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Mini Review

Recent progress in asymmetric intermolecular C–H activation by rhodium carbenoid intermediates

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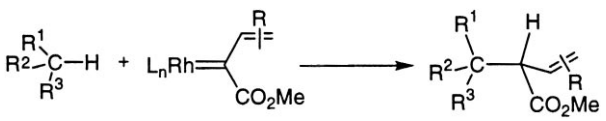
Abstract

Intermolecular C–H insertion with rhodium carbenoid intermediates is a very promising method for C–H activation. By using carbenoids derived from vinyl and phenyl diazoacetates, highly selective C–H insertions can be achieved. High asymmetric induction is obtained when dirhodium tetraprolinates (**24**–**27**) are used as catalysts. Remarkably, with certain substrates, excellent diastereocontrol is also possible.

Keywords: C–H activation; Rhodium carbenoid; Chiral catalysts

1. Introduction

The development of novel organometallic reagents for functionalization of unactivated C–H bonds has been extensively studied over the last 20 years [1–3]. In this review, our progress in achieving a practical and catalytic method for asymmetric intermolecular C–H activation using rhodium–carbenoid intermediates will be described (Eq. (1)). The first portion of the review will give a brief overview of the traditional organometallic methods to achieve C–H activation. The inherent advantages of the carbenoid method will be discussed. An argument will be presented that the traditional rhodium–carbenoids are not sufficiently selective to achieve practical intermolecular C–H insertions. The second portion of this review will describe the reactivity of rhodium–carbenoids that contain both electron donor and acceptor groups. These carbenoids are much more chemoselective than the traditional carbenoids, and much better suited for intermolecular C–H insertion. The third section of this review will describe the chiral catalysts that we have developed for asymmetric transformations with donor–acceptor substituted carbenoids. Finally, the progress we have achieved in asymmetric C–H insertions will be described. In addition to the enantioselectivity of the chemistry, issues of chemoselectivity and diastereoselectivity will be addressed.



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2. Background of C–H activation

Even though there are a number of high temperature industrial processes for C–H activation that use metal complexes as catalysts, the development of practical laboratory methods for catalytic C–H activation has been challenging [2,3]. One of the most extensively studied strategies has been the generation of highly reactive metal complexes, such as **1**, that are capable of undergoing oxidative addition across a C–H bond (Eq. (2)) [4]. Even though excellent mechanistic studies have been carried out on these types of reactions [3], the development of a catalytic process is extremely difficult because regeneration of the highly reactive complex to continue the catalytic cycle is unfavorable. Recently, Hartwig has devised a process, using rhodium catalyst **2**, to catalytically couple linear alkanes with borane **3**

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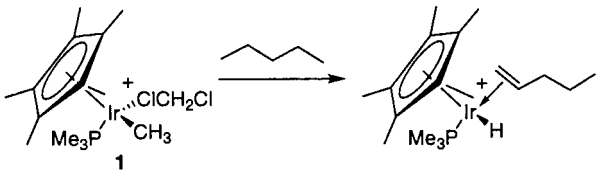
through a C–H insertion process to give good yields of linear alkylboranes **4** (Eq. (3)) [5]. Due to the high desirability of a practical C–H activation process and the tremendous challenges with achieving C–H activation, the reaction has been popularly described as the 'Holy Grail' for organometallic chemistry [2].



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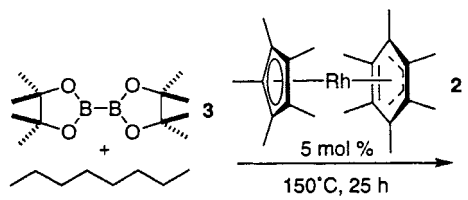

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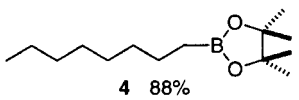
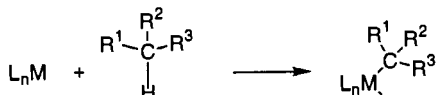


Even though the C–H insertion of a rhodium–carbenoid [6] is not generally included in the reviews on C–H activation [1–3,7], this process does lead to the functionalization of an unactivated C–H bond. The similar relationship between the classic C–H activation by oxidative addition, and the C–H activation by carbenoid C–H insertion is shown in Eqs. (4) and (5). Both reactions involve insertion across the alkane C–H bond, but in the first instance, the metal undergoes the insertion while in the second case, it is the carbenoid.

A major advantage of carbenoid C–H activation over traditional C–H activation is a catalytic cycle which is extremely favorable (Fig. 1) [6]. The starting metal complex **5** is reasonably stable and the energy for the cycle is derived from the carbenoid precursor, typically a diazo compound (**6**). Decomposition of the diazo compound generates molecular nitrogen and the high energy carbenoid intermediate **7**, which is then able to undergo the C–H insertion step. This will then release the functionalized product **8**, and regenerate the starting catalyst **5**, which allows the catalytic cycle to continue.



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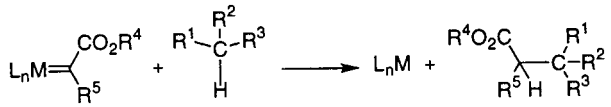

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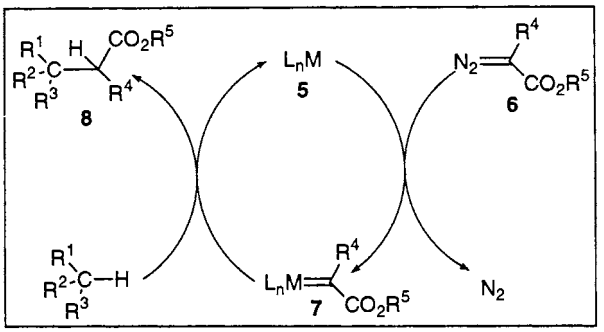
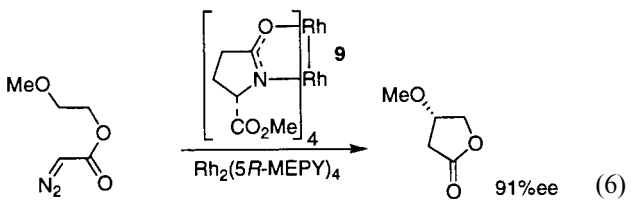


Fig. 1. Metal–carbenoid C–H activation.

