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Substrate and Catalyst Effects in C−H insertion reactions of α-Diazoacetamides

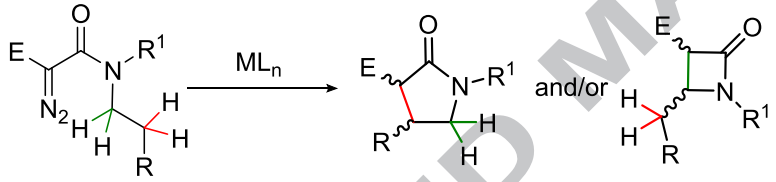
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Graphical Abstract



Abstract

Intramolecular C–H insertion reactions of α-diazocarbonyl compounds typically proceed with preferential five-membered ring formation. However, the presence of a heteroatom such as nitrogen can activate an adjacent C–H site toward insertion resulting in regiocontrol issues. In the case of α-diazoacetamide derivatives, both β- and γ-lactam products are possible owing to this activating effect. Both β- and γ-lactam products are powerful synthetic building blocks in the area of organic synthesis, as well as a common scaffold in a range of natural and pharmaceutical products and therefore C–H insertion reactions to form such compounds are attractive processes.

Keywords: C-H insertion; diazoacetamides; catalyst effects; ß-lactams; gamma-lactams

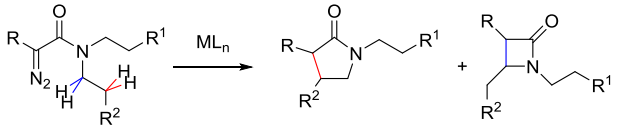
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Introduction

α-Diazocarbonyl compounds act as precursors to carbenes, neutral species which possess a divalent carbon.[1–3] Formation of these species can occur through decomposition of α-diazocarbonyl precursors *via* thermolytic or photolytic means, and the resulting carbenes can partake in a number of reactions; however, these processes tend to be unselective and difficult to control and, as a result, of little synthetic value.[1,2] Complexation of the α-diazocarbonyl substrates with transition metal catalysts leads to formation of metal-carbenoids which retain the synthetic versatility of free carbenes, while also exhibiting enhanced chemo-, regio- and stereoselectivity.

For a given substrate, several reaction pathways may be available, and the chemoselectivity of such processes is dependent on the nature of both the substrate and the catalyst. The C–H insertion process is an important reaction at it functionalises unreactive C–H bonds resulting in formation of a new C–C bond.[4–8] The intramolecular version of this transformation can, depending on the substrates, lead to the formation of carbocyclic and heterocyclic compounds. The focus of this review will be intramolecular C–H insertion reactions of α-diazoacetamides which allow formation of lactams through C–H functionalisation. The area of rhodium(II)-catalysed intramolecular C–H insertion reactions of α-diazoacetamides was reviewed by Afonso and co-workers in 2004,[9] and thus this review will focus predominantly on developments since 2004 with inclusion of only the most significant examples prior to 2004. A very recent review has covered the selective synthesis of β-lactams via C–H insertion reactions.[10]

A major challenge for the synthetic development of C–H insertion reactions remains control of insertion chemo- and/or regioselectivity.[1,4,6,11–13] Taber's seminal work in the 1980s showed intramolecular C–H insertion reactions generally proceed with preferential formation of five-membered carbocycles.[14–19] However, addition of a heteroatom such as nitrogen to the α-diazocarbonyl substrate can facilitate four-membered ring formation owing to the activating effect of the heteroatom (Scheme 1). Thus competitive 1,4- and 1,5-C–H insertion can be observed for these types of compounds, although 1,5-C–H insertion is typically observed as the major pathway.[4]



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Scheme 1. 1,5- and 1,4-C–H insertion

This review will be divided into two sections; section one will deal with the impact of the substrate structure on the C–H insertion reaction, while the second section will focus on the catalyst effect and ultimately the importance of catalyst choice for these reactions.

The impact of substrate structure

Structural aspects of the reacting substrate can dramatically affect the reactivity of the diazo compound, but also various features of the reaction including efficiency, chemo-, regio- and diastereoselectivity. Thus careful design of the α-diazoacetamide framework is imperative in an effort to manipulate and control the ensuing C–H insertion reaction. Features of the α-diazoacetamides which control the reaction outcome in terms of substrate effect include (1) the amide group (2) the α-substituent (Figure 1).

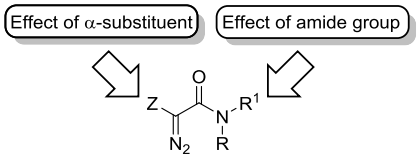


Figure 1. Aspects of α-diazoacetamide framework which can affect reaction outcome

Influence of α-substituent

α-Diazocarbonyl compounds can be classified according to their functionality alpha to the diazo moiety. Substrates which bear only one electron-withdrawing group such as a keto, ester or amide group α to the diazo group are precursors to acceptor-substituted metal-carbenoids (Figure 2).[4] In this case the α-substituent is a hydrogen atom.

