

# Intermolecular reactions of electron-rich heterocycles with copper and rhodium carbenoids

Huw M. L. Davies\* and Simon J. Hedley

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This *tutorial review* describes the reactions of the electron-rich heterocycles pyrrole, furan, indole and benzofuran with copper and rhodium carbenoids. Two main reaction pathways are possible, involving either a concerted non-synchronous cyclopropanation or zwitterionic intermediates. A diverse range of products are possible and the outcome is very dependent on the structure of the heterocycle and the carbenoid. To emphasize this point the carbenoids are considered in terms of three classes: acceptor, acceptor–acceptor and donor–acceptor carbenoids. Unusual catalytic asymmetric transformations can be achieved with this chemistry while the asymmetric induction is strongly influenced by how the carbenoid can approach the heterocycles. This *tutorial review* gives an overview of the general features that govern the chemistry of metal carbenoids with heterocycles and presents a mechanistic rationale for the range of products that can be formed.

Aromatic heterocycles are ubiquitous in nature and consistently remain at the forefront of biological and medicinal chemistry research. In pharmaceutical drug design, a variety of heterocycles are repeatedly used as the pharmacophore for the development of therapeutic targets. Therefore, there is considerable interest in new methods for the formation and elaboration of heterocycles. In this *tutorial review*, the intermolecular reactions of electron-rich oxygen and nitrogen heterocycles with copper and rhodium carbenoids will be discussed.

Metal carbenoids are readily generated by metal-catalyzed decomposition of diazoacetates and occupy an established position as versatile synthetic intermediates in organic chemistry.<sup>1</sup> In comparison to free carbenes, metal carbenoids are endowed with increased stability, and are capable of highly selective reactions.<sup>2</sup> They are highly electrophilic but their reactivity profile is very dependent on the structure of the carbenoid and the metal. Most of the early literature on

metal-catalyzed carbenoid reactions used copper complexes as the catalysts and ethyl diazoacetate as the carbenoid source.<sup>1,2</sup> In recent years dirhodium tetracarboxylates have become the catalysts of choice<sup>3</sup> and a much wider range of carbenoid precursors has been developed. Many carbenoid reactions that were inefficient using the traditional copper catalysts have now been transformed into high yielding, selective processes when using rhodium catalysis.<sup>1,2</sup>

Metal carbenoids readily cyclopropanate electron-rich alkenes.<sup>4</sup> Extending the reaction to electron-rich heterocycles can lead to a variety of products. The cyclopropanation occurs in a concerted, non-synchronous mode with build-up of positive charge at either the 2- or 3-positions as shown in **1** and **2** (Scheme 1).<sup>5</sup> Alternatively if the heterocycle and carbenoid are effective at charge stabilization, zwitterionic intermediates **3** or **4** can be formed, leading to different types of products.<sup>5</sup>

The structure of the metal carbenoid has a major influence on the outcome of this chemistry.<sup>6</sup> In order to illustrate this point, the carbenoids will be categorized into three classes

Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260-3000, United States of America. E-mail: hdavies@buffalo.edu; Fax: +1 7166456547; Tel: +1 7166456800



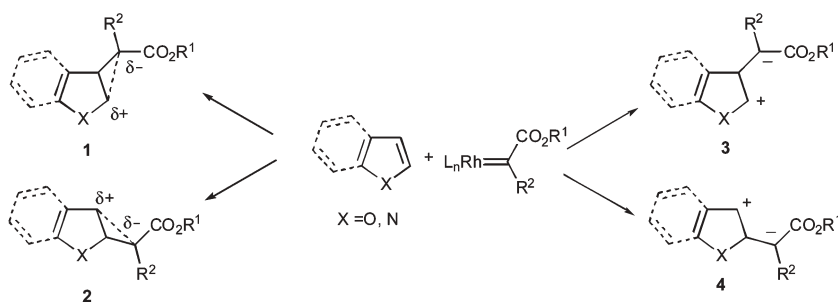
Huw M. L. Davies

Huw M. L. Davies was born in Aberystwyth, Wales. He received his BSc degree from University College Cardiff, Wales in 1977 and his PhD degree from the University of East Anglia, England in 1980. After a post-doctoral position at Princeton University, he joined the faculty at Wake Forest University. In 1995 he moved to the University at Buffalo, the State University of New York, where he currently holds the position of Larkin Professor of Organic Chemistry.

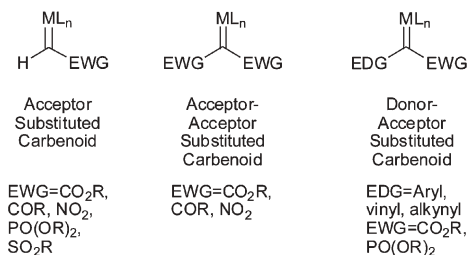


Simon J. Hedley

Simon J. Hedley received his MSc degree and in 1999 and his PhD degree in 2002, both from the University of Sheffield, UK. In 2003 he took up a post-doctoral position at the University at Buffalo, where he worked on the reaction of rhodium carbenoids with heterocycles. In 2006 he started a medicinal chemistry position at Amgen, Inc.



**Scheme 1** Electrophilic substitution reactions of electron-rich aromatic heterocycles.



**Fig. 1** Classification of metal carbenoids.

according to the functionality around the carbenoid (Fig. 1): acceptor; acceptor–acceptor; and donor–acceptor, where the terms “donor” and “acceptor” refer respectively to the donation or withdrawal of electron density at the carbenoid center by resonance. This is an important consideration, as metal carbenoids that are very electrophilic will tend to react *via* zwitterionic intermediates while the donor–acceptor carbenoids, and to a lesser extent the acceptor carbenoids, will tend to react in a concerted manner. Very electron-rich heterocycles would also be expected to favor the formation of zwitterionic intermediates.<sup>5</sup>

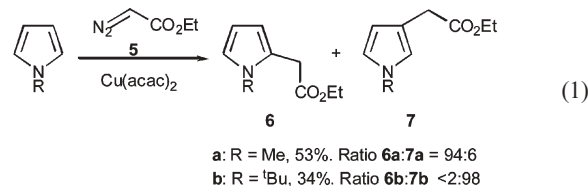
## Reactions with pyrroles

In terms of classical electrophilic substitution reactions, pyrroles are considerably more reactive than furans.<sup>7</sup> This is due to the powerful electron-donating ability of the nitrogen lone pair, which leads to a very electron-rich heterocycle. The reaction of carbenoids with *N*-H or *N*-alkyl pyrroles tend to proceed *via* zwitterionic intermediates, such as **3** or **4**, leading to alkylation products, while cyclopropane products are predominantly formed with *N*-acyl pyrroles, arising from intermediates **1** and **2**.<sup>5</sup>

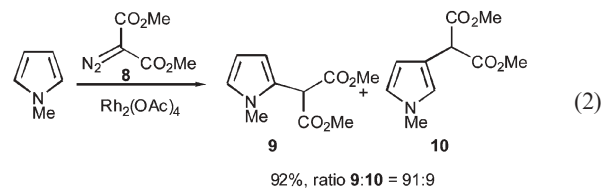
### Reactions with *N*-H and *N*-alkyl pyrroles