Traditionally the catalysts used for decomposition of the diazo compounds were copper based, and the resulting copper–carbenoid complexes showed little tendency towards clean C–H insertions [8]. In the 1970s, however, Teyssie and co-workers introduced dirhodium tetracarboxylates as catalysts for diazo decomposition, and discovered that rhodium–carbenoids are effective at C–H insertion reactions [9]. Very impressive progress has been made in asymmetric intramolecular C–H insertions of diazoacetates and diazoketones as illustrated in Eqs (6)–(8) [10–12]. Both rhodium amide (**9**) and rhodium carboxylate (**10** and **11**) catalysts have been developed that result in impressive levels of asymmetric induction [6,13]. In general, five membered rings are formed (Eq. (6)), although the formation of other ring sizes can occur in exceptional cases (Eqs. (7) and (8)). Competition studies have been used to confirm the insertion preferences for $3° > 2° \gg 1°$ C–H bonds [6]. This selectivity is very intriguing because it is the opposite to that observed with the traditional organometallic C–H activation [1]. Extensive studies on the effect of substituents have been carried out, and activation was found to be favored adjacent to electron donating groups such as alkyl and silyl ethers, as well as azido substituents [6]. It was also determined that electron withdrawing groups such as esters and acetoxy groups are deactivating [6].



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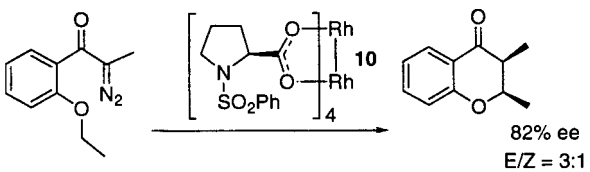

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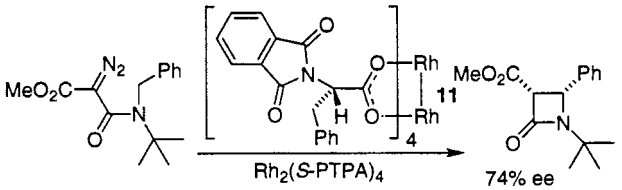
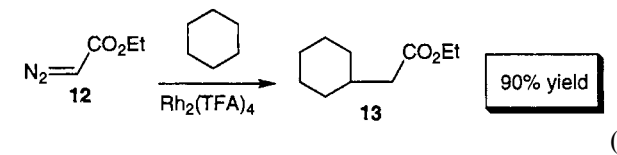


(8)

In contrast to the developments in intramolecular C–H insertions, the intermolecular reaction was not considered to be of great synthetic utility [6,14]. The major difficulty is that carbenoids derived from diazoacetates (**12**) are very prone to dimerization unless an efficient trap is present [15]. Furthermore, this class of carbenoids is not very chemoselective [9,16]. A high yield of C–H insertion (**13**) has been achieved with cyclohexane, but only when the electron deficient dirhodium trifluoroacetate was used as a catalyst and very slow syringe pump addition of the diazo compound (**12**) was followed (Eq. (9)) [9b]. Poor selectivity results from the C–H insertion reaction with various alkanes, which give a mixture of products. Reaction with 2-methylbutane gave all four possible products (**14**–**17**) (Eq. (10)), and even though the ratio of products was dependent on the catalyst used, a mixture was invariably formed [9b]. Consequently, it appeared that for the intermolecular C–H insertion to be a practical reaction, it would be necessary to use rhodium–carbenoid intermediates that are less prone to dimerization and exhibit improved chemoselectivity.



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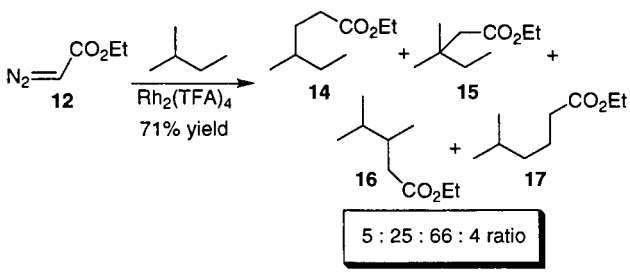

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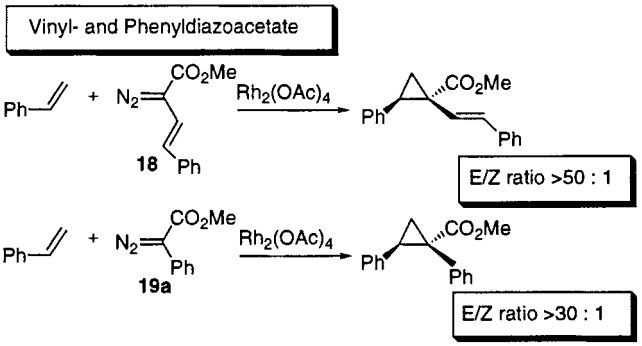
3. Carbenoid development

For many years our research group has been interested in the chemistry of the rhodium–carbenoids derived from vinyldiazoacetates (**18**) and phenyldiazoactetates (**19a**) [17]. These carbenoids undergo highly diastereoselective cyclopropanations as illustrated in Eq. (11) [18]. Diastereoselectivity ratios of $>30{:}1$ are common with these systems. These results are remarkable considering that the same reaction with ethyl diazoacetate (**12**) results in an E/Z ratio of 1.8:1 (Eq. (12)) [19].