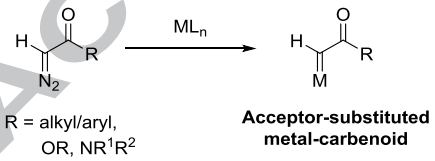


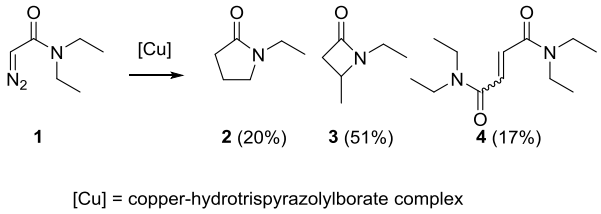
Figure 2. Formation of acceptor-substituted metal-carbenoids

These substrates tend to be more reactive substrates and require mild conditions in order to undergo reaction. However, this increased reactivity can lead to competing side reactions such as homocoupling.[4]

This has been effectively demonstrated by Perez and co-workers in their copper-catalysed C–H insertion reactions of acceptor-type *N*-alkyl-α-diazoacetamides.[20] In copper-catalysed

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reactions of 2-diazo-*N*,*N*-diethylacetamide **1** (Scheme 2), the homocoupling product **4** was typically observed as the major product of the reaction. The reaction was repeated using rhodium(II) acetate and in this case preferential formation of γ-lactam **2** was observed; however, **4** was still observed as a minor product. Perez also investigated reactions of 2-diazo-*N*,*N*-diisopropylacetamide and found C–H insertion was observed as the major reaction pathway for copper and rhodium catalysts.[20] However, in some instances, homocoupling was observed as a minor reaction pathway. Interestingly, homocoupling is not an issue for acceptor-substituted α-diazoacetamides bearing cyclic amido diazo substrates. In these cases, reactions are observed to proceed with high efficiencies for C–H insertion.[21]



Scheme 2. Copper-catalysed reaction of 2-diazo-N,N-diethylacetamide

Introduction of electron-donating groups (or donor groups) such as aryl or vinyl groups as α-substituents can affect the reactivity by reducing the electrophilicity of the derived carbene and thus offering greater selectivity (Figure 3).[4,22] Doyle and co-workers recently reported highly regio-, diastereo- and enantioselective reactions of donor/acceptor-substituted enoldiazoacetamides to afford β-lactams.[23]

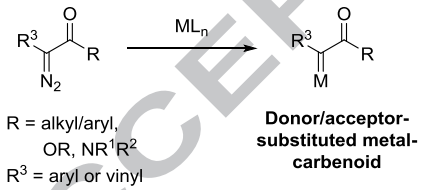


Figure 3. Formation of donor/acceptor-substituted metal-carbenoids

The third class of diazo compounds, which are precursors to acceptor/acceptor-substituted metal-carbenoids, are those which possess two electron-withdrawing groups alpha to the diazo group (Figure 4). As a result, the diazo compounds are highly stable, and require more forcing reaction conditions than the more reactive acceptor and donor/acceptor-substituted compounds.[4,6]

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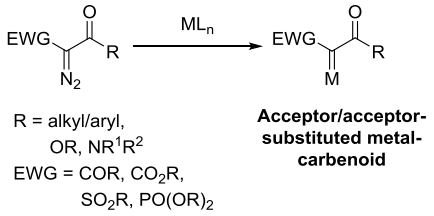
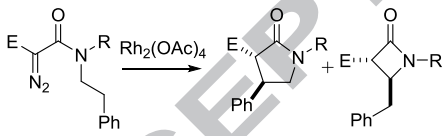


Figure 4. Formation of acceptor/acceptor-substituted metal-carbenoids

The electron-withdrawing nature of the α-substituent can also affect the ensuing reaction (Table 1).[9] The more electron-withdrawing ketone group as the α-substituent can result in less selective reactions (Table 1, entry1), while higher selectivity can be achieved by less electron-withdrawing groups such as ester or sulfonyl groups (Table 1, entries 2–4).[9] This difference in selectivity may be attributed to the reactivity of the resulting metal-carbenoids which, owing to the increased electrophilicity of the carbene carbon, are less stabilised than metal-carbenoids derived from diazo substrates containing less electron-withdrawing groups. In the last ten to fifteen years, α-diazoacetamides bearing α-substituents such as sulfonyl and phosphoryl groups, in particular have demonstrated particular efficiency and selectivity in formation of γ-lactams *via* C–H insertion.[24–32]

Table 1. Comparison of effect of different α-substituents on the regioselectivity of C–H insertion reactions of α-diazoacetamides)