**Acceptor substituted carbenoids.** All three classes of carbenoids react with pyrrole or *N*-alkyl pyrroles to form alkylation products. A detailed study of the reaction of ethyl diazoacetate (**5**) with *N*-alkyl pyrroles showed that copper-catalyzed reactions lead to the formation of alkylation products in fairly low to moderate yields.<sup>8</sup> Interestingly,  $\text{Rh}_2(\text{OAc})_4$  is an ineffective catalyst for this reaction, even though rhodium(II) carboxylates are the catalysts of choice in most carbenoid transformations. The efficiency and regioselectivity of the reaction is very dependent on the *N*-alkyl substituent and the

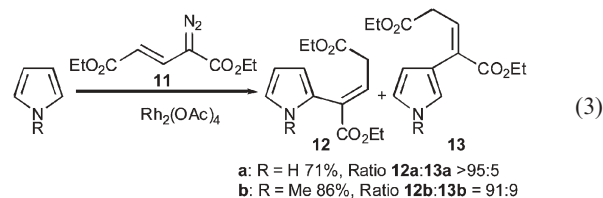
type of catalyst used (eqn (1)). The size of the alkyl substituent determines whether the electrophilic carbenoid will attack at the 2- or 3-position. A relatively small substituent will favor the 2-alkylation product, *e.g.* **6a**, while in the case of *N*-*tert*-butyl pyrrole the 3-alkylation product **7b** was formed exclusively.<sup>8</sup> With unsubstituted pyrrole, competing *N*-H insertion was found to be negligible.



**Acceptor–acceptor substituted carbenoids.** The reaction of dimethyl diazomalonnate (**8**) with *N*-methyl pyrrole (eqn (2)) is a much cleaner reaction than the corresponding reaction of ethyl diazoacetate (**5**).<sup>9</sup> In this case, a mixture of alkylation products **9** and **10** is formed. There is a marked preference for regioisomer **9** with substitution at the 2-position. When  $\text{Rh}_2(\text{OAc})_4$  is used as catalyst, higher yields of **9** and **10** (92%) than the corresponding copper-catalyzed processes (30–76% yield) were obtained.



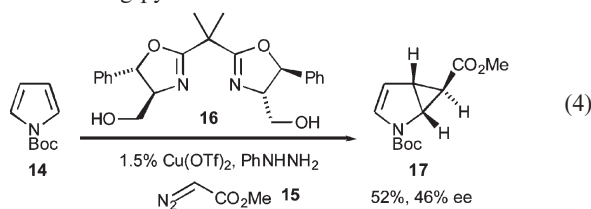
**Donor–acceptor substituted carbenoids.** Pyrrole and *N*-methyl pyrrole both undergo an efficient and highly regioselective alkylation with vinyl diazoacetate **11**.<sup>10</sup>  $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of **11** in the presence of pyrrole resulted in the formation of a single alkylation product **12a** in 71% yield, while the reaction with *N*-methyl pyrrole resulted in a 91 : 9 mixture of **12b** and **13b** in 86% yield (eqn (3)).



The alkylation products can be considered to be derived from two possible pathways (Scheme 1). The first possibility involves a concerted non-synchronous reaction *via* **1** or **2** to generate cyclopropanes, which then undergo ring opening and proton transfer to form the alkylation products.<sup>5</sup> Alternatively, the reaction proceeds by electrophilic attack of the carbenoid on the pyrrole to generate zwitterionic intermediates **3** and **4**, which then rearrange by a 1,2-proton shift and concurrent aromatization.<sup>5</sup> While it is not possible to discriminate unequivocally between these two possible mechanisms, the results are more consistent with the latter proposal. The increased preference of alkylation at the 2-position is consistent with the electrophilic substitution reactions of pyrroles. The product distribution is sensitive to the catalyst used, and the effect of increasing steric bulk at nitrogen makes attack at the 3-position more favorable. Additionally, the most effective reactions were observed with diazoacetates **8** and **11**, which are especially suited to the stabilization of the anion portion of the zwitterionic intermediates **3** and **4**.

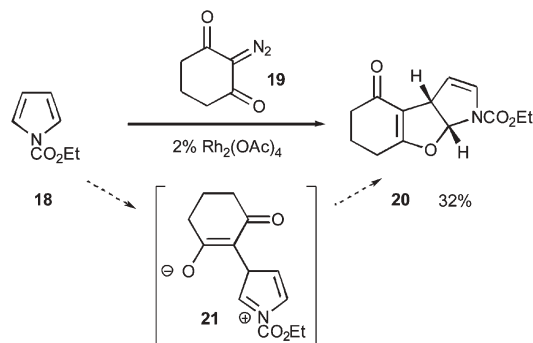
### Reactions with *N*-acyl pyrroles

**Acceptor substituted carbenoids.** The incorporation of an *N*-acyl substituent significantly alters the reactivity of the pyrrole ring. As the nitrogen lone pair is now in conjugation with the carbonyl group, the aromatic ring is not as electron-rich, and behaves more typically like a diene towards metal carbenoids. A recent example with an acceptor substituted carbenoid is the enantioselective cyclopropanation in 46% ee of *N*-Boc pyrrole (**14**) with methyl diazoacetate (**15**) using the chiral copper catalyst derived from bisoxazoline **16** (eqn (4)).<sup>11</sup> One of the distinctive features of this reaction is that the monocyclopropanation product **17** is formed even though the enamine functionality in **17** would be expected to be more reactive than the starting *N*-Boc pyrrole **14**. This is because these carbenoids are highly reactive and unselective, and generally do not discriminate between the product **17** and the excess of starting pyrrole **14**.



**Acceptor-acceptor carbenoids.** An unusual tricyclic product **20** is generated in the  $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of 2-diazo-1,3-cyclohexanedione **19** with *N*-carboethoxy pyrrole **18** (Scheme 2).<sup>12</sup> The product **20**, being somewhat unstable, can be isolated in low yield (32%).

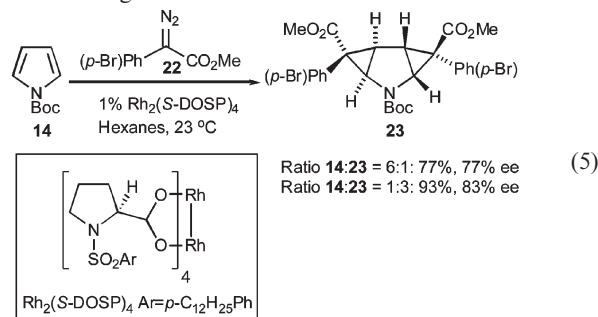
The reaction presumably involves zwitterionic intermediate **21**, followed by ring closure of the oxyanion onto the iminium portion. The zwitterionic intermediate **21** would be expected to be stabilized by the presence of the two electron-withdrawing groups. However, from comparison with the reactions of *N*-alkyl pyrroles with acceptor-acceptor substituted carbenoids (eqn (2)), the alkylation of the carbenoid would be expected to occur at the 2-position, rather than at the



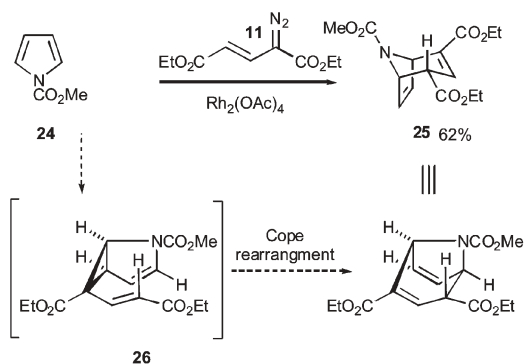
**Scheme 2**  $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of 2-diazo-1,3-cyclohexanedione **19** in the presence of *N*-carboethoxy pyrrole **18**.