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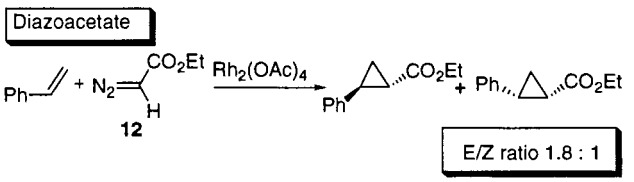

(12)

Over the years we have applied this method for the synthesis of vinylcyclopropanes to many target molecules [18,20]. Most notable is the reaction between vinyldiazoacetates and dienes that lead to the stereoselective synthesis of highly functionalized cycloheptadienes by a tandem cyclopropanation/Cope rearrangement [20b]. During the course of these extensive cyclopropanation studies, we discovered certain characteristics of this class of carbenoid which indicated that it could hold promise in selective C–H insertions. Firstly, dimerization of the carbenoid was not a significant side reaction with these carbenoids [21]. Thus, it was not necessary to use syringe pump techniques for very slow addition of the diazo compounds in order to avoid carbenoid dimerization. Secondly, the carbenoid displayed very demanding steric requirements. Cyclopropanations of *cis* double bonds are readily achieved, while *trans* double bonds are unreactive [21,22]. An illustration of this is shown in the key step that was used for the synthesis of (±)-tremulenolide A [17e]. Reaction occurred cleanly at the Z-double bond to give the *cis*-divinylcyclopropane intermediate **20**, which undergoes Cope rearrangement to give **21**, with full control of stereochemistry at three stereogenic centers (Eq. (13)).

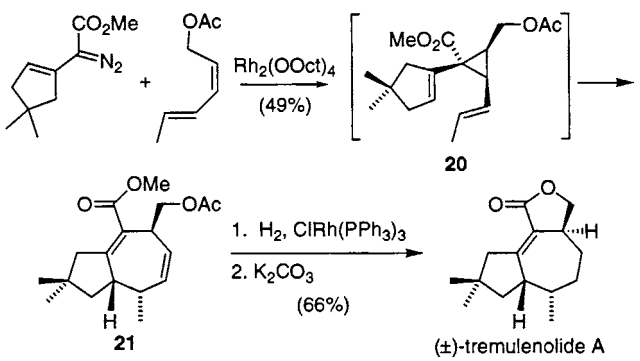

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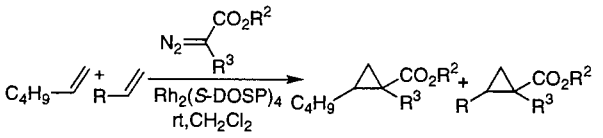
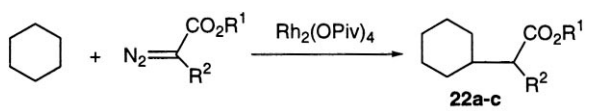
Table 1
Relative rate versus 1-hexene



R	H, CO_2Et, N_2 **12**	Ph, CO_2Me, N_2 **18**	Ph, CO_2Me, N_2 **19a**
p-$MeOC_6H_4$	3.0	415	420
p-$CH_3C_6H_4$	3.3	195	95
p-ClC_6H_4	3.3	65	55
C_6H_5	3.3	50	50
p-$CF_3C_6H_4$	2.3	20	22
	ρ ~ 0	ρ = −1.0 (σ^+)	ρ = −1.0 (σ^+)

The chemoselectivity differences between the carbenoids containing both electron donor and acceptor substituents, and the traditional carbenoids derived from diazoacetate have been quantified in competition studies (Table 1) [23]. For the diazoacetate (**12**) system, only a threefold rate difference exists between the reaction with hexene and styrene, where the electronic influence of substituents on the styrene is virtually non-existent. These results are consistent for a highly reactive carbenoid that reacts with alkenes through a very early transition state. In contrast, the carbenoids derived from **18** and **19a** show a 50-fold difference in reactivity between styrene and hexene, and the substituted styrenes display selective reactivity leading to a Hammett plot with a ρ of -1.0 (σ^+ scale). This is consistent with a reaction that involves a non-synchronous cyclopropantion with build up of positive charge at the benzylic carbon in the transition state.

In order to evaluate the effect of carbenoid structure on the efficiency of intermolecular C–H insertions, a series of reactions were carried out with different carbenoids under identical reaction conditions [24]. The rhodium pivalate catalyzed reaction of ethyl diazoacetate (**12**) added over 5 min and cyclohexane results in only a 10% yield of the C–H insertion product **22a** (Eq. (14)). Carbene dimers were the predominant products. In contrast, the parallel reaction with phenyldiazoacetate **19a** generated the C–H insertion product **22b** in 94% yield. Similarly the reaction with vinyldiazoacetate **23** generated the C–H insertion product **22c** in 67% yield.

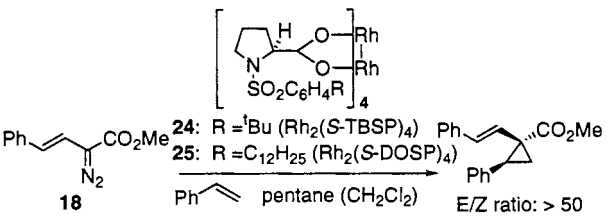


Diazo	R^1	R^2	yield, %
12	Et	H	10
19a	Me	Ph	94
23	Et	CH=CHCO$_2$Et	67

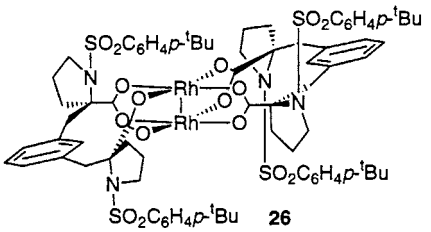
(14)

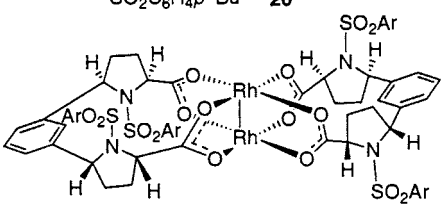
4. Chiral catalysis

A chiral catalyst system that is especially well suited for the phenyldiazoacetates and the vinyldiazoacetates is the dirhodium tetraprolinate system [25,26]. The optimum catalysts are Rh_2(*S*-TBSP)$_4$ (**24**) and Rh_2(*S*-DOSP)$_4$ (**25**), which are soluble in hydrocarbon solvents. This is important because with the prolinate catalysts, the highest ee is obtained in non-polar solvents [21,26]. Rh_2(*S*-DOSP)$_4$ is soluble in pentane, even at -78°C, and under these conditions cyclopropanation can be achieved in 98% ee (Eq. (15)) [21]. Since our original studies, several other types of catalysts including copper and rhodium amide based catalysts have been evaluated in intermolecular cyclopropanations with donor–acceptor diazo's, but none have out performed the prolinates [27]. Recently, the bridged prolinates, **26** [28] and **27** [29] (Rh_2(*S*-biDOSP)$_2$) have been prepared, and these catalysts do not require the use of hydrocarbon solvents for high asymmetric induction. Rh_2(*S*-biDOSP)$_2$, in particular, can outperform Rh_2(*S*-DOSP)$_4$ in certain cases [21,29].