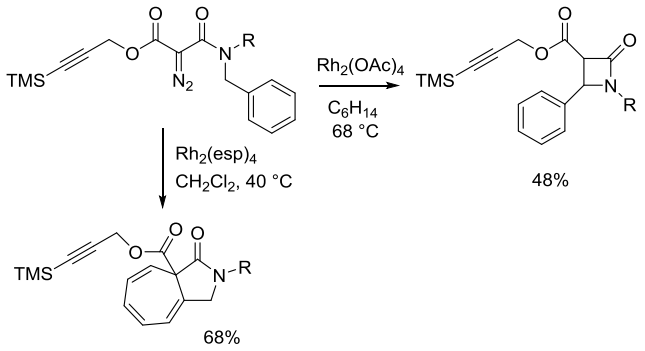


Entry	E	R	Yield	β/γ
1	$COCH_3$	^{t}Bu	94	49/51[33]
2	CO_2CH_3	*p*-CH_3O-C_6H_4	76	1/99[34]
3	$PhSO_2$	^{t}Bu	95	-/95[24]
4	$PO(OEt)_2$	^{t}Bu	95	-/95[30]

Inclusion of remote functionality in acceptor/acceptor-substituted α-diazoacetamides can result in chemoselectivity issues which must be carefully considered. Padwa and co-workers

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described rhodium(II) catalysed reactions of β-amido-α-diazo esters bearing *N*-benzyl groups and ester groups possessing alkyne bonds (Scheme 3).[35] Unsurprisingly, the chemoselectivity was affected by the ligands within the catalyst, and the *N*-substituent, however, it was also discovered that solvent choice affects the chemoselectivity of the reaction.

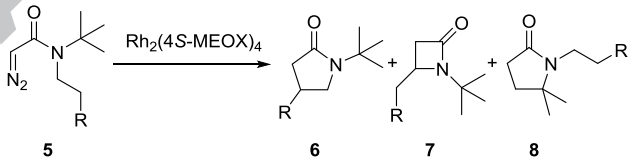


Scheme 3.

Influence of amido group

Typically the regioselectivity of intramolecular C–H insertion reactions of α-diazoacetamides is heavily influenced by the amide group.[4,7,13,36,37] Alkyl amide groups are observed to generally undergo C–H insertion to give γ-lactams,[13] as shown in Table 2. As demonstrated by Doyle and co-workers, placement of an oxygen α to the 1,5-insertion site can further activate this position resulting in complete suppression of the other C–H insertion pathways (Table 2, entry 2).[36] However, placement of an electron-withdrawing groups such as an ester group at the γ-position of the *N*-alkyl chain will deactivate this site resulting in formation of other regioisomers which would typically be unfavourable (Table 2, entries 3).[36]

Table 2. Effect of different substituents at γ-CH site in Rh(II) catalysed reactions of α-diazoacetamides

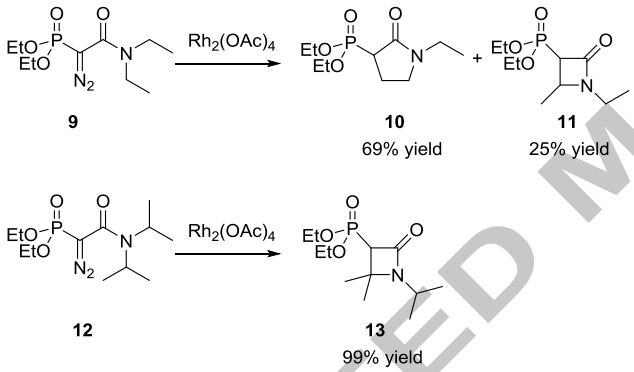


Entry	R	Ratio of **6** : **7**: **8**
1	C_2H_5	91:9:0

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2	OC_2H_5	100:0:0
3	$CO_2C_2H_5$	2:25:73

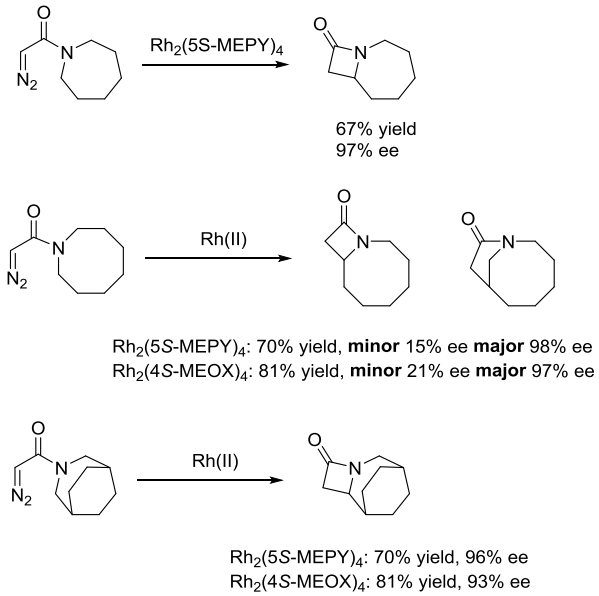
Additionally, substitution along the *N*-alkyl chain can also enhance regioselectivity.[30,38] As observed in Scheme 4, the rhodium(II) acetate catalysed reaction of 2-diazo-*N*,*N*-diethyl-2-(diethoxyphosphoryl)acetamide **9** proceeds with moderate regiocontrol, with the γ-lactam **10** observed as the major product.[30] In contrast, placement of a methyl group at the α-CH position results in a methine CH bond at that position (Scheme 4). As a result, 1,4-C–H insertion to form **13** was observed almost exclusively for 2-diazo-*N*,*N*-diisopropyl-2-(diethoxyphosphoryl)acetamide **12** (Scheme 4).[30]