3-position which is observed in Scheme 2.<sup>9</sup> Pirrung *et al.* proposed that a cyclopropane intermediate was formed initially which undergoes ring-opening to intermediate **21**.<sup>12</sup> It could be argued that the steric effect of having an *N*-acyl substituent combined with a bulky rhodium carbenoid may switch the regioselectivity to the 3-position. This regioselectivity is observed in the reactions of *N*-Boc pyrrole with donor-acceptor carbenoids (*vide infra*),<sup>13</sup> which supports a direct alkylation in this case.

**Donor-acceptor carbenoids.** The reaction of donor-acceptor carbenoids with *N*-acyl pyrroles is very different from the reactions of the other types of carbenoids because these carbenoids display much greater chemo- and stereoselectivity.<sup>6</sup> This influence is clearly seen in the reaction of the aryldiazoacetate **22** with *N*-Boc pyrrole (**14**) (eqn (5)).<sup>13</sup> The  $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction results in the formation of the bicyclic product **23** even when a large excess (6 equiv.) of the pyrrole **14** is used. The monocyclopropane could be isolated only when pyrrole **14** was used as solvent. This demonstrates the greater chemoselectivity apparent when donor-acceptor carbenoids are used, as the monocyclopropane is more efficiently cyclopropanated than the pyrrole **14** even though this is in large excess. This reaction also illustrates the high stereoselectivity exhibited by the donor-acceptor carbenoid because **23**, which has six stereogenic centers, is formed as a single diastereomer in 77–83% ee.



The rhodium-catalyzed reaction of vinyl diazoacetates with *N*-acyl pyrroles is a very efficient method for the synthesis of tropanes,<sup>10</sup> because the initially formed divinylcyclopropane is capable of ring expansion *via* a Cope rearrangement. An example of this is the reaction of vinyl diazoacetate **11** with *N*-carboxymethyl pyrrole (**24**), which results in the formation



**Scheme 3** Tandem cyclopropanation–Cope rearrangement.

of the tropane **25** in 62% yield (Scheme 3).<sup>10</sup> The facile Cope rearrangement requires the stereoselective formation of the *cis*-divinylcyclopropane **26**, and this type of stereoselectivity is a distinctive feature of the reactions of donor–acceptor substituted carbenoids.<sup>4</sup>

The vinyl diazoacetate **27**, which lacks functionality at the vinyl terminus, displays a more complicated reactivity profile because it can be attacked at either the carbenoid site to form **28** or the vinylogous position to form **29** (Table 1).<sup>14</sup> One of the major advantages of the dirhodium tetracarboxylates is the possibility of changing the electron density around the catalyst.<sup>15</sup> In this case electron-deficient catalysts and relatively polar solvents favor vinylogous reactivity, while electron-rich catalysts and hydrocarbon solvents favor carbenoid reactivity.<sup>14</sup>

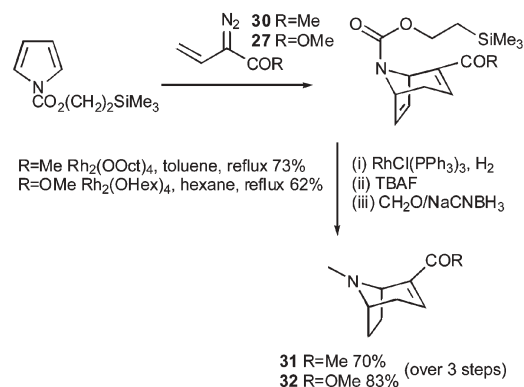
The utility of this methodology in tropane synthesis is shown in the racemic total synthesis of two alkaloids, ferruginine **31** and anhydroecgonine methyl ester **32**.<sup>14</sup> Using the optimized conditions derived from Table 1 ( $\text{Rh}_2(\text{OHex})_4$  or  $\text{Rh}_2(\text{OOct})_4$  catalyst, non-polar solvent), vinyl diazoacetates **27** and **30** undergo the [4 + 3] cycloaddition process in good yield. Completion of the synthesis can be achieved by standard reaction manipulations (Scheme 4).

Another impressive example of the use of the [4 + 3] cycloaddition in natural product synthesis is Kende *et al.*'s total synthesis of isostemofoline **36**.<sup>16</sup> A key nortropinone intermediate was acquired through the tropane **35**, formed by the [4 + 3] cycloaddition of pyrrole **33** and siloxy-substituted vinyl carbenoid **34** in 90% yield (Scheme 5).

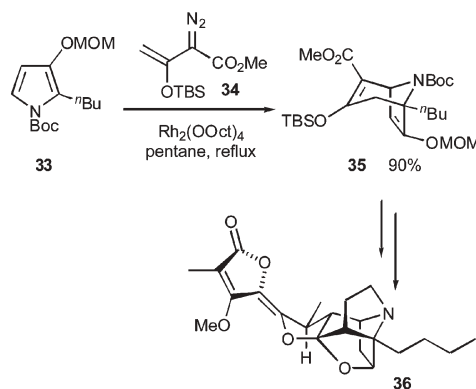
Unexpected products can be generated if conditions favor the formation of zwitterionic intermediates. This can be clearly

**Table 1** Vinylogous *versus* carbenoid reactivity

Catalyst	Solvent	<b>28</b> Yield (%)	Ratio <b>28</b> : <b>29</b>
$\text{Rh}_2(\text{OAc})_4$	$\text{CH}_2\text{Cl}_2$	35	55 : 45
$\text{Rh}_2(\text{tfa})_4$	$\text{CH}_2\text{Cl}_2$	16	15 : 85
$\text{Rh}_2(\text{OHex})_4$	Hexane	75	>95 : 5



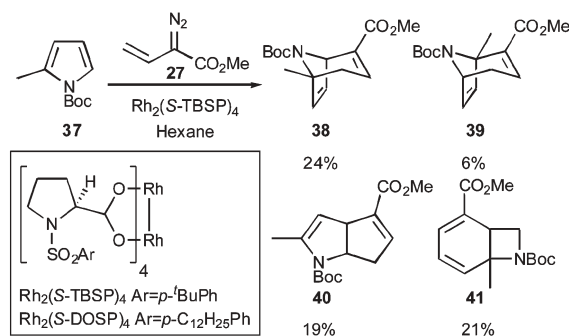
**Scheme 4** Total synthesis of ferruginine (**31**) and anhydroecgonine methyl ester (**32**).