catalyst	temp, °C	ee, %
Rh_2(*S*-TBSP)$_4$	25	90 (74)
Rh_2(*S*-DOSP)$_4$	25	92 (74)
Rh_2(*S*-DOSP)$_4$	-78	98

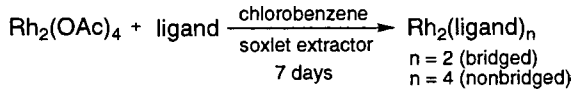




(15)

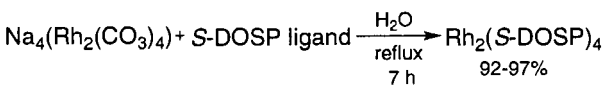
The synthesis of these catalysts involves the preparation of the appropriate ligand, followed by a high temperature ligand exchange with rhodium(II) acetate over approximately 7 days (Eq. (16)) [30]. An alternative method is also available for the synthesis of the non-bridged ligands, which go on the rhodium much

more easily. Refluxing the *S*-DOSP ligand in water with $Na_2(Rh_2(CO_3)_4)$ [30] gives the Rh_2(*S*-DOSP)$_4$ catalyst in 92–97% yield in only 7 h (Eq. (17)) [21]. Once formed, these catalysts are extremely stable and can be stored for long periods of time on the benchtop without adversely affecting their reactivity.



catalyst	yield, %
Rh_2(*S*-DOSP)$_4$	69
Rh_2(*S*-biDOSP)$_4$	50
26	50

(16)



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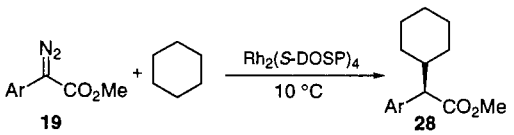
5. Intermolecular C–H activation by aryldiazoacetates

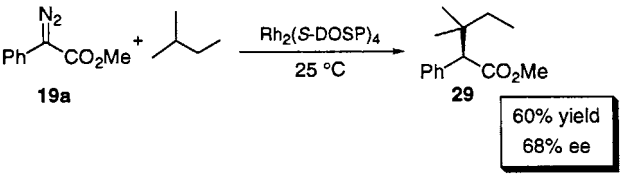
Rh_2(*S*-DOSP)$_4$ catalyzed decomposition of phenyldiazoacetate (**19a**) in refluxing cyclohexane generated the C–H insertion product **28a** in 87% ee [31]. By carrying out the reaction at 10°C, the enantioselectivity can be improved to 95% ee [32]. The reaction is applicable to a range of aryldiazoacetates (**19a–j**) as illustrated in Table 2. In most instances, the reaction proceeds with $>90\%$ ee.

Good regiocontrol is possible in reactions with certain alkanes. Reaction of **19a** with 2-methylbutane results in the formation of C–H insertion product **29** in 60% yield and 68% ee (Eq. (18)) [32]. This was the only C–H insertion product that is observed, which is in marked contrast to the reaction of 2-methylbutane with ethyl diazoacetate (**12**) in which all four **14–17** possible products are formed (Eq. (10)) [9b]. A highly regioselective reaction was also obtained in the reaction with adamantane, from which product **30** was obtained in 90% ee (Eq. (19)) [32].

Table 2
C–H insertion into cyclohexane with various aryl substituted diazos



	Ar	Yield (%)	ee (%)
a	C_6H_5	80	95
b	*p*-$CF_3C_6H_4$	78	94
c	*p*-BrC_6H_4	64	95
d	*m*-BrC_6H_4	62	95
e	*o*-BrC_6H_4	72	90
f	*p*-ClC_6H_4	76	94
g	*m*-ClC_6H_4	47	94
h	*o*-ClC_6H_4	81	90
i	*p*-MeC_6H_4	63	93
j	*p*-(MeO)C_6H_4	23	88



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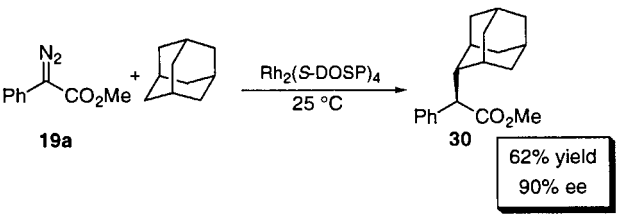
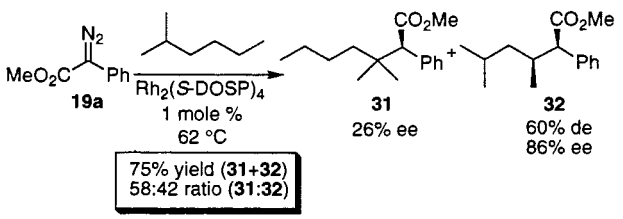


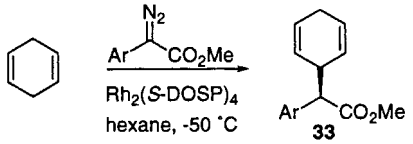
(19)

The reaction of phenyldiazoacetate (**19a**) with 2-methylhexane illustrates the delicate balance that exists for the regiochemistry in these reactions (Eq. (20)). Two C–H insertion products were obtained arising from attack at the methine (**31**) and one of the methylene (**32**) positions [32]. Thus it appears that reactions are equally likely to occur at methine and unencumbered methylene positions. However, C–H insertion does not occur at a methyl or hindered methylene position. Presumably, electronic factors favor C–H insertion into a tertiary site but the steric demand of the carbenoid complex also influences the chemoselectivity of these reactions.