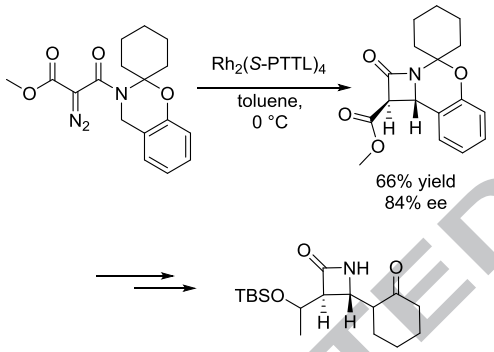
Scheme 4.

Insertion reactions employing diazo substrates bearing cyclic amides have also been reported.[25,28,39,40] In general, the outcome of the reaction is directly related to the ring size of the amide as well as substitution on the amide group. Smaller ring sizes such as seven-membered rings and conformationally strained cyclic systems are observed to undergo 1,4-C–H insertion reactions almost exclusively while larger rings such as eight membered rings can undergo both 1,4- and 1,5-insertion (Scheme 5).[21] Use of substituted cyclic amide groups such as *cis*-2,6-dimethyl piperidine[12] or tetrahydro-1,3-oxazine systems[41–43] as the amide moieties resulted in preferential 1,4-C–H insertion. The latter group was subsequently used as the main step in the synthesis of a key intermediate in the synthesis of trinem antibiotics (Scheme 6).[44]

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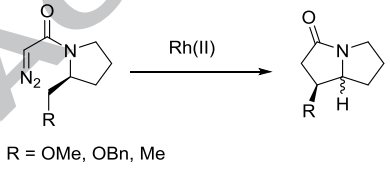


Scheme 5.



Scheme 6.

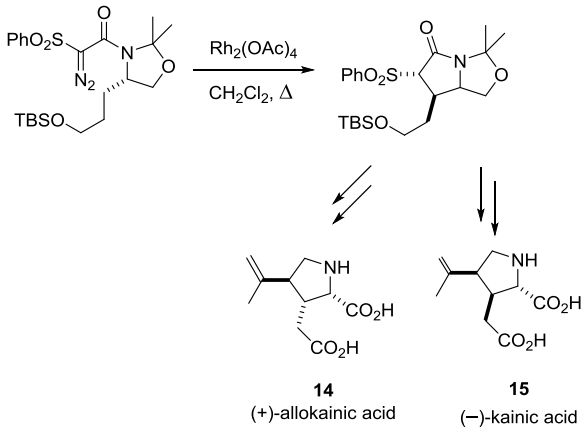
The addition of longer alkyl chains along the cyclic amide provide further sites for C–H insertion, and can allow formation of γ-lactam products which would otherwise be disfavoured for smaller cyclic amides (Scheme 7).[25,28,39,40]



Scheme 7.

This strategy was used as key step in the synthesis of (−)-heliotridane,[40] (−)-pseudoheliotridane,[40] and more recently kainic acids such as (+)-allokainic acid **14** and (–)-α-kainic acid **15** (Scheme 8).[28]

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Scheme 8.

As discussed by Doyle and co-workers, the presence of different groups on the nitrogen atom of the amide moiety within the α-diazoacetamide substrate greatly affects the chemoselectivity of the resultant reaction.[9,45] The *N*-substituents typically orient themselves such that the largest substituent is as far away in space as possible from the carbene so as to avoid unfavourable steric interactions, while the smaller substituent is in close proximity to the carbene carbon and will undergo preferential insertion (Figure 5).

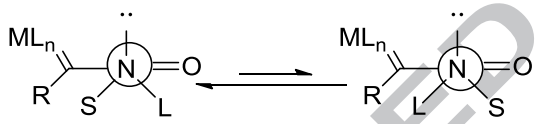
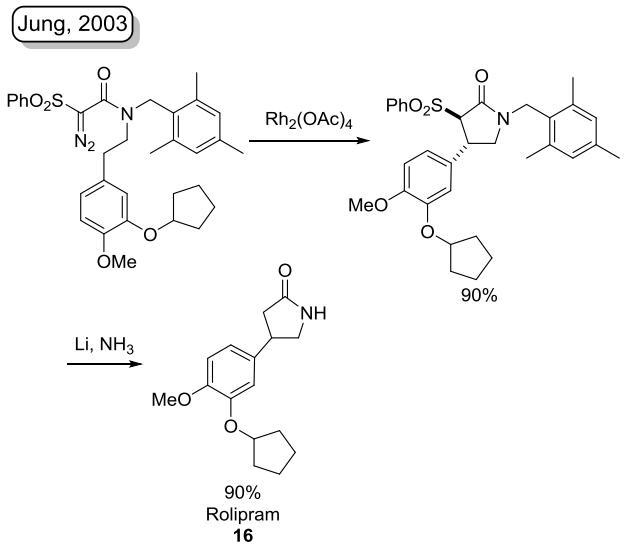


