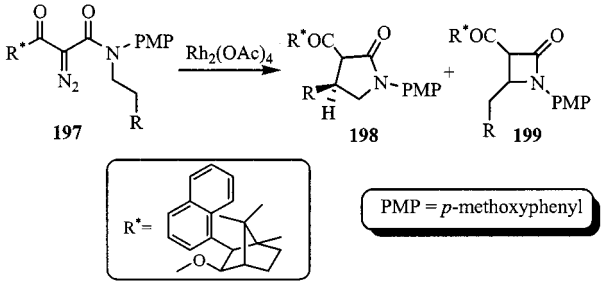
The methyl group at C-5 of the tetrahydro-1,3-oxazine ring system directs the cyclisation towards the β-lactam formation, exerting a 1,3-asymmetric induction in the insertion process.

Wee et al.[67] performed the $Rh_2(OAc)_4$ asymmetric C−H insertion reaction in chiral α-diazoanilines **197** yielding optically active 4-substituted γ-lactams **198**. A preference for



Scheme 57

γ-lactam formation was observed except in the cyclisation of α-diazoaniline **197e**, where a 1:1 mixture of both isomers was obtained. The asymmetric induction resulting from the presence of the naphthylcamphor auxiliary is evident in substrates bearing sterically demanding substituents near the insertion centre, such as cyclohexyl and phenyl moieties (Scheme 58, Entries 2 and 3). Insertion of the flexible linear *n*-hexyl *N*-substituent resulted in a modest diastereoselectivity.

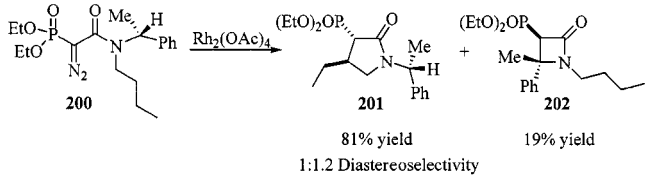


Entry	Diazoacetamide **197**	R	**199/198**	Yield [%]	*ee* [%] **198**	Config.
1	**a**	Bu	1:3.4	80	45	*R*
2	**b**	c-C_6H_{11}	1:5.0	84	98	*S*
3	**c**	Ph	1:23	98	79	*S*
4	**d**	3,4-$(MeO)_2$Ph	0:100	84	50	*S*
5	**e**	2-MeOPh	1:1	84	37	*S*
6	**f**	3-MeOPh	0:100	76	67	*S*
7	**g**	3-NO_2Ph	-	70	77	*S*

Scheme 58

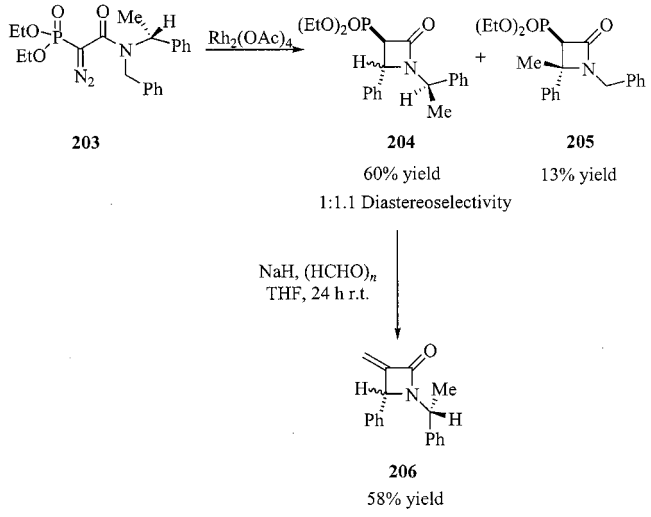
In our related studies[39a] on the diastereoselective C−H activation of α-phosphono-α-diazoacetamides, we envisioned that asymmetric induction could be effected with the use of a chiral *N*-substituent. The chiral α-phosphono-α-diazoacetamide **200** underwent $Rh_2(OAc)_4$-catalysed cyclisation, as shown in Scheme 59. The chiral *N*-substituent directs the insertion towards γ-lactam formation and only 19% of the β-lactam resulting from insertion of the chiral auxiliary was observed. Nonetheless, almost no asymmetric induction occurred, probably due to the conformation adopted by the intermediate, in which the larger *N*-substituent is placed *syn* to the sterically less demanding amide car-

bonyl group, distanced from the reactive metal-carbene centre.



Scheme 59

Although the *N*-substituent is important in determining the stereoselectivity of the β-lactam formation, little asymmetric induction was again observed in the cyclisation of α-phosphono-α-diazoacetamide **203**, as illustrated in Scheme 60.



Scheme 60

General Remarks

As part of the exciting field of activation of unreactive C−H bonds, the dirhodium(II)-catalysed cyclisation of α-diazoacetamides is a synthetically powerful methodology for the preparation of cyclic compounds such as β- and γ-lactams. Moreover, a knowledge of the particular features of this reaction allows the rational design of substrates which, upon C−H insertion reaction, will yield extremely useful heterocyclic compounds. The dirhodium(II)-catalysed cyclisation of α-diazoacetamides is a relatively well-understood reaction; nevertheless, the development of new dirhodium(II) catalysts and the construction of α-diazoacetamides with new α-substituents and new *N*-protecting groups opens up new areas of research. The enantioselective preparation of β- and γ-lactams with this methodology is still a challenge with the design of efficient chiral dirhodium(II) catalysts and their immobilization and reuse as the main goal.

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