PERSPECTIVE

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Catalytic and enantioselective allylic C–H activation with donor–acceptor-substituted carbenoids

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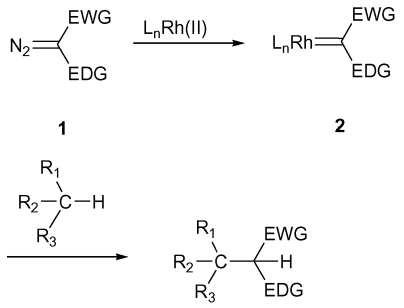
In this perspective we give an overview of enantioselective C–H activation at allylic sites by means of rhodium(II)-stabilized donor–acceptor-substituted carbenoids. This methodology has been proven to be both an equivalent to established asymmetric reaction sequences and a new synthetic approach with no established counterpart in organic synthesis.

Introduction

The functionalization of unreactive carbon–hydrogen bonds is an active field of investigation.[1–7] Transition metal complexes which undergo oxidative addition across the C–H bond have been used with great success.[4,8–12] However, developing truly catalytic processes using this approach has been found to be challenging. The active metal catalyst undergoes various changes in its oxidation state during the reaction and the regeneration of the catalytically active metal species is often difficult.[2,4,5] An alternative approach towards C–H activation is metal carbenoid-induced C–H insertion.[13,14] Yet, efficient processes using C–H insertions of carbenoids were limited to intramolecular reactions, as intermolecular variants of this reaction tended to give mixtures of products and suffered from competing side reactions.[13,15–17] Gratifyingly, in recent years it became apparent that intermolecular carbene C–H insertion reactions have great synthetic appeal if donor–acceptor-stabilized carbenoids of structure **2** are employed (Scheme 1).[18–20] Due to the presence of a donor group (*e.g.* vinyl or aryl) these carbenoids are much more attenuated in their reactivity and show greater chemoselectivity than conventional carbenes which contain only electron acceptor groups (*e.g.* ester, keto, phosphonate, sulfonate, cyano or nitro).[13,21] Carbenoids of structure **2** are available from the decomposition of appropriately substituted diazoacetates **1**, which are readily prepared even on large scales *via* diazo group transfer reactions.[22]



Scheme 1

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 UB Distinguished Professor and Larkin Professor of Organic Chemistry. His research interests include: catalytic asymmetric C–H activation, new synthetic methodology based on carbenoid intermediates, chiral catalysts for asymmetric synthesis, total synthesis of biologically active natural products, and development of chiral therapeutic agents. Some of his chiral dirhodium catalysts are now commercially available from Aldrich and Strem. Dr Davies has published over 150 articles and holds 10 patents. He is the recipient of a 2005 Cope Scholar Award and is currently the Chair of the Organic Division of the American Chemical Society.

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Joachim Nikolai was born in Ulm, Germany. He studied chemistry at the Universities of Ulm, Germany and Lausanne, Switzerland. In 2000 he received his MS from the University of Ulm where he pursued his studies under the guidance of Professor Gerhard Maas to obtain his PhD in 2004. In the same year, with a postdoctoral fellowship from the Deutsche Forschungsgemeinschaft (DFG), he joined the research group of Professor Huw Davies at Buffalo. His research interests are in the area of synthetic methodology development and computational chemistry applied to organic mechanisms and molecular structure.

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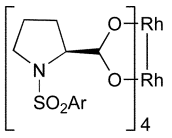
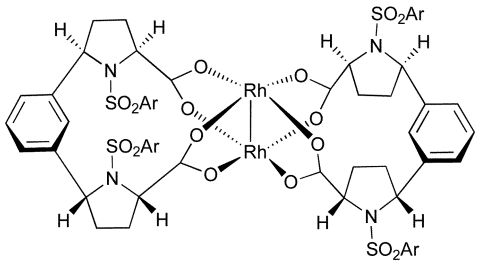
The decomposition of diazo compounds **1** can be catalyzed by air-, moisture- and heat-stable dirhodium tetraprolinates like Rh_2(*S*-DOSP)$_4$ (**3a**) or Rh_2(*S*-TBSP)$_4$ (**3b**). Second generation catalysts with more elaborate ligands are the bridged variants like Rh_2(*S*-biDOSP)$_2$ (**4a**) or Rh_2(*S*-biTISP)$_2$ (**4b**) (Fig. 1). Furthermore, highly asymmetric induction can be obtained routinely with these catalysts.[23–25]



3

a: Ar = *p*-$C_{12}H_{25}C_6H_4$ Rh_2(*S*-DOSP)$_4$
b: Ar = *p*-*t*-BuC_6H_4 Rh_2(*S*-TBSP)$_4$



4

a: Ar = *p*-$C_{12}H_{25}C_6H_4$ Rh_2(*S*-biDOSP)$_2$
b: Ar = 2,4,6-*i*-PrC_6H_2 Rh_2(*S*-biTISP)$_2$

Fig. 1 Chiral rhodium(II)-prolinate catalysts.