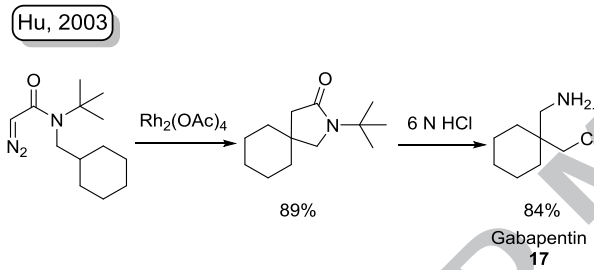
Figure 5 Conformational effects of different N-substituents

The major outcome of this conformational effect is that the reactions can be manipulated so that insertion occurs at a specific substituent. Use of bulky *N*-substituents or groups which do not allow or disfavour C–H insertion can facilitate insertion into the other *N*-substituent.[24,26,36,37,46–50] These groups include *tert*-butyl,[24,36,51] *N*,*N*-bis[(trimethylsilyl)-methyl],[48] 2,4,6-trimethylbenzyl,[26] and *para*-nitrophenyl.[52] This route has been used by a number of groups as a key step in the synthesis of biologically active or potentially active compounds.[26,49–55] A select number of examples are presented in Schemes 9–11, and include the synthesis of the selective phosphodiesterase-4 inhibitor rolipram **16** (Scheme 9),[26] and the syntheses of γ-amino-butyric acid analogues gabapentin **17** (Scheme 10),[54] GABOB **18**, and baclofen **19** (Scheme 11).[51]

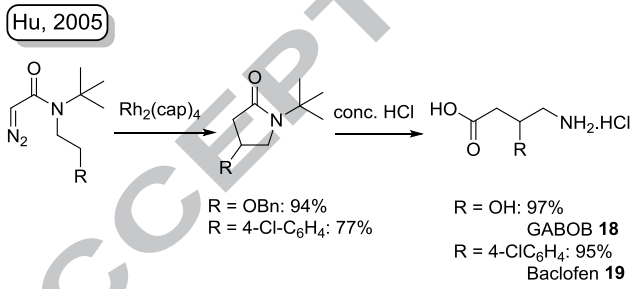
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Scheme 9



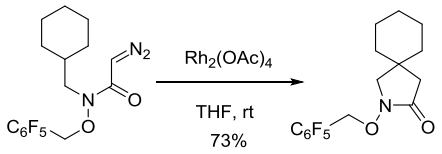
Scheme 10



Scheme 11

Wolan has demonstrated the efficacy of the *N*-pentafluorobenzyloxy group as a nitrogen-blocking group in the synthesis of *N*-(2,3,4,5,6-pentafluorobenzyloxy)-γ-lactams by rhodium-catalyzed cyclisation of diazo amides (Scheme 12). A range of lactams were obtained, with up to 91% yield and 88% ee. The The N–O bond in the product can be reductively cleaved with samarium iodide.[56]

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Scheme 12

The impact of the catalyst complex

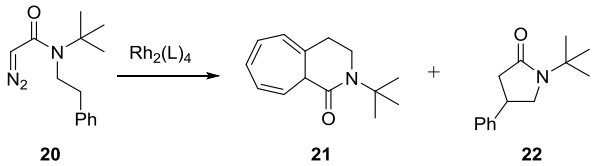
Rhodium(II) catalysts

The majority of work carried out in the area of transition metal-catalysed intramolecular C–H insertion reactions of α-diazoacetamides has employed rhodium(II) catalysts.[9] Both achiral and chiral rhodium(II) catalysts have been applied to this process.[57] In general, variation of the ligands within the rhodium(II) complex can have a dramatic effect on the chemoselectivity of the reaction.[4,7–9,13,58] In practice, a delicate balance must be struck between the initial electrophilicity of the diazo carbon, and in turn the carbene carbon, and the electrophilicity of the resulting carbenoid. While the electrophilicity of the carbene is determined by the groups adjacent to the diazo carbon, the electrophilicity of the resulting carbenoid is dependent upon a combination of catalyst and substrate effects, and can be tuned by variation of the ligands within the catalyst complex. If the carbenoid is too electrophilic it will be very reactive and thus less selective. Conversely, if the carbenoid is not electrophilic enough it may be too unreactive to undergo reaction. Substrates which bear electrophilic carbenes such as acceptor/acceptor type may be stabilised through use of rhodium(II) catalysts which bear electron-donating ligands, such as acetamide,[9] which will stabilise the carbenoid complex through increased back-donation. In contrast, less electrophilic substrates may be made more reactive through use of rhodium(II) catalysts which possess electron-withdrawing ligands, such as perfluorobutyrate.