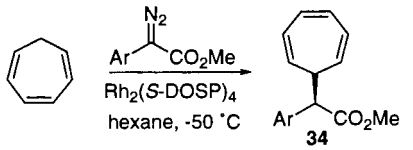
(20)

Even more favorable C–H insertions are possible if the site is further activated by other functionally. Very favorable C–H insertions occur at allylic positions as shown in Eqs. (21) and (22). These reactions can be carried out at -50°C and this leads to the formation of **33** and **34** in greater than 90% ee [33]. Carrying out these reactions at low temperature generally enhances the enantioselectivity. Subsequent studies by Muller have shown that the formation of **33** at room temperature resulted in only 71% ee [34].



Ar	Yield, %	ee, %
p-chlorophenyl-	84	95
p-methylphenyl-	84	94
p-methoxyphenyl-	69	93
2-napthyl-	64	92

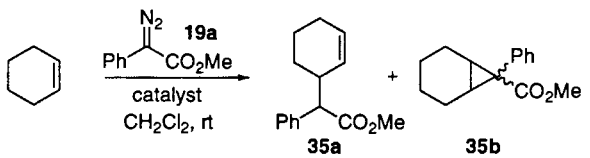
(21)



Ar	Yield, %	ee, %
phenyl	55	95
p-chlorophenyl-	64	95
p-methylphenyl-	60	94
2-napthyl-	53	91

(22)

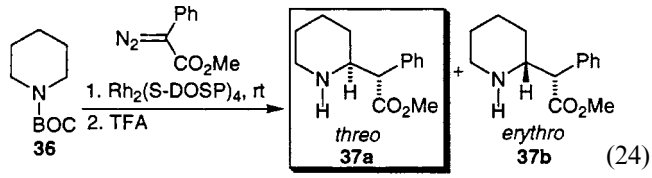
Muller also described the decomposition of phenyldiazoacetate (**19a**) by various catalysts in the presence of cyclohexene [34]. With $Rh_2(S\text{-DOSP})_4$ as the catalyst, a majority of C–H insertion product (**35a**) versus cyclopropanation (**35b**) (80:20 ratio) was obtained. The C–H insertion product **35a** was obtained as an inseparable mixture of diastereomers (52:48). Hydrogenation of the mixture gives a cyclohexyl derivative in 75% ee. Running the reaction with $Rh_2(S\text{-MEPY})_4$ as the catalyst gave an improved ratio of C–H insertion product (**35a**) to cyclopropanation (**35b**) (93:7 ratio), however the ee of the product decreased to only 45% (Eq. (23)).



catalyst	yield (a+b), %	ratio a:b	a, dr	a, ee, %
$Rh_2(OAc)_4$	50	75:25	—	—
$Rh_2(S\text{-DOSP})_4$	33	80:20	52:48	75
$Rh_2(S\text{-MEPY})_4$	50	93:7	37:63	45

(23)

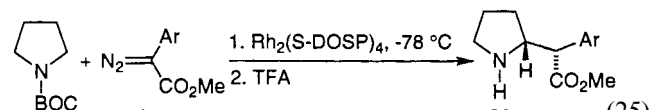
A very active position for C–H insertions is adjacent to nitrogen functionality. The reaction with *N*-BOC piperidine (**36**) results in a direct synthesis of methylphenidate **37a** (marketed racemically as Ritalin™), as illustrated in Eq. (24) [35]. The best catalyst we found for this reaction is $Rh_2(S\text{-biDOSP})_2$ (**27**) which results in the formation of **37a** in 86% ee. Winkler has explored a similar reaction using $Rh_2(R\text{-MEPY})_4$ as the catalyst, and reported the formation of **37a** in 45% yield and 69% ee [36].



catalyst	diazo equiv	yield, %	threo/erythro ratio	threo ee, %	erythro ee, %
$Rh_2(S\text{-DOSP})_4$	0.25	49	43:57	34 (2*S*)	81 (2*S*)
$Rh_2(S\text{-DOSP})_4$	4.0	86	50:50	25 (2*S*)	79 (2*S*)
$Rh_2(S\text{-biDOSP})_2$	4.0	73	71:29	86 (2*R*)	65 (2*R*)
$Rh_2(R\text{-MEPY})_4$	0.25	45	97:3	69 (2*R*)	—

(24)

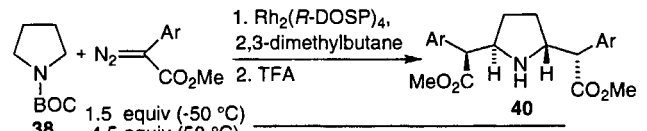
The diastereoselectivity in this reaction is very delicately balanced, as can be seen in the reaction with *N*-BOC pyrolidine (**38**). C–H inserted products **39** are formed with high diastereoselectivity (92–94%) and enanatioselectivity (93–94%). Furthermore, they are the opposite diastereomer to that formed with *N*-BOC piperidine (**36**) [35] (Eq. (25)).



Ar	yield, %	de, %	ee, %
Ph	72	92	94
4-ClPh	72	94	94
4-MePh	67	94	93
2-naphthyl	49	92	93

(25)

As *N*-BOC pyrolidine (**38**) contains two sites that are activated for C–H insertion, a double insertion is possible if **38** is used as the limiting reagent. The bis-inserted products (**40**), are formed in 88–97% ee with full control of stereochemistry at four stereogenic centers (Eq. (26)) [35]. Compounds such as **40** represent a very interesting class of C_2-symmetric amines that would be extremely difficult to prepare by any other means.