Examples illustrating the synthetic usefulness of donor–acceptor substituted carbenoids in conjunction with Rh(II)-prolinate catalysts are selective C–H insertion reactions α to heteroatoms such as nitrogen and oxygen and at benzylic sites.[26–30] This approach gives the opportunity to use the chemistry as a strategic surrogate for conventional synthetic reactions such as Mannich or aldol reactions.[26,27] Chemoselective C–H insertion at a benzylic site offered an excellent opportunity to accomplish a short and stereoselective synthesis of the lignans (+)-imperanene and (−)-α-conidendrin.[29]

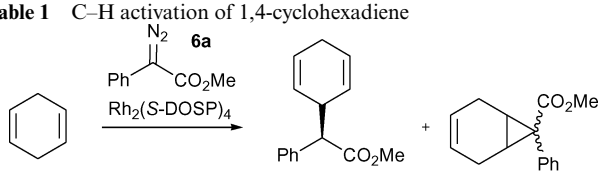
In depth discussions of various aspects of this work have been published in four reviews.[18–20,31] In this perspective we will focus on C–H activation at allylic sites employing donor–acceptor-stabilized Rh(II)-carbenoids, which opens new routes to non-conventional disconnection approaches in organic synthesis.

Allylic C–H insertions with aryldiazoacetates

A study published by Davies and coworkers first disclosed that in reactions catalysed by Rh_2(*S*-DOSP)$_4$ at −50 °C, donor–acceptor carbenoids prefer mono allylic C–H insertion into 1,4-cyclohexadiene (**5**) over cyclopropanantion of the *cis* double bonds (Table 1).[32] Under the optimized conditions using 2,2-dimethylbutane (2,2-DMB) as solvent, the C–H insertion product was formed in 80% yield and 91% ee. In comparison, the cyclopropanation is by far the most favored process in the reaction of 1,4-cyclohexadiene with ethyl diazoacetate.[33] When the reaction was conducted at room temperature, inferior enantioselectivities for C–H insertion product **7** were observed. Typically, these reactions are catalyzed with 1–2 mol% of Rh_2(*S*-DOSP)$_4$ but much lower catalyst loadings have also been used successfully.[32–34]

A similar trend was seen in the reaction of cyclohexene (**9**) with phenyldiazoacetate **6a**. A dramatic increase in enantioselectivity in the formation of C–H insertion product (**10**) was observed when a non polar solvent like 2,2-dimethylbutane (2,2-DMB) was used (Table 2).[35] These findings are in full agreement with results gained from earlier studies on cyclopropanation indicating that non polar solvent systems like 2,2-DMB at low temperatures give in general better stereoinduction in Rh_2(*S*-DOSP)$_4$ catalyzed reactions.[23,25] It is believed that these conditions help stabilize the D_2-symmetric conformation of the Rh_2(*S*-DOSP)$_4$ catalyst.

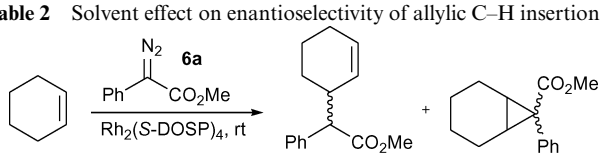
Table 1 C–H activation of 1,4-cyclohexadiene



5 **7** **8**

Temp./°C	Solvent	Yield (%)	Ratio **7** : **8**	Ee (**7**) (%)
−50	2,2-DMB	80	> 98 : 2	91
rt	CH_2Cl_2	98	> 98 : 2	65
rt	Pentane	50	> 98 : 2	71
rt	$CF_3C_6H_5$	37	> 98 : 2	72