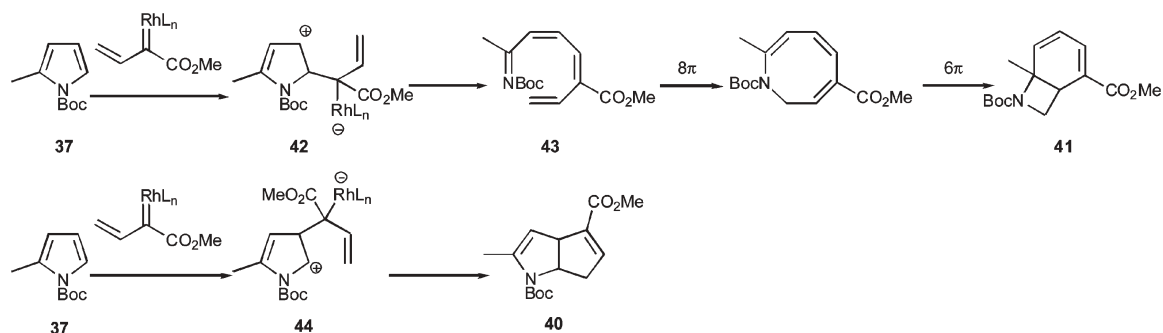
**Scheme 5** Total synthesis of isostemofoline **36**.

seen in the  $\text{Rh}_2(S\text{-TBSP})_4$ -catalyzed reaction of vinyl diazoacetate **27** with 2-methyl-*N*-Boc-pyrrole (**37**) (Scheme 6).<sup>17</sup> Although the dirhodium tetraprolineates  $\text{Rh}_2(S\text{-TBSP})_4$  and  $\text{Rh}_2(S\text{-DOSP})_4$  are excellent chiral catalysts for asymmetric cyclopropanation with donor–acceptor carbenoids,<sup>18</sup> in this case the reaction goes awry.<sup>17</sup> In addition to a regioisomeric mixture of tropanes **38** and **39**, two other major products, the azabicyclo[3.3.0]octane **40** and the azabicyclo[4.2.0]octane **41**, are formed.

An explanation for the formation of such a complex mixture is given in Scheme 7.  $\text{Rh}_2(S\text{-TBSP})_4$  is a relatively electron-deficient catalyst and so the formation of zwitterionic intermediates is enhanced.<sup>5,17</sup> The tropanes **38** and **39** would



**Scheme 6**  $\text{Rh}_2(S\text{-TBSP})_4$ -catalyzed reaction of vinyl diazoacetate **27** with 2-methyl-*N*-Boc-pyrrole (**37**).



**Scheme 7** Proposed mechanism for the formation of **40** and **41**.

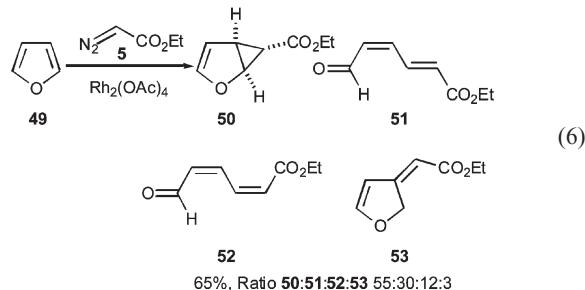
be expected to be formed by a standard, concerted, non-synchronous cyclopropanation followed by a Cope rearrangement,<sup>14</sup> but the unexpected products **40** and **41** would be derived from zwitterionic intermediates. Attack of the rhodium carbenoid at the 2-position of the pyrrole would generate the zwitterion intermediate **42**, which would initiate a cascade reaction of ring-opening to trienamine **43**, followed by a successive  $8\pi$  and  $6\pi$  electrocyclization to form **41**. Alternative attack at the 3-position would generate the zwitterionic intermediate **44**, which could then close to **40**.

A solution to achieving asymmetric induction without side reactions due to zwitterionic intermediates has been to use chiral auxiliaries.<sup>17</sup> The reaction of *N*-Boc pyrrole **14** and vinyl diazoacetates **45** and **47** with the inexpensive chiral auxiliaries (*S*)-lactate and (*R*)-pantolactone gives the desired tropane products **46** and **48** in good yields and reasonably high levels of asymmetric induction (Scheme 8). The carbonyl of the auxiliary is considered to coordinate to the carbenoid, thereby not only causing the asymmetric induction, but also, modulating the carbenoid reactivity.

## Reaction with furans

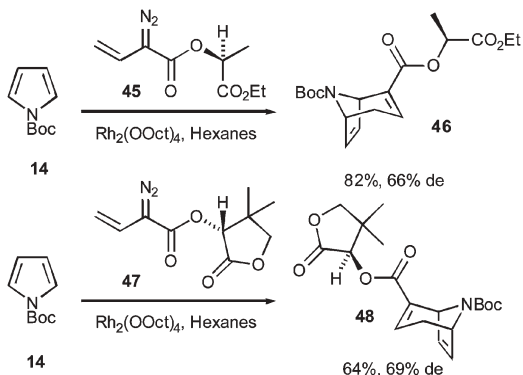
**Acceptor substituted carbenoids.** The reaction of furans with carbenoids usually leads to unravelling of the heterocycle, resulting in differentially functionalized dienes in good yield.<sup>19,20</sup> The  $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction between ethyl diazoacetate **5** with furan (**49**) revealed the formation of four

products (eqn (6)), including cyclopropane **50**, two isomeric dienes **51** and **52**, as well as alkylation product **53**.<sup>20</sup> Additionally, cyclopropane **50** is unstable and rearranges to diene **51** upon prolonged standing.

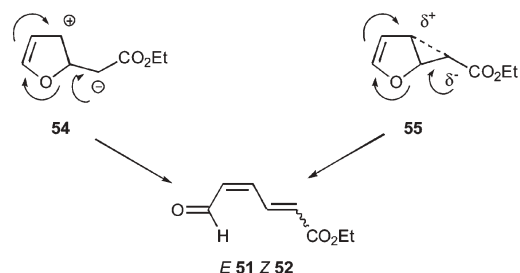


The formation of dienes **51** and **52** can be proposed from several intermediates.<sup>19,20</sup> One possibility is that a zwitterionic intermediate **54** forms by electrophilic addition of the carbenoid to the furan ring at the 2-position. The cycloreversion reaction to the corresponding dienes **51** or **52** then proceeds as depicted in Scheme 9. However, the observation that cyclopropane **50** can also rearrange to diene **51** upon standing means that a cyclopropane intermediate cannot be ruled out, although this rearrangement would need to be catalyzed under the reaction conditions. Also, this would not be consistent with the fact that the cyclopropane **50** rearranges exclusively to diene **51**.