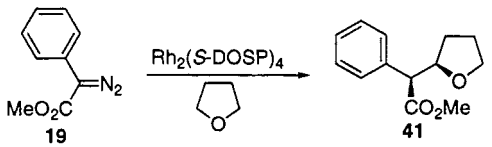


Ar	yield, %	ee, %
Ph	78	97
p-Cl-Ph	50	96
p-Me-Ph	51	96
2-Naphthyl	40	88
p-MeO-Ph	62	97

(26)

Selective C–H insertion is also possible at sites adjacent to oxygen functionally. In initial studies with te-

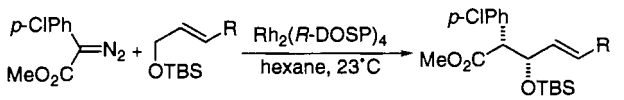
trahydrofuran, a mixture of diastereomers was formed and the enantioselectivity for the major diastereomer (**41**) was only 60% ee (Eq. (27)) [37]. Presumably, tetrahydrofuran would behave as a polar solvent in these reactions, while non-polar solvents are required for the catalyst to perform with high enantioselectivity. Thus, the reaction was optimized by carrying out the reaction at −50°C using two equivalents of THF in hexane as a solvent. Even in the presence of a vast excess of hexane, efficient C–H insertion occurs to form **41** in 97% ee [32].



(27)

solvent	temp, °C	yield, %	Diastereomer ratio	Major isomer ee, %
THF	60	82	2.3	60
THF	24	68	2.5	82
hexane/THF (2 eq.)	24	78	2.5	85
hexane/THF (2 eq.)	-50	67	4.0	97

A remarkable example of the C–H insertion adjacent to oxygen functionality is the reaction with allyl silyl ethers (**42**). These reactions occur with exceptionally high diastereoselectivity, leading to products (**43**) that are equivalent to *syn*-aldol products in 96–98% de and 74–90% ee (Eq. (28)) [38].



(28)

R	yield, %	de, %	ee, %
Me	72	96	80
Ph	70	97	85
CH=CHMe	71	98	74
H	35	98	90

Competition studies were performed to explore the relative rates of reaction with phenyldiazoacetate **19a** decomposed by $Rh_2(S\text{-DOSP})_4$ (Fig. 2) [32]. With the rate of C–H insertion into cyclohexane normalized to 1, insertion into tertiary C–H bonds, although electronically favored, occurred at a slower relative rate due to steric congestion near the insertion site. On the other hand, C–H insertion adjacent to oxygen and nitrogen functionality occurred at a much faster rate, indicating that these are favored sites and explaining the high chemoselectivity observed in these reactions. C–H insertion into the doubly-allylic position of 1,4-cyclohexadiene occurs at about the same rate as cyclopropanation of styrene and Si–H bond insertion, which are known to be highly favorable reactions.

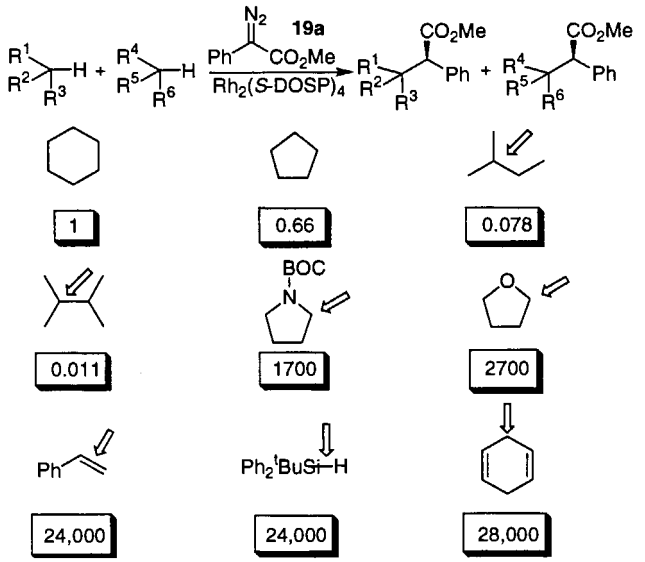


Fig. 2. Relative rates of reaction.

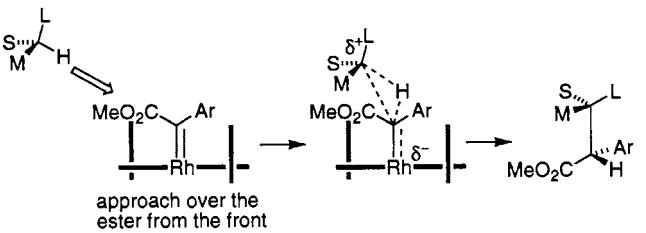


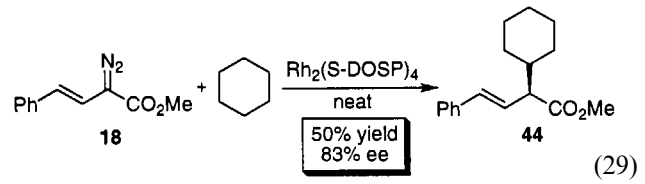
Fig. 3. Predictive model for asymmetric induction.

Asymmetric induction in these C–H insertion reactions is generated through the use of the chiral $Rh_2(S\text{-DOSP})_4$ catalyst. We have proposed recently that intermolecular C–H insertion occurs in a concerted, but non-synchronous manner, with buildup of positive charge at the carbon of the C–H bond [32]. A model illustrating the proposed approach and mechanism of this asymmetric induction is shown in Fig. 3. Approach is thought to occur over the ester from the front with the C–H bond approaching side on in the same plane as the large group which is pointing up in the least sterically demanding position. The medium group faces away from the catalyst while the small group (H) faces into the catalyst, and gives a product with the stereochemistry shown.

6. Intermolecular C–H activation by vinyldiazoacetates

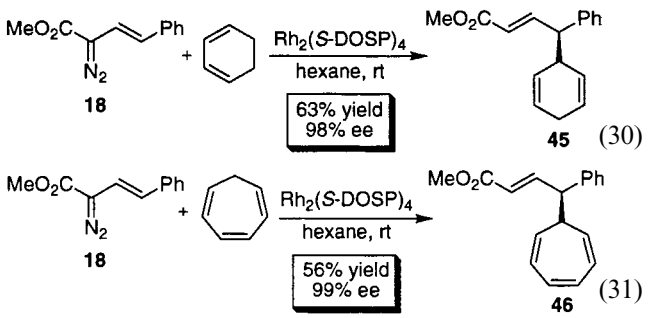
A complete study on the asymmetric reactions of vinyldiazoacetates with alkanes has not been carried out. The one example reported so far indicates that vinyldiazoacetates are also capable of undergoing effective asymmetric C–H insertions into alkanes. The reaction of vinyldiazoacetate **18** with cyclohexane resulted

in formation of the C–H insertion product **44** in 50% yield and 83% ee (Eq. (29)) [31].