Table 2 Solvent effect on enantioselectivity of allylic C–H insertion



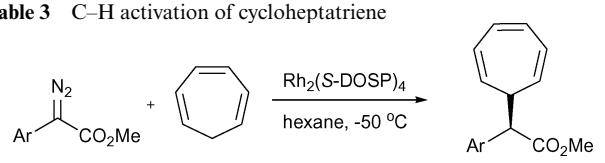
9 **10** **11**

Solvent	Yield **10** + **11** (%)	Ratio **10** : **11**	Ee **10** (%)
CH_2Cl_2	33	20 : 80	75
2,2-DMB	73	21 : 79	93

Aryldiazoacetates (**6a–d**) also prefer C–H insertion over cyclopropanation in reactions with cycloheptatriene (**12**). Remarkably, less then 5% cyclopropanation product was observed and high levels of enantioinduction could be achieved for reactions carried out at −50 °C in a hydrocarbon solvent (Table 3).[36] In these experiments ethyl diazoacetate once again showed clear preference for cyclopropanation over C–H insertion. These observations underpinned earlier results gained from C–H insertion reactions of donor–acceptor-stabilized Rh(II)-carbenoids into alkanes showing that these carbenoids display unique chemo- and stereoselectivity for C–H insertion reactions when compared to conventional mono- or bis-acceptor substituted carbenes.[37]

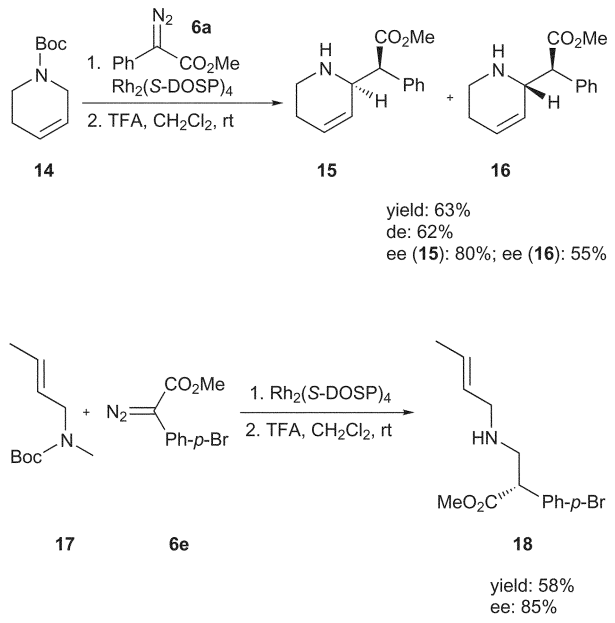
The C–H activation chemistry of donor–acceptor-substituted carbenoids is highly discriminating and can be strongly influenced by electronic and steric effects. An interesting example of this phenomenon is the C–H activation of *N*-Boc-1,2,3,6-tetrahydropyridine (**14**) which afforded C–H insertion products **15** and **16** in 63% yield with the predominant *erythro* diastereomer **15** being formed in 80% ee (Scheme 2).[38] No