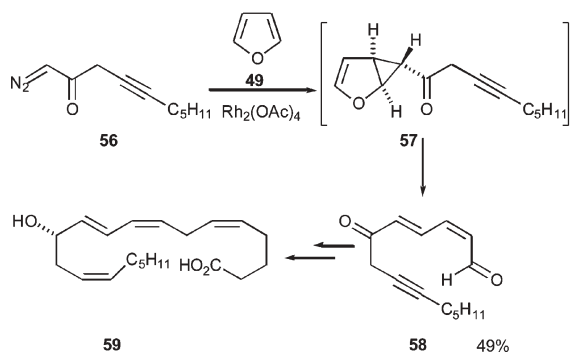
The ability to form functionalized dienes has been exploited in the synthesis of leukotrienes, such as 12-hydroxyeicosatetraenoic acid (**59**).<sup>21</sup>  $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of diazoacetate **56** with furan **49** generates cyclopropane **57** which, on standing, reverts predominantly to the (*Z,E*)-diene **58**, a key intermediate in the synthesis of target **59** (Scheme 10). The strategy is quite general and has been applied to a series of related compounds.<sup>22</sup>



**Scheme 8** Asymmetric formal [4 + 3] cycloaddition reactions using  $\alpha$ -hydroxyester chiral auxiliaries.



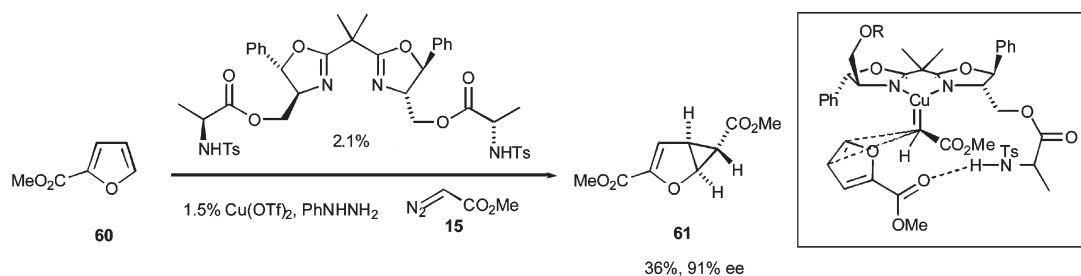
**Scheme 9** Possible mechanisms for the formation of dienes **51** and **52**.



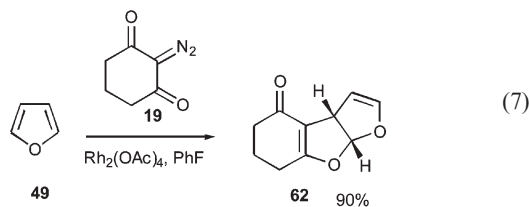
**Scheme 10** Total synthesis of 12-hydroxyeicosatetraenoic acid **59**.

Reiser *et al.* report that the enantioselective cyclopropanation of furan **49** with acceptor carbenoids is a poor reaction. The use of a copper bisoxazoline catalyst results in moderate enantioselectivities (<50% ee) and very low yields (>20%).<sup>11</sup> However, the situation changes dramatically when methyl furan-carboxylate **60** is subjected to cyclopropanation with this catalyst system. While the yields in these reactions are still not ideal (19–46%), the cyclopropanation is regioselective for the less-substituted, more electron-rich double bond, and highly diastereoselective, with only the *exo*-adduct **61** isolated (Scheme 11). Additionally, high enantioselectivity (up to 91% ee, with recrystallization from pentane providing a product with 99% ee) can be achieved in these reactions. The authors propose that the major change in reactivity is due to hydrogen bond interaction between the bisoxazoline ligand and the ester group of the substrate **60** as depicted in Scheme 11 to control the approach of the substrate **60** to the metal center of the catalyst.<sup>11</sup>

**Acceptor–acceptor carbenoids.** Pirrung *et al.* reported that furan **49** reacts with 2-diazo-1,3-cyclohexanedione **19** to generate tricycle **62** in good yield (eqn (7)).<sup>23</sup> The reaction likely proceeds through a zwitterionic species similar to the reaction of **19** with *N*-acyl pyrroles<sup>12</sup> (Scheme 2). A puzzling feature of this transformation is the fact that **62** would need to be derived from a zwitterionic intermediate derived from attack of the carbenoid at the 3-position, which is electronically disfavored. Pirrung *et al.* suggested that the regiochemistry is due to the stereoelectronics involved in ring-opening of the furanocyclopropane.<sup>12,23</sup> This reaction has been extended to a range of furan derivatives with variable success.<sup>23</sup>

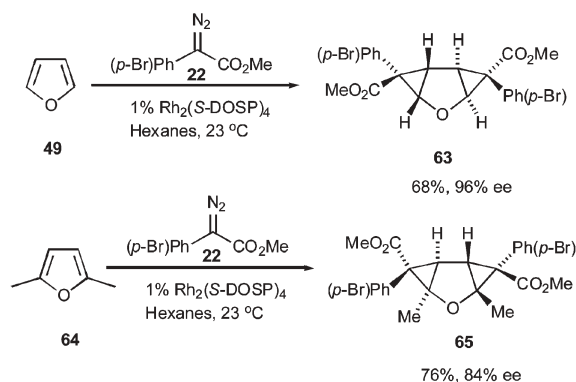


**Scheme 11** Asymmetric cyclopropanation of methyl furan-2-carboxylate **60**.

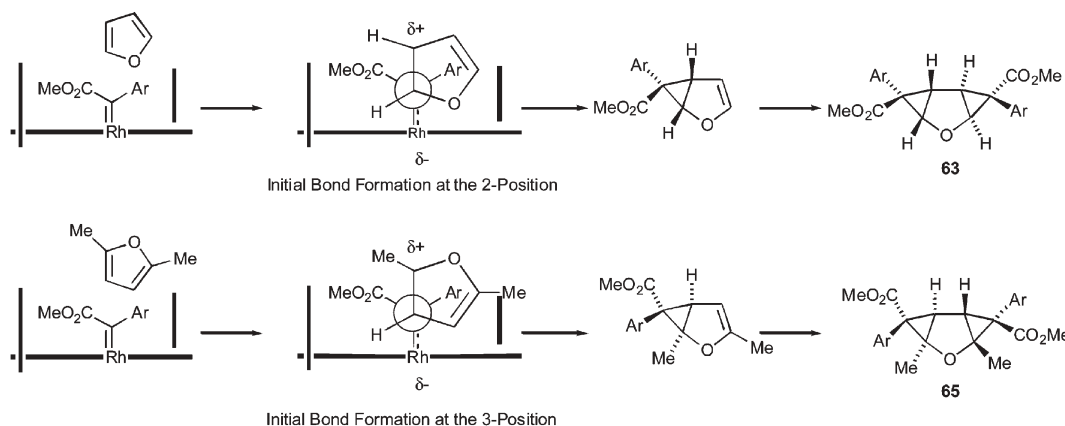


**Donor–acceptor carbenoids.** The  $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of aryldiazoacetates with furans reveals some very interesting trends as illustrated in Scheme 12.<sup>13</sup> The reaction of the aryldiazoacetate **22** with furan (**49**) gave predominantly the bicyclopentane **63** when **22** was used in a three-fold excess. The tendency towards double cyclopropanation is not as pronounced with furan as it is with *N*-Boc pyrrole and when furan is used in excess the monocyclopropane product becomes the dominant product. Most interestingly, when the reaction is conducted with 2,5-dimethylfuran (**64**), the bicyclopentane **65** is formed, which has the opposite sense of absolute configuration to **63**. Furthermore, the sense of the asymmetric induction in the formation of **65** is the same as observed for the reaction of **22** with *N*-Boc pyrrole (eqn (5)).