(29)

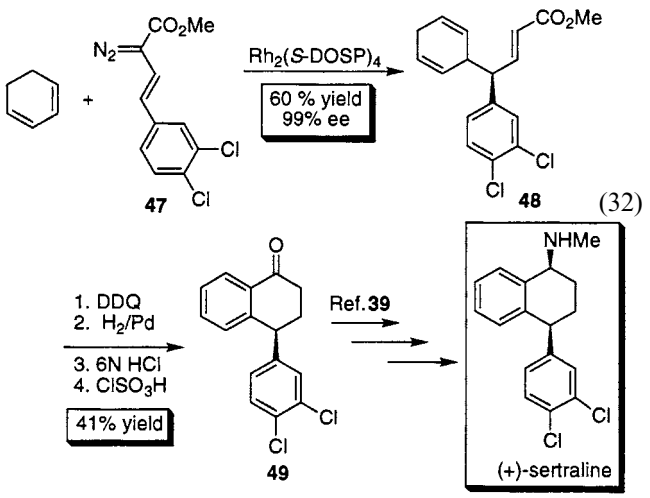
A major difference between vinyldiazoacetates and phenyldiazoacates is seen in C–H insertion reactions at allylic positions. Reaction of the vinyldiazoacetate **18** with 1,3-cyclohexadiene results in the formation of the 1,4-cyclohexadiene **45** (Eq. (30)) [33a]. The product appears to be that from a C–H insertion followed by a Cope rearrangement. The reaction, however, is more complex because the C–H insertion product is actually more stable than the product (**45**) and therefore cannot be an intermediate in the formation of **45**. A similar product is obtained in the reaction of **18** with cycloheptatriene leading to the formation of **46** in 99% ee (Eq. (31)) [33b]. At this stage, the mechanistic details of this reaction are not fully understood but it is probably an interrupted C–H insertion, in which C–H insertion begins but before the process is complete, Cope rearrangement occurs to give the observed product.



(30)

(31)

The combined C–H insertion/Cope rearrangement has been used in a formal asymmetric synthesis of (+)-sertraline (Zoloft™) (Eq. (32)). Reaction of **47** with 1,3-cyclohexadiene generates **48** in 60% yield and 99% ee [33a].



(32)

Aromatization of the cyclohexadiene in **48** with DDQ followed by hydrogenation, hydrolysis, and Friedel–Crafts acylation generated the tetralone **49** [39], which has been previously converted to (+)-sertraline.

7. Future outlook

The future outlook for this chemistry will depend on the generality of the process. Further studies are needed to define the scope of this chemistry and expand the range of systems that can lead to highly stereoselective processes. Mechanistic studies in this area of chemistry need to become more sophisticated such that the basic understanding of the reaction is improved. Finally, the utility of this chemistry needs to be demonstrated by its application to challenging synthetic targets.

Acknowledgements

Several post-doctoral associates, graduate students and undergraduate students have made major contributions to the chemistry described in this review. Without their dedication and ingenuity, this chemistry would not have reached its current level of broad synthetic utility. The co-workers who developed the foundation of the carbenoid and chiral catalyst studies have been listed previously [26a]. Dr Tore Hansen initiated the asymmetric C–H activation project and since then, Evan Antoulinakis, Dr Darrin Hopper and Douglas Stafford have been actively involved in expanding this research area. These studies were generously supported by the National Science Foundation (CHE 9726124) and by PHS grants DA-06301 and DA-05886.

References

[1] (a) A.E. Shilov, G.B. Shul'pin, Chem. Rev. 97 (1997) 2879. (b) G. Dyker, Angew. Chem. Int. Ed. Engl. 28 (1999) 1698.
[2] B.A. Arndtsen, R.G. Bergman, T.A. Mobley, T.H. Peterson, Acc. Chem. Res. 28 (1995) 154.
[3] (a) H. Mimoun, in: G. Wilkinson, R.D. Gillard, J.A. McCleverty, (Eds.), Comprehensive Coordination Chemistry, vol. 6, Pergamon, New York, 1989. (b) J.A. Davies, P.L. Watson, A. Greenberg, J.F. Liebman (Eds.), Selective Hydrocarbon Activation, VCH, New York, 1990. (c) C.L. Hill (Ed.), Activation and Functionalization of Alkanes, Wiley, New York, 1989.
[4] B.A. Arndsten, R.G. Bergman, Science 270 (1995) 1970.
[5] H.Y. Chen, S. Schlecht, T.C. Semple, J.F. Hartwig, Science 287 (2000) 1995.
[6] M.P. Doyle, M.A. McKervey, T. Ye, Modern Catalytic Methods for Organic Synthesis with Diazo Compounds, Wiley-Interscience, New York, 1998, pp. 112–162.
[7] Y. Guari, S. Sabo-Etienne, B. Chaudret, Eur. J. Inorg. Chem. (1999) 1047.
[8] G. Mass, Topics in Current Chemistry, vol. 137, Springer-Verlag, New York, 1987, pp. 75–254.