Table 3 C–H activation of cycloheptatriene

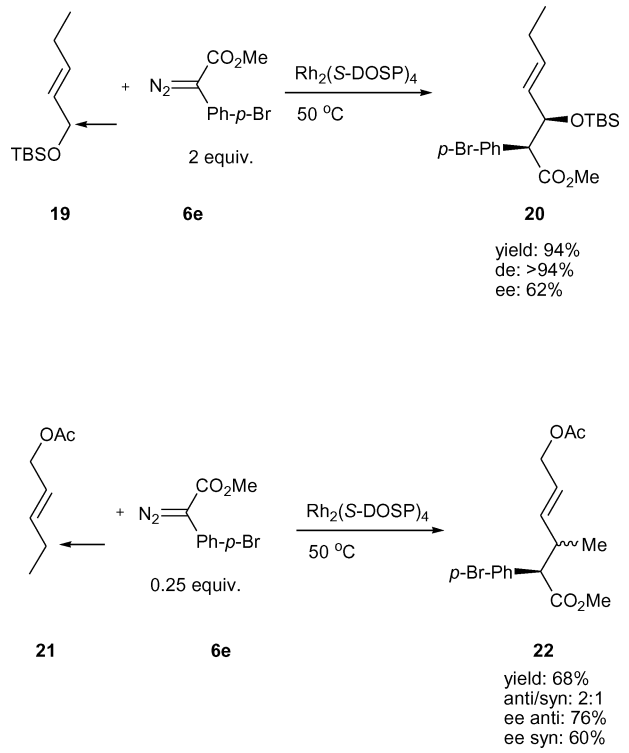


6a-d **12** **13a-d**

13	Ar	Yield [%]	Ee [%]
a	Ph	55	95
b	*p*-Cl-Ph	64	95
c	*p*-CH_3-Ph	60	94
d	2-Naphthyl	53	91



Scheme 2



Scheme 3

cyclopropanation of the *cis* double bond in **14** was observed. The only site of C–H activation was found to be the allylic methylene group α to the nitrogen atom. At this position, the build-up of positive charge occurring in the C–H insertion event can efficiently be stabilized by the C=C double bond as well as by the adjacent nitrogen atom. Electronic stabilization can be counterbalanced by steric effects as the rhodium carbenoid behaves as a sterically very encumbered species. Steric effects are readily seen in the C–H activation of *N*-Boc protected amine **17** (Scheme 2). In this case, no C–H insertion occurs at the electronically favoured allylic site, but instead C–H activation of the *N*-methyl group occurs.[27,39]

Another class of compounds that display impressive selectivity are protected allyl alcohols. The reaction of TBS-ether **19** with two equivalents of *p*-bromophenyldiazoacetate (**6e**) afforded aldol product **20** with very high yield (94%) and diastereoselectivity (>94% de). In contrast, C–H insertion products were formed in low yield in the reaction of 2-pentenyl acetate (**21**) under identical conditions (Scheme 3).[26] A much better reaction was achieved when 5 equivalents of **21** were used, although the product formed was derived from C–H activation at the alternate allylic site.[26]

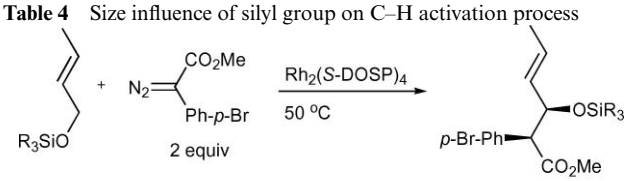
Reacting hexadienyl silyl ether **23** with *p*-bromophenyldiazoacetate (**6e**) yielded compound **24** with excellent regio- and stereoselectivity. The analogous reaction with hexadienyl acetate **25** afforded a mixture of **26** and **27**, where the major product **26** is derived from C–H insertion at the methyl site. In this case the electronically deactivating effect of the acetoxy group makes C–H insertion into an allylic methyl site dominate over the normally more reactive methylene site (Scheme 4).[26]

Considerable difference in reactivity is seen in substrates with potential C–H insertion sites neighbouring a siloxy or an acetoxy group. For example, substrate **28**, with differentially protected alcohols, afforded **29** with excellent regio- and diastereoselectivity from C–H insertion adjacent to the activating siloxy group (Scheme 5).[26]

Allylic C–H insertion α to an oxygen atom also displays significant dependence on steric effects: The high diastereoselectivity in the formation of the protected aldol products (**31**) is independent of the nature of the silyl group, but highest yields were observed with the smallest silyl group (**30a**) (Table 4).[26]

The C–H activation strategy of allyl *tert*-butyldimethyl silyl allyl ethers has been applied to a range of substrates.[26] The most significant results are summarized in Table 5. The reaction of phenyldiazoacetate (**6a**) with *trans*-cinnamyl TBS-ether afforded

Table 4 Size influence of silyl group on C–H activation process



30a-c **6e** **31a-c**

	R_3Si	Yield (%)	De (%)	Ee (%)
a	Me_3Si	93	>94	65
b	*t*-$BuMe_2Si$	71	>94	68
c	*t*-$BuPh_2Si$	64	>94	18

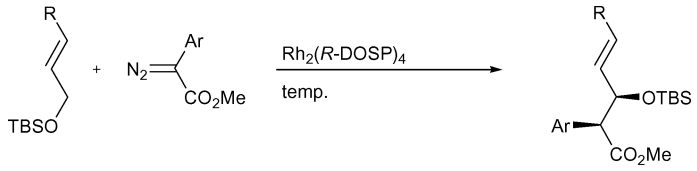
the C–H insertion product even at −25 °C in 94% yield (entry 1, Table 5). Due to the intrinsic stability of the donor–acceptor substituted carbenoids, these reactions can be carried out with the substrate as the limiting agent with even improved yields (entries 2 *vs.* 3 and 4 *vs.* 5).