The selectivity of acceptor-type diazo substrates such as **20** which can suffer from competing reaction pathways can be tuned depending on the ligand in the rhodium complex.[33] Padwa and Doyle demonstrated that for substrate **20**, the highest selectivity toward formation of the γ-lactam **22** was observed with rhodium caprolactamate (Table 3, entry 3**)**. In contrast, rhodium perfluorobutyrate demonstrated the highest selectivity toward aromatic addition (Table 3**,** entry 2).

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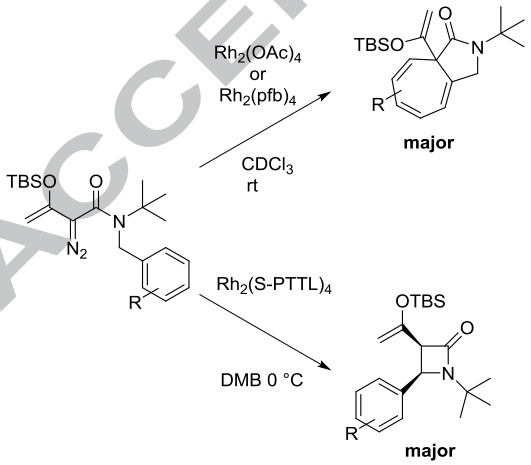
*Table 3 Effect of ligands in rhodium complex on chemoselectivity of reactions of **20***



20 **21** **22**

Entry	L	Product ratio **21**: **22**
1	OAc	68:32
2	pfb	95:5
3	cap	3:97
4	acam	23:77

Ligand choice has been demonstrated to have a dramatic effect on the chemoselectivity of reactions of donor-acceptor and acceptor-acceptor type diazo compounds.[23,59,60] In reactions of enoldiazoacetamides (donor/acceptor type diazo substrates), preferential C–H insertion was observed in the case of Hashimoto's Rh_2(*S*-PTTL)$_4$ catalyst (Scheme 13), while use of $Rh_2(OAc)_4$ or $Rh_2(pfb)_4$ resulted in aromatic addition as the preferred reaction pathway.[23]



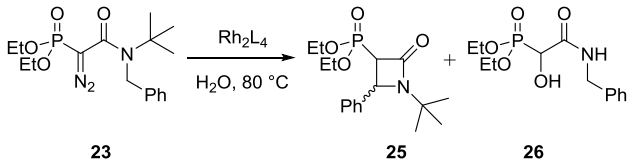
Scheme 13

Afonso and co-workers reported dramatic ligand effects in rhodium-catalysed C–H insertion reactions of β-amido-α-diazophosphonates (acceptor/acceptor type diazo substrates).[60] In his

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study, reactions were conducted using water as the reaction solvent, and as a result O–H insertion was observed as a competitive reaction pathway (Table 4 and Table 5). In the case of substrate **23** (Table 4), higher levels of C–H insertion were observed with rhodium catalysts bearing perflurorobutyrate or octanoate ligands (Table 4, entries 2 and 3). A similar result was observed in the case of substrate **24** (Table 5).

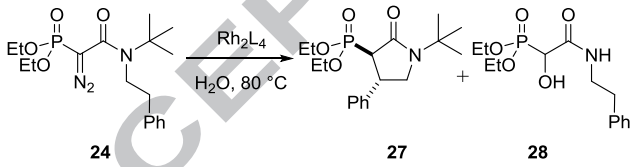
Table 4 Effect of ligands in rhodium(II) complex on competitive 1,4-C–H insertion vs. intermolecular O–H insertion



23 **25** **26**

Entry	Ligand	Yield (%) **25**	Yield (%) **26**
1	OAc	57	27
2	pfb	84	-
3	oct	97	-

Table 5 Effect of ligands in rhodium(II) complex on competitive 1,5-C–H insertion vs. intermolecular O–H insertion



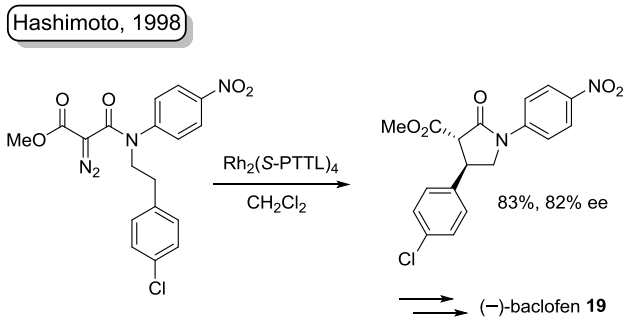
24 **27** **28**

Entry	Ligand	Ratio **27**:**28**
1	OAc	1:2.4
2	pfb	1:0.1
3	oct	1:0.0

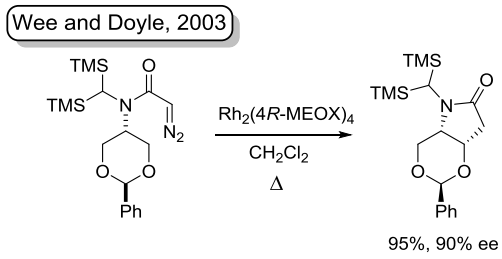
Application of chiral rhodium catalysts to intramolecular C–H insertion reactions of α-