The intriguing phenomenon that the enantiomer formed is dependent on the structure of the heterocycle can be rationalized by considering the point of initial attack by the carbenoid.<sup>13</sup> The model shown in Scheme 13 is derived from the predictive model for the asymmetric induction for  $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed cyclopropanation.<sup>24</sup> The non-synchronous cyclopropanation would be expected to initiate at the 2-position of furan and the 3-position of 2,5-dimethylfuran.<sup>13</sup>



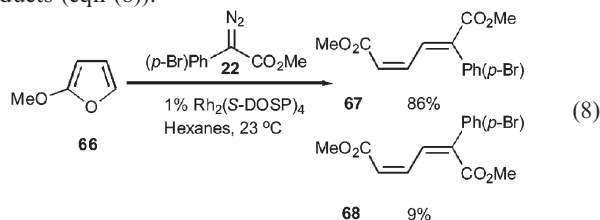
**Scheme 12**  $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of **22** with furan and 2,5-dimethylfuran.



**Scheme 13** Model for  $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed cyclopropanation of furan and 2,5-dimethylfuran (Ar = (*p*-Br)Ph).

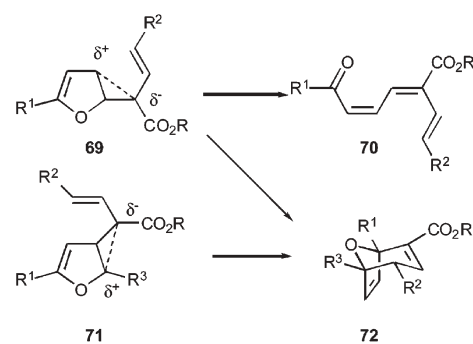
This results in the formation of the same diastereomer but opposite enantiomers, even though the same enantiomer of the catalyst is used in both cases. The fact that the reaction with *N*-Boc pyrrole gives the opposite asymmetric induction to furan suggests that the steric influence of the *N*-Boc group causes the cyclopropanation to be initiated at the C-3 position.<sup>13</sup>

In the reactions described above, products derived from unravelling of the furan ring were only very minor side products. Thus, the donor groups in the donor-acceptor substituted carbenoids seem to make these carbenoids less prone to the formation of zwitterionic intermediates compared to the acceptor carbenoids. However, if electron-donating groups are incorporated into the furan, then zwitterionic transformations can become the dominant reaction pathway.<sup>25</sup> This is clearly seen in the reaction with 2-methoxyfuran (**66**) with **22** where the dienes **67** and **68** become the exclusive products (eqn (8)).<sup>13</sup>



Furans are excellent substrates for the vinylcarbenoid formal [4 + 3] cycloaddition reactions leading to the formation of 8-oxabicyclo[3.2.1]octadienes **72**.<sup>25,26</sup> The [4 + 3] cycloadduct **72**, however, is not always the dominant product in this reaction, as a competing reaction involving ring-opening of the furan ring to form triene **70** can take place (Scheme 14). The reactions are believed to occur through dipolar intermediate **69**, when bond formation at the 2-position is more advanced than at the 3-position. The ring system becomes prone to cleavage, and opens to triene **70** in competition with the Cope rearrangement to form **72**. The ratio of **70** to **72** is dependent on the extent of charge build up in the transition state. In contrast, when bond formation at the 3-position is more advanced during the initial cyclopropanation, *i.e.* **71**, the Cope rearrangement to form **72** proceeds uneventfully.

Because the nature of the dipolar intermediate **69** or **71** is crucial to the reaction, the product distribution is heavily

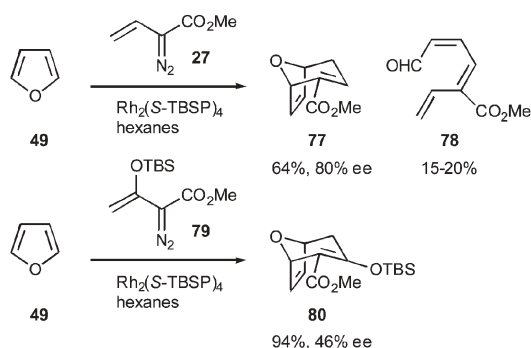


**Scheme 14** Formation of triene **70** and 8-oxabicyclo[3.2.1]octadiene **72** in the reactions of vinylcarbenoids with furans.

influenced by the substituents on both the diazoacetate **73** and the furan **74** (Table 2).<sup>25,27</sup> It can be seen that furans with electron-donating substituents, such as methoxy, lead to exclusive formation of the ring-opened triene product **76**.<sup>25</sup> In contrast, 2,5-dimethylfuran generates only the tandem cyclopropanation-Cope rearrangement product **75**. Reaction with furan forms a mixture of these two products, in favor of **75** when the vinyl diazoacetate is functionalized with either one or two electron-withdrawing groups. The relative amount of **76** in the product distribution can be increased by using 2-methylfuran, as the increased electron density relative to

**Table 2**  $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of vinyl diazoacetate **73** in the presence of furan **74**

R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	<b>75</b> Yield (%)	<b>76</b> Yield (%)
Et	H	CO <sub>2</sub> Et	OMe	H	0	92
Et	H	CO <sub>2</sub> Et	Me	Me	70	0
Et	H	CO <sub>2</sub> Et	H	H	62	26
Et	H	CO <sub>2</sub> Et	Me	H	8	74
Me	H	H	H	H	51	15
Me	OTBS	H	H	H	90	0

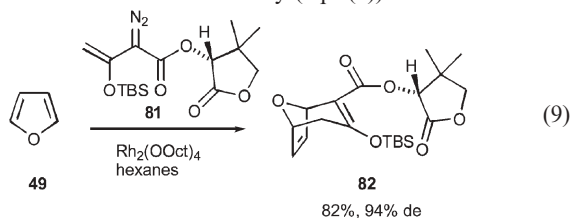


**Scheme 15**  $\text{Rh}_2(\text{S-TBSP})_4$ -catalyzed decomposition of vinyl diazoacetates **27** and **79** in the presence of furan **49**.

furan helps stabilize the developing charges on intermediate **69**. The reaction of furan with siloxy-substituted diazoacetate eliminates the competing triene formation to generate product **75** in high yield (90%).<sup>27</sup>

The 8-oxabicyclo[3.2.1]octadiene **75** is a versatile building block in organic synthesis.<sup>28</sup> This compound can generally be prepared by the [4 + 3] annulation between allyl cations and furans.<sup>29</sup> However, diastereocontrol is not assured using this method, and so the vinylcarbenoid approach provides a useful alternative in this case. The methodology is amenable to an asymmetric reaction when the chiral catalyst  $\text{Rh}_2(\text{S-TBSP})_4$  is used (Scheme 15).<sup>27</sup> Reaction with vinyl diazoacetate **27** generates the desired [4 + 3] adduct **77** in reasonable enantioselectivity (80% ee), but the reaction was hampered by the formation of the triene side product **78**. Formation of trienes such as **78** can be inhibited by using silyloxy-substituted vinyl diazoacetate **79** (Table 2), but in this case the product **80** was isolated with only moderate enantioselectivity (46% ee).