One of the most exciting aspects of C–H insertion chemistry is that it offers new strategic reactions for organic synthesis. For example, asymmetric allylic C–H insertion of silyl enol ethers generates silyl-protected 1,5-dicarbonyl compounds normally obtained from an asymmetric Michael addition (Scheme 6).[40]

From previous studies it had been established that highly diastereoselective reactions at methylene sites are possible if the methylene substituents are of different size.[19,30,41] The reaction of vinyl ether **38** with the aryldiazoacetate **6e** afforded the diastereomeric Michael products **39** and **40** in 81% overall yield and a diastereomeric ratio of 81 : 19. The high selectivity of the reaction is highlighted by the fact that only one pair of diastereomers was formed despite the presence of three allylic sites in **38** (Scheme 7).[40]

Extension of this methodology to acyclic enol ethers **41a**,**b** afforded compounds **42a**,**b**. Significantly improved diastereoselectivity (>90%) was observed in these reactions presumably because the methylene substituents (C=C(OSiR_3)Ph and CH_3) are very different in size. At −30 °C, the enol ethers could be used as the limiting reagent without loss of yield (Table 6).[40]

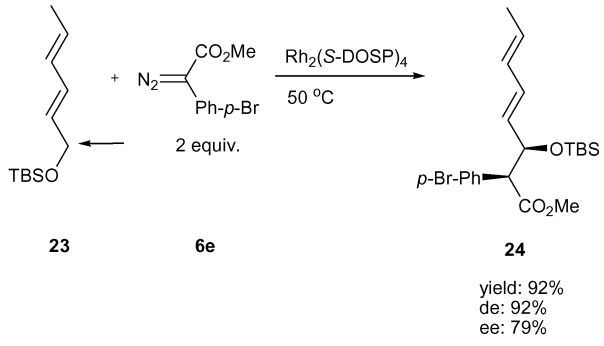
Table 5



32 **6a,b** **33-37**

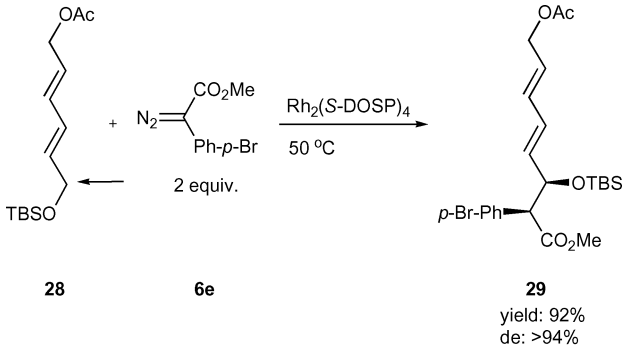
Entry	R	Ar	Diazo (eq.)	Temp./°C	Product	Yield (%)	De (%)	Ee (%)
1	Ph	Ph	2.0	−25	**33**	94	> 94	88
2	Ph	Ph	2.0	23	**34**	98	> 94	74
3	Ph	Ph	0.5	23	**35**	73	> 94	77
4	CO_2CH_3	*p*–Cl–Ph	2.0	23	**36**	93	> 94	48
5	CO_2CH_3	*p*–Cl–Ph	0.5	23	**37**	34	> 94	51[a]

[a] Reaction was conducted with Rh_2(*S*-DOSP)$_4$.