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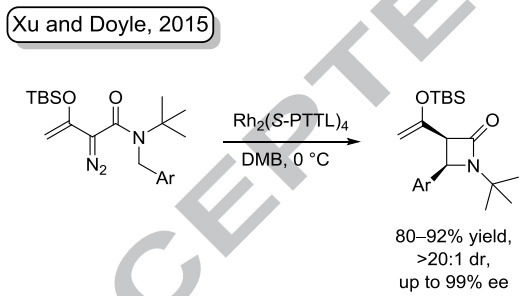
diazoacetamides has resulted in formation of both γ- and β-lactams in moderate to high enantiopurities.[4,7,8,12,21,23,42,48,49,52,53,55,60,61] A number of enantioselective rhodium(II) catalysed C–H insertion reactions of α-diazoacetamides are highlighted in Schemes 14–16.



Scheme 14



Scheme 15



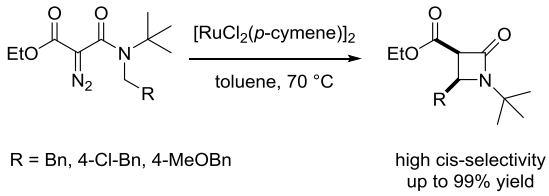
Scheme 16

Other catalysts

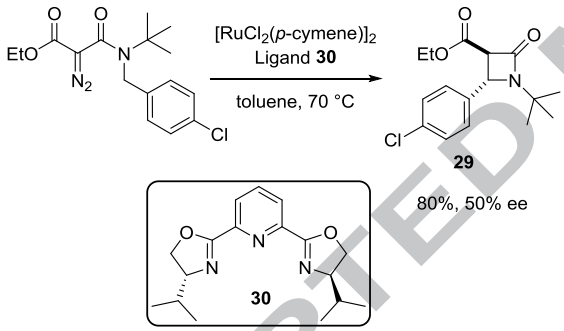
Recently ruthenium(II) catalysts have been reported as effective catalysts for the intramolecular C–H insertion reaction of acceptor type and acceptor/accepter type diazo substrates.[38,62–64] In 2006, Maas and co-workers demonstrated that in the case of acceptor type compounds, the efficiency and chemoselectivity of the reactions was strongly dependent on the amide moiety, and typically rhodium(II) catalysts were observed to demonstrate higher selectivity than their ruthenium(II) counterparts.[38]

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Che and co-workers reported use of ruthenium(II) dichloro(*p*-cymeme) in reactions of β-amido-α-diazoesters (Scheme 17).[62] High yields and high *cis*-selectivity were observed in C–H insertion reactions employing *N*-benzyl-*N*-*tert*-butyl substrates. An enantioselective version of the reactions was also carried out and the β-lactam product **29** was isolated in high yield and moderate enantiopurity (Scheme 18). Interestingly, in this reaction, *trans*-selectivity was observed, although Doyle has suggested that this selectivity is due to isomerisation of the *cis*-β-lactam.[23]



Scheme 17



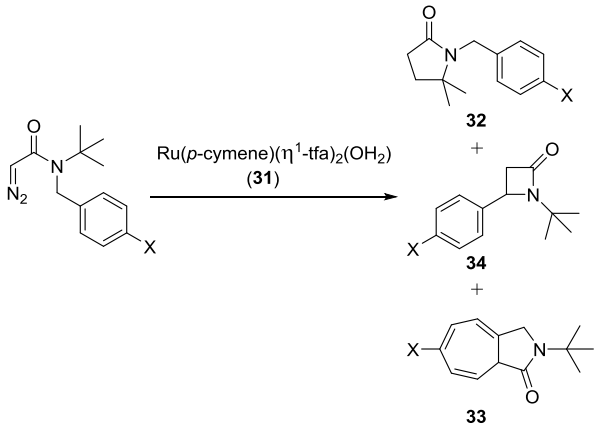
Scheme 18

Later work by Che involved use of acceptor-substituted *N*-benzyl-*N*-*tert*-butyl diazo substrates (Table 6). In this study, use of a ruthenium carboxylate catalyst **31** was found to result in highly selective reactions. However, use of catalyst **31** also resulted in a switch in the expected chemoselectivity of the reaction. It was observed that insertion into a methyl C–H bond was generally preferred to insertion into a methylene C–H bond which also happens to be a benzylic site (Table 6).[64] For substrates possessing a hydrogen or electron-withdrawing group in the *para*-position of the aromatic ring of the benzyl group, γ-lactam **32** was observed as the only product of the reaction (Table 6, entries 1–4). In the case of a methyl group in the *para*-position of the aromatic ring in the benzyl group, lower chemoselectivity was observed and the aromatic cycloaddition product **33** was observed as a minor component of the reaction mixture (Table 6, entry 5). The presence of a methoxy group in the *para*-position in the aromatic ring in the benzyl group resulted in much lower

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chemoselectivity (Table 6, entry 6). This study highlights that the chemoselectivity of the C–H insertion reactions of α-diazoacetamides can be affected by a combination of substrate and catalyst effects.