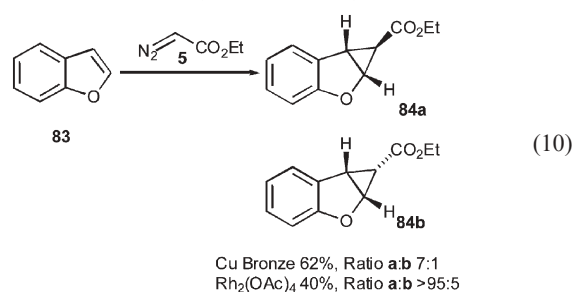
As the chiral catalyst  $\text{Rh}_2(\text{S-TBSP})_4$  is not especially effective in these reactions, the chiral auxiliaries which proved to be effective for the [4 + 3] annulation between vinyl diazoacetates and pyrroles (Scheme 8)<sup>17</sup> become a viable alternative. Accordingly, the  $\text{Rh}_2(\text{OOct})_4$ -catalyzed reaction of (*R*)-pantolactone-based vinyl diazoacetate **81** provides oxabicyclic **82** in good yield and diastereoselectivity (eqn (9)).<sup>27</sup>



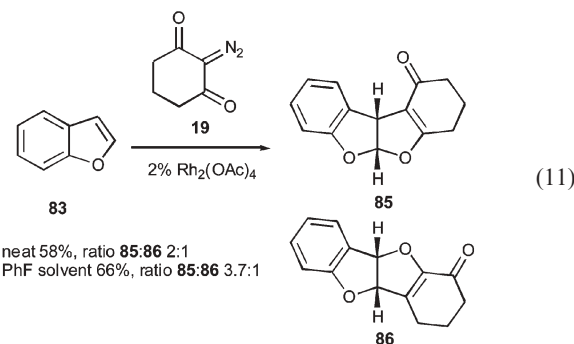
## Reactions with benzofurans

**Acceptor substituted carbenoids.** Benzo-fused heterocycles offer an opportunity of reaction with carbenoids at either the benzene or heterocycle portion, although it would be expected that reaction at the latter would predominate as it is more electron-rich. Wenkert *et al.* report the copper-catalyzed reaction of ethyl diazoacetate **5** with benzofuran **83** undergoes cyclopropanation of the enol ether double bond to provide a 7 : 1 mix of diastereoisomers **84a** and **84b** (eqn (10)).<sup>30</sup> A more

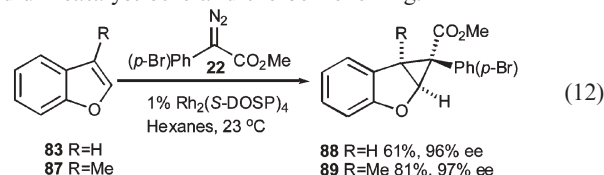
recent example of this reaction using  $\text{Rh}_2(\text{OAc})_4$  isolated the *exo* isomer **84a** exclusively in moderate yield.<sup>31</sup>



**Acceptor-acceptor substituted carbenoids.**  $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of 2-diazo-1,3-cyclohexanedione **19** in the presence of benzofuran **83** yields two regiomer cycloadducts **85** and **86**, arising from competition between initial bond formation at the 2- and 3-positions (eqn (11)).<sup>23</sup> The ratio of these compounds is dependent on the reaction conditions, with a greater amount of **85** formed in fluorobenzene than when the reaction is conducted neat in benzofuran **83**.



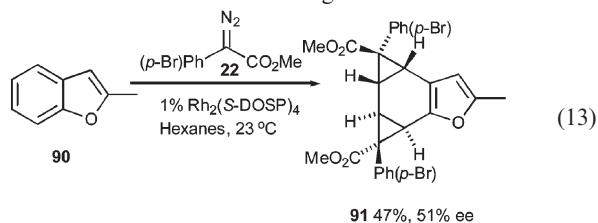
**Donor-acceptor carbenoids.** The reaction of benzofuran **83** or 3-methylbenzofuran **87** with **22** provided a single diastereomer **88** or **89** with very high enantioselectivity using  $\text{Rh}_2(\text{S-DOSP})_4$  catalyst (eqn (12)).<sup>13</sup> The high enantioselectivity can be explained by an extension of the model shown in Scheme 13. Cyclopropanation with initial bond formation at the 2-position proceeds to give the enantiomer observed. A cyclopropanation reaction to give the opposite enantiomer necessarily has to proceed with initial bond formation at the 3-position, and this would involve a steric clash between the rhodium catalyst core and the benzene ring.



Further evidence of the subtleties of this chemistry is seen in the reaction of 2-methylbenzofuran **90** with **22**. In this case, no cyclopropanation of the enol ether double bond is observed, and the product results from double cyclopropanation of the benzene ring to give **91** (eqn (13)).<sup>13</sup> The reaction at the enol ether is effectively blocked at the 3-position by the benzene ring, and at the 2-position by the methyl group. It is particularly noteworthy that the steric demands of this

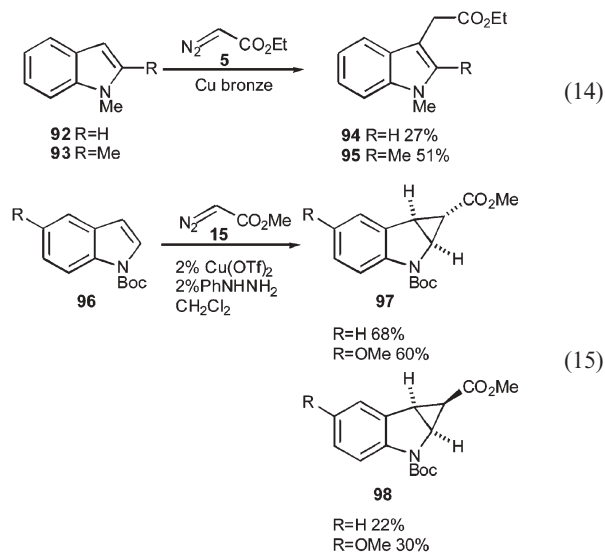


reaction lead to the disruption of a more stable benzene ring over a more electron-rich furan ring.

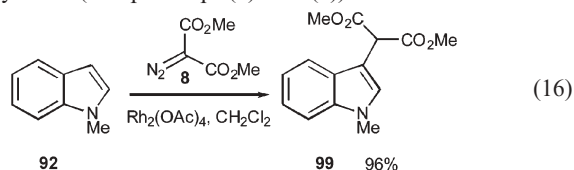


## Reactions with indoles

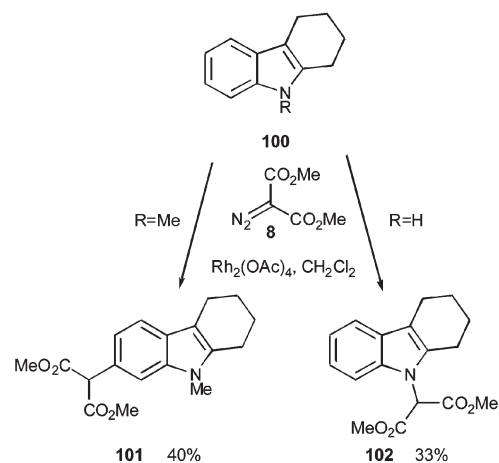
**Acceptor substituted carbenoids.** *N*-Alkyl indoles **92** and **93** form alkylation products in a manner similar to *N*-alkyl pyrroles (eqn (1)), although the regioselectivity of this transformation is switched so that the 3-substituted product **94** or **95** is the only product (eqn (14)).<sup>30</sup> This is consistent with the electrophilic substitution reactions of indole derivatives—indoles behave more like isolated enamines, which react with electrophiles at the 3-position. The incorporation of an electron-withdrawing group in the case of *N*-Boc indole **96** allows cyclopropane products to be isolated as a mixture of the two diastereomers **97** and **98** (eqn (15)).<sup>32</sup>



**Acceptor-acceptor substituted carbenoids.** Upon treatment of *N*-alkyl indoles such as **92** with dimethyl diazomalonate **8**, alkylation product **99** is obtained (eqn (16)).<sup>33</sup> Again the yield is much higher than the corresponding reaction with ethyl diazoacetate **5** (eqn (14)), showing the same trends observed with pyrroles (compare eqn (1) and (2)).