23 **6e** **24**

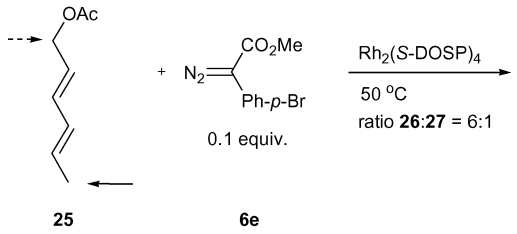
yield: 92%
de: 92%
ee: 79%



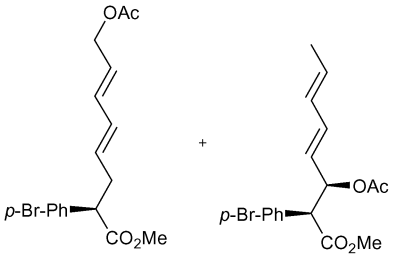
28 **6e** **29**

yield: 92%
de: >94%
ee: 72%

Scheme 5



25 **6e**



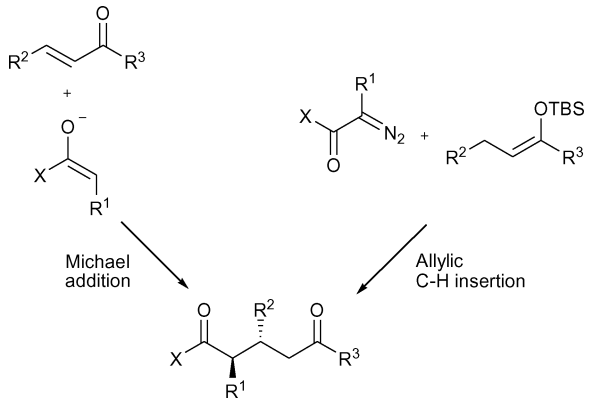
26 **27**

yield: 54%
ee: 84%

yield: 5%
de: 86%
ee: 70%

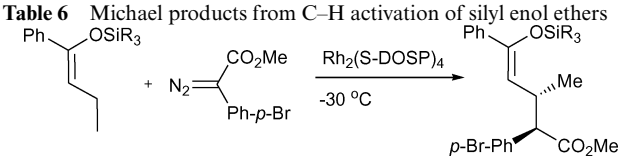
Scheme 4

An appealing feature of the allylic C–H insertion is the opportunity to introduce two stereocenters in a defined way by virtue of one single catalytic reaction. The synthesis of γ,δ-unsaturated esters, compounds normally assembled by an asymmetric Claisen rearrangement, is an interesting example of the strategic opportunities available through this chemistry (Scheme 8).[35]



Scheme 6

Table 6 Michael products from C–H activation of silyl enol ethers

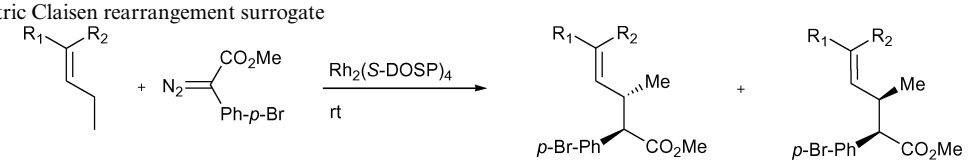


41a,b **6e** **42a,b**

	R_3Si	Yield (%)	De (%)	Ee (%)
a	TIPS	66	> 90	71
b	TBDPS	65	> 90	84

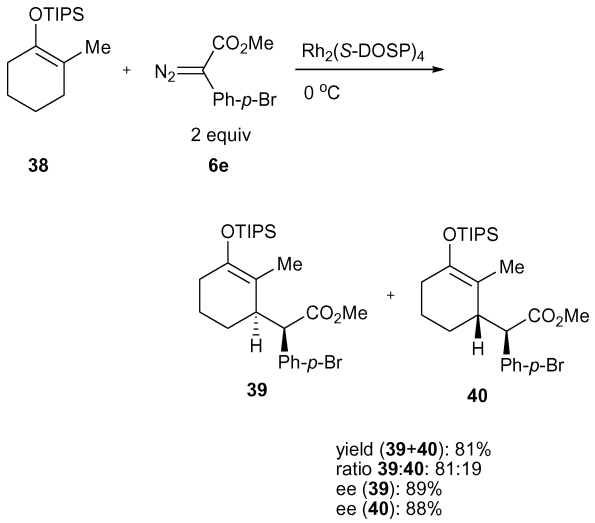
Table 7 summarizes the results obtained from C–H insertion reactions into acyclic allylic substrates. Only traces of C–H insertion (<4%) into the allylic methyl site were observed for substrate **43a**. In all instances, the major diastereomer **44** was formed with high asymmetric induction (86–96% ee).[35]

Table 7 Asymmetric Claisen rearrangement surrogate

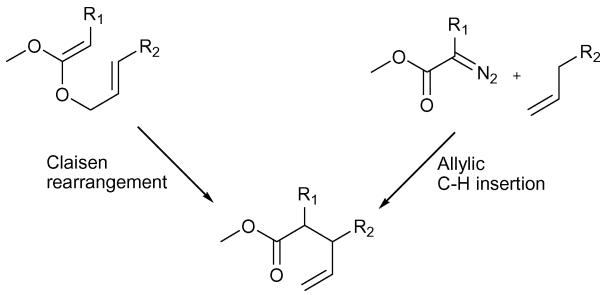


43a-c **6e** **44a-c** **45a-c**

43	R_1	R_2	Yield (**44** + **45**) (%)	Dr **44** : **45** (%)	Ee (**44**) (%)	Ee (**45**) (%)
a	Me	Me	67	75 : 25	86	66
b	Et	H	56	56 : 44	92	80
c	Ph	Ph	33	85 : 15	96	30