Table 6 Ruthenium(II) catalysed C–H insertion reactions of acceptor type α-diazoacetamides



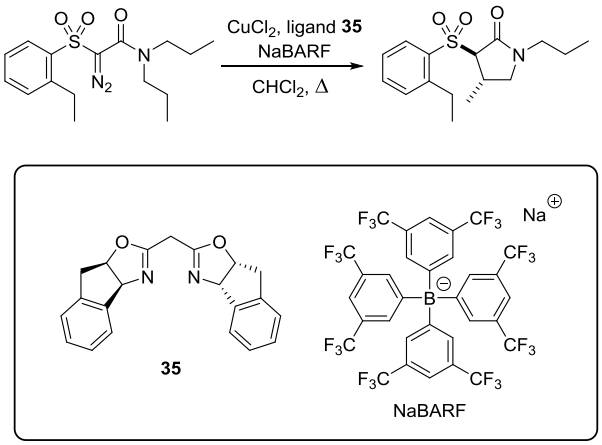
Entry	X	Yield	Ratio **32: 34: 33**
1	H	98	100:0:0
2	F	98	100:0:0
3	Cl	97	100:0:0
4	Br	96	100:0:0
5	Me	95	82:0:18
6	OMe	95	39:43:18

Che and co-workers have also demonstrated that rhodium(III) porphyrin complexes are catalytically active for intramolecular carbene C–H insertions of α-diazoacetamides, giving rise to cis-β-lactams or trans-γ-lactams in yields up to 99% with regioselectivities up to 100% and cis/trans ratios up to 83:17 for β-lactams.[65]

Limited examples exist whereby copper catalysts have been successfully applied to this transformation.[20,29] Maguire and co-workers recently reported the first chiral copper-catalysed C–H insertion reactions of α-diazoacetamides (Scheme 19).[29] In this case, *trans*-γ-

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lactams were isolated in moderate yields in enantiomeric excesses up to 82% ee.



Scheme 19

Solvent Effects

While the catalyst complex can affect the reaction outcome, the reaction medium can also have an effect on the ensuing reaction. In general, C–H insertion reactions of α-diazoacetamides tend to be carried out in an appropriate solvent which allows solubility of substrate and catalyst unless the catalyst is immobilised. To date, while C–H insertion reactions employing immobilised catalysts have been reported, so far these studies have not extended to reactions employing α-diazoacetamides. Highly unreactive substrates may require higher boiling point solvents to induce reaction. Thus, solvent choice must also be considered when carrying out these reactions. In recent times, attempts have been made by Afonso and co-workers to carry out intramolecular C–H insertion reactions of α-diazoacetamides using greener methods, such as the use of ionic liquids,[31] water,[60,61] and supercritical carbon dioxide as the reaction medium.[66] Padwa and co-workers have also demonstrated the importance of solvent choice in rhodium(II) catalysed reactions of β-amido-α-diazo esters bearing alkyne functionality within the ester moiety (see Scheme 3).[35]

Conclusions

Clearly, the C–H insertion reactions of α-diazoacetamides are synthetically powerful transformations which have been exploited in the synthesis of lactams. In contrast to C–H insertion reactions leading to carbocycles, the influence of the nitrogen leads to complexity in terms of regiocontrol; the C–H bond adjacent to the nitrogen atom is activated towards

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insertion thereby enabling four-membered ring formation to compete with the standard five-membered ring formation. The conformational features of the acetamide group (Figure 5) also impact significantly on the outcome of the insertion reaction. It is evident that both substrate and catalyst effects are important and an optimum outcome, in terms of both efficiency and enantiocontrol, can be achieved only by careful consideration of both. Since thus far there is no universally applicable catalyst, applications to synthesis of complex target molecules must be considered on a case-by-case basis. Access to enantioenriched β- and γ-lactams is important due to the prevalence of these compounds as direct targets and synthetic intermediates. While rhodium(II) catalysts has dominated the field, ruthenium(II) and copper(II) catalysts have recently emerged as promising catalysts; there is still considerable scope for development of new catalysts, especially those with broad applicability, and further applications of this powerful transformation.

List of carboxylate ligand abbreviations

acam	acetamidate
cap	caprolactamate
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionate
4(*S*)-MACIM	methyl 1-acetyl-2-oxoimidazolidine-4(*S*)-carboxylate
4(*S*)-MEOX	methyl 2-oxazolidone-4(*S*)-carboxylate
5(*S*)-MEPY	methyl 2-pyrrolidone-5(*S*)-carboxylate
oct	octanoate
pfb	perfluorobutyrate
PTTL	*N*-phthaloyl-*tert*-leucinate

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Highlights

- Metal-carbene C–H insertion of diazoacetamides leads to the formation of lactams
- Substrate and catalyst effects determine reactivity and selectivity
- Excellent chemo-, regio-, and stereocontrol can be achieved

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