[9] (a) R. Paulissen, H. Reimlinger, E. Hayez, A.J. Hubert, P. Teyssie, Tetrahedron Lett. 14 (1973) 2233 (b) A. Demonceau, A.F. Noels, A.J. Hubert, P. Teyssie, J. Chem. Soc. Chem. Commun. (1981) 688. (c) A. Demonceau, A.F. Noels, A.J. Hubert, P. Teyssie, Bull. Soc. Chim. Belg. 93 (1984) 945. (d) A. Demonceau, A.F. Noels, A.J. Hubert, P. Teyssie, J. Mol. Catal. 49 (1988) L13.
[10] M.P. Doyle, A. van Oerveren, L.J. Westrum, M.N. Protopopova, T.W. Clayton, Jr., J. Am. Chem. Soc. 113 (1991) 8982.
[11] (a) M.A. McKervey, T. Ye, J. Chem. Soc. Chem. Commun. (1992) 823 (b) T. Ye, C.F. Garcia, M.A. McKervey, J. Chem. Soc. Perkin Trans. 1 (1995) 1373.
[12] N. Wanatabe, M. Anada, S. Hashimoto, M. Shiro, S. Ikegami, Synlett (1994) 1031.
[13] G.A. Sulikowski, K.L. Cha, M.M. Sulikowski, Tetrahedron: Asymmetry 9 (1998) 3145.
[14] (a) T. Ye, M.A. McKervey, Chem. Rev. 94 (1994) 1091. (b) D.M. Spero, J. Adams, Tetrahedron Lett. 33 (1992) 1143.
[15] (a) M.P. Doyle, D. van Leusen, W.H. Tamblyn, Synthesis (1981) 787. (b) D.S. Wulfman, B.W. Pearce, R.S. McDaniel Jr., Tetrahedron 32 (1976) 1251.
[16] For representative examples of intermolecular C–H insertions, see: (a) L.T. Scott, G.J. DeCicco, J. Am. Chem. Soc. 96 (1974) 322. (b) R.A. Ambramovitch, J. Roy, J. Chem. Soc. Chem. Commun. (1965) 542. (c) J. Adams, M.A. Poupart, L. Greainer, C. Schaller, N. Quimet, R. Frenette, Tetrahedron Lett. 30 (1989) 1749. (d) H.J. Callott, F. Metz, Tetrahedron Lett. 23 (1982) 4321. (e) H.J. Callott, F. Metz, Nouv. J. Chim. 9 (1985) 167. (f) A. Domenceau, A.F. Noels, J.L. Costa, A. Hubert, J. Mol. Catal. 58 (1990) 21.
[17] For recent examples, see: (a) H.M.L. Davies, N. Kong, M.R. Churchill, J. Org. Chem. 63 (1998) 6586. (b) H.M.L. Davies, L. Rusiniak, Tetrahedron Lett. 39 (1998) 8811. (c) H.M.L. Davies, G. Ahmed, R.L. Calvo, M.R. Churchill, D.G. Churchill, J. Org. Chem. 63 (1998) 2641. (d) H.M.L. Davies, L.M. Hodges, C.T. Thornley, Tetrahedron Lett. 39 (1998) 2707. (e) H.M.L. Davies, B.D. Doan, J. Org. Chem. 63 (1998) 657. (f) H.M.L. Davies, D.G. Stafford, B.D. Doan, J.H. Houser, J. Am. Chem. Soc. 120 (1998) 3326.
[18] H.M.L. Davies, Tetrahedron 49 (1993) 5203.
[19] (a) M.P. Doyle, J.H. Griffin, V. Bagheri, R.L. Dorow, Organometallics 3 (1994) 53. (b) M.P. Doyle, Chem. Rev. 86 (1986) 919.
[20] (a) H.M.L. Davies, Curr. Org. Chem. 2 (1998) 463. (b) H.M.L. Davies, in: M.E. Haramata (Ed.), Advances in Cycloaddition, JAI Press, 1999, vol. 5, pp. 119–164.
[21] H.M.L. Davies, P. Bruzinski, D.K. Hutcheson, M.J. Fall, J. Am. Chem. Soc. 118 (1996) 6897.
[22] H.M.L. Davies, B. Hu, Heterocycles 35 (1993) 385.
[23] H.M.L. Davies, S.A. Panaro, Tetrahedron 56 (2000) 4871.
[24] H.M.L. Davies, L.M. Hodges, J.J. Matasi, T. Hansen, D.S. Stafford, Tetrahedron Lett. 39 (1998) 4417.
[25] M. Kennedy, M.A. McKervey, A.R. Maguire, G.H.P. Roos, J. Chem. Soc. Chem. Commun. (1990) 361.
[26] (a) H.M.L. Davies, Eur. J. Org. Chem. (1999) 2459. (b) H.M.L. Davies, Aldrichim. Acta 30 (1997) 105.
[27] M.P. Doyle, Q.L. Zhou, C. Charnsangavej, M.A. Longoria, M.A. McKervey, C.F. Garcia, Tetrahedron Lett. 37 (1996) 4129.
[28] H.M.L. Davies, N. Kong, Tetrahedron Lett. 38 (1997) 4203.
[29] H.M.L. Davies, S.A. Panaro, Tetrahedron Lett. 40 (1999) 5287.
[30] G.H.P. Roos, M.A. McKervey, Synth. Commun. 22 (1992) 1751.
[31] H.M.L. Davies, T. Hansen, J. Am. Chem. Soc. 119 (1997) 9075.
[32] H.M.L. Davies, T. Hansen, M.R. Churchill, J. Am. Chem. Soc. 122 (2000) 3063.
[33] (a) H.M.L. Davies, D.G. Stafford, T. Hansen, Org. Lett. 1 (1999) 233. (b) H.M.L. Davies, D.G. Stafford, T. Hansen, M.R. Churchill, K.M. Keil, Tetrahedron Lett. 41 (2000) 2035.
[34] P. Muller, S. Tohill, Tetrahedron 56 (2000) 1725.
[35] H.M.L. Davies, T. Hansen, D. Hopper, S.A. Panaro, J. Am. Chem. Soc. 121 (1999) 6509.
[36] J.M. Axten, R. Ivy, L. Krim, J.D. Winkler, J. Am. Chem. Soc. 121 (1999) 6511.
[37] H.M.L. Davies, T. Hansen, J. Am. Chem. Soc. 119 (1997) 9075.
[38] H.M.L. Davies, E.G. Antoulinakis, T. Hansen, Org. Lett. 1 (1999) 383.
[39] E.J. Corey, T.G. Gant, Tetrahedron Lett. 35 (1994) 5373.