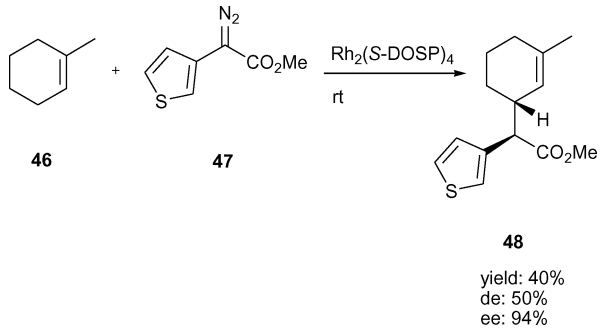


Scheme 7 Michael products from C–H activation chemistry.



Scheme 8

C–H insertion with donor–acceptor carbenoids is not limited to substituted phenyldiazoacetates. Although methyl thiophen-3-yldiazoacetate (**47**) has been found to be unproductive in C–H insertions with simple alkanes, it can be used in a straightforward manner in allylic C–H insertion chemistry. The synthesis of **48** in 94% ee highlights the possibility of incorporating heterocycles *via* C–H insertion reactions. (Scheme 9).[42]

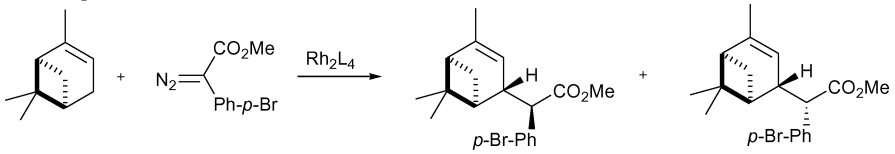


Scheme 9

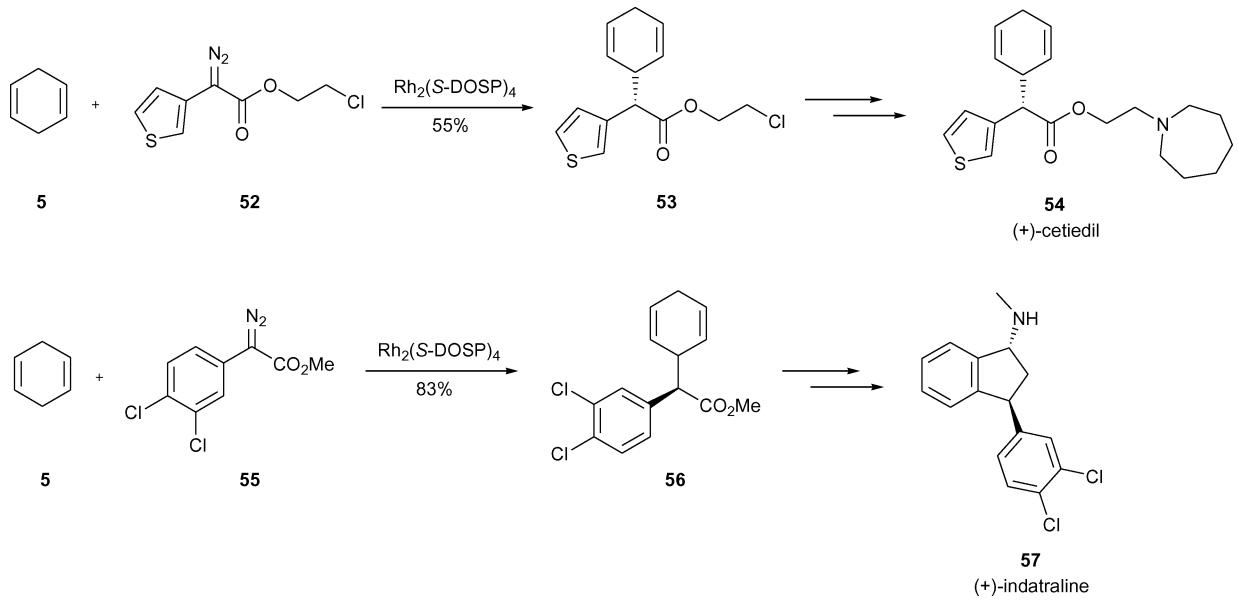
Using a C–H insertion approach, kinetic resolution of racemic substrate mixtures has been proven to be a very easy and reliable process.[35] The Rh_2(*S*-DOSP)$_4$ catalyzed reaction of (+)-**49** and *p*-bromo-phenyldiazoacetate (**6e**) resulted in the formation of C–H insertion products **50** and **51** in 93% combined yield and a diastereomeric ratio of 98 : 2 (Table 8). In contrast, the reaction of (+)-**49** with Rh_2(*R*-DOSP)$_4$ was found to be a mismatched reaction with only 62% yield for compounds **50** and **51**. In this reaction the diastereomeric ratio was reversed to 24 : 76. Starting from a racemic mixture of (±)-α-pinene (**49**) a very efficient kinetic resolution of the substrate produced C–H insertion product **50** in 99% ee (Table 8).[35]