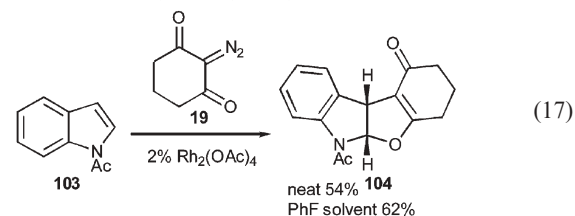
If both the 2- and 3-positions are blocked in a substrate such as **100**, alkylation can be observed at the 6-position on the benzene ring to give **101** (Scheme 16). Additionally, in contrast



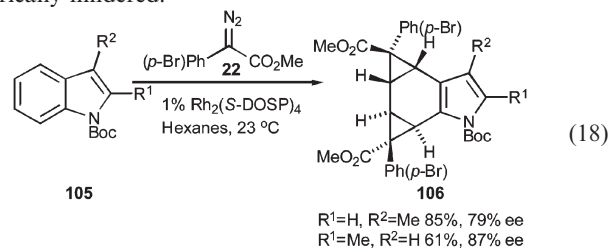
**Scheme 16**  $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of dimethyl diazomalonate **8** in the presence of indole **100**.

to the reactions of pyrrole derivatives,<sup>8</sup> unless the nitrogen atom has a substituent, *N*-H insertion to form **102** is a competing process.<sup>33</sup>

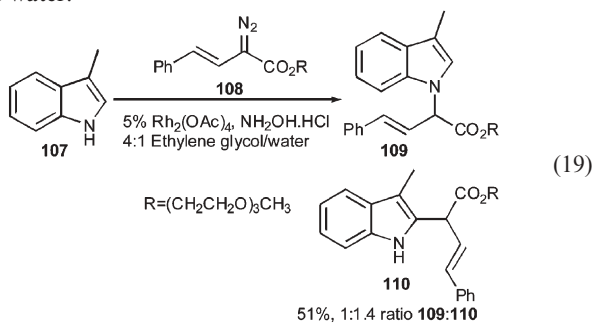
With *N*-acyl indole **103** and 2-diazo-1,3-cyclohexanedione **19**, a tetracyclic product **104** is observed (eqn (17)) in common with Pirrung *et al.*'s other results in this area.<sup>23</sup> However, in contrast to the reaction with benzofuran **83** (eqn (11)), in the reaction with **103** only a single regioisomer is formed.



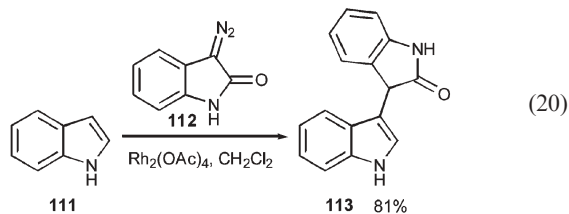
**Donor-acceptor carbenoids.** The  $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of 2- or 3-methyl-*N*-Boc indole **105** with **22** resulted in double cyclopropanation of the benzenoid ring to isolate **106** as a single diastereomer (eqn (18)).<sup>13</sup> The apparent inert reactivity of the pyrrole ring can be rationalized by comparison to other systems—cyclopropanation with initial bond formation at the 3-position is blocked by the benzene ring as demonstrated in the benzofuran series (see Scheme 13), while the reaction with initial bond formation at the 2-position is hindered by the bulky *N*-Boc substituent. Apparently the less stringent steric demands of the acceptor carbenoid allow cyclopropanation of the heterocycle to occur (eqn (15)).<sup>32</sup> The more sterically demanding carbenoids derived from diazoacetates **8** and **22** demonstrate that reaction with the benzene portion of indole can occur as long as the pyrrole portion is sterically hindered.<sup>13,33</sup>



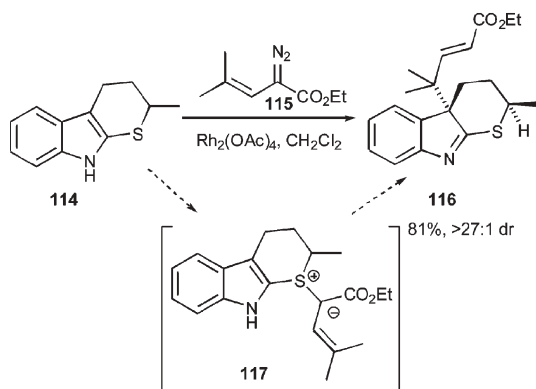
Reaction of a donor–acceptor carbenoid **108** with 3-methylindole **107** has been reported by Antos and Francis, and provides a mixture of *N*-alkyl product **109** and 2-alkyl product **110** (eqn (19)).<sup>34</sup> Nevertheless, this result shows that in the absence of a sterically-blocking *N*-substituent donor–acceptor carbenoids can undergo bond-forming reactions with indoles at the 2-position to form **110**. The use of diazoacetate **108** allows the reaction to be carried out in aqueous media, despite the anticipated reaction of the metal carbenoid intermediate with water.



Muthusamy *et al.* have reported that cyclic diazo compound **112** reacts with indole **111** to generate alkylation product **113** in good yield as a single regioisomer (eqn (20)).<sup>35</sup> *N*-Alkyl groups on both the indole **111** and the diazo compound **112** were tolerated in the reaction, but electron-withdrawing groups on **112** result in a lower yield of **113**.



Rainier *et al.* have reported an intriguing transformation involving the reaction of vinyldiazoacetate **115** with thioindole **114** (Scheme 17).<sup>36</sup> Product **116** arises from a Claisen rearrangement of intermediate sulfur ylide **117**, allowing the generation of indolines having quaternary substitution at the 3-position. The racemic thioindole is capable of transferring chirality from the position adjacent to sulfur to the 3-position of the indole to result in a highly diastereoselective formation of **116**.



**Scheme 17**  $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of vinyldiazoacetate **115** in the presence of thioindole **114**.

## Conclusions

The chemistry of metal carbenoids with electron-rich heterocycles can lead to a variety of interesting transformations. By considering the steric and electronic factors associated with the heterocycle and the metal carbenoid, a consistent mechanistic explanation for this chemistry can be made. This will greatly assist in the development of further synthetic advances in this area.

## Acknowledgements

Our studies on the reaction of rhodium carbenoids with electron-rich heterocycles were supported by the National Science Foundation (CHE-0350536) and the National Institutes of Health (DA-06301 and DA-15225).

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