Allylic C–H activation *via* rhodium(II)-catalysed insertion of donor–acceptor carbenoids has found application in the asymmetric synthesis of pharmaceutically interesting substances: C–H insertion of heteroaryl diazo compound **52** into 1,4-cyclohexadiene (**5**) set up the stereocenter in the asymmetric synthesis of the antiepileptic drug cetiedil (**54**) (Scheme 10).[42] Again using 1,4-cyclohexadiene (**5**) as the substrate, the Rh_2(*S*-DOSP)$_4$ catalysed reaction of 3,4-dichlorophenyldiazoacetate (**55**) set up the required stereocenters in the very first step of the synthesis of indatraline (**57**), a psychoactive substance with

Table 8 Kinetic resolution of α-pinene



49	Rh_2L_4	Temp./°C	Yield (%)	Dr **50** : **51**	Ee (**50**) (%)
(+) 0.5 eq.	Rh_2(*S*-DOSP)$_4$	25	93	98 : 2	—
(+) 0.5 eq.	Rh_2(*R*-DOSP)$_4$	25	62	24 : 76	—
(±) 10.0 eq.	Rh_2(*S*-DOSP)$_4$	0	52	88 : 12	99



Scheme 10 Synthesis of (+)-cetiedil (**54**) and (+)-indatraline (**57**).

high binding and inhibitory affinity for neuronal monoamine reuptake sites like the dopamine or serotonin transporter (Scheme 10).[42]

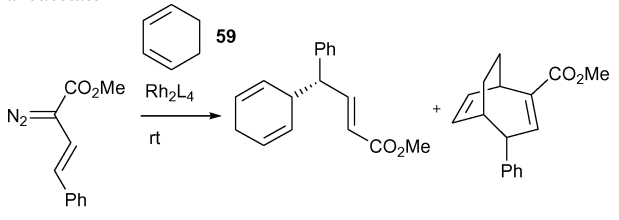
Allylic C–H insertion with arylvinyldiazoacetates

Allylic C–H insertion with arylvinyl substituted Rh(II)-carbenoids results in an unusual transformation. The reaction of phenylvinyldiazoacetate (**58**) with 1,3-cyclohexadiene (**59**) did not result in the formation of the expected C–H insertion product but rather the 1,4-cyclohexadiene derivative **60** was isolated in 63% yield and 98% ee (Table 9).[32] Bridged cycloheptene **61**, formed in a tandem cyclopropanation–Cope rearrangement[43] was identified as a side product. The ratio in which compounds **60** and **61** are formed depends on the steric and electronic effects (Table 9). For example, rhodium octanoate [$Rh_2(OOct)_4$] and the strongly electron deficient rhodium trifluoroacetate [$Rh_2(TFA)_4$] produced predominantly **61**. So far, $Rh_2(S\text{-DOSP})_4$ is the best catalyst for limiting the cyclopropanation reaction.[32]

The same mode of reaction seen for diazo compound **58** was observed with carbenoids derived from diazo compounds **62** and **64** and in the reaction of **58** with cycloheptatriene (**12**) (Scheme 11).[32,36] A distinctive feature of the depicted transformations is the exceptionally high enantioselectivity (97–99% ee) routinely obtained.

Mechanistically, these reactions can be interpreted as a combined C–H activation–Cope rearrangement (Scheme 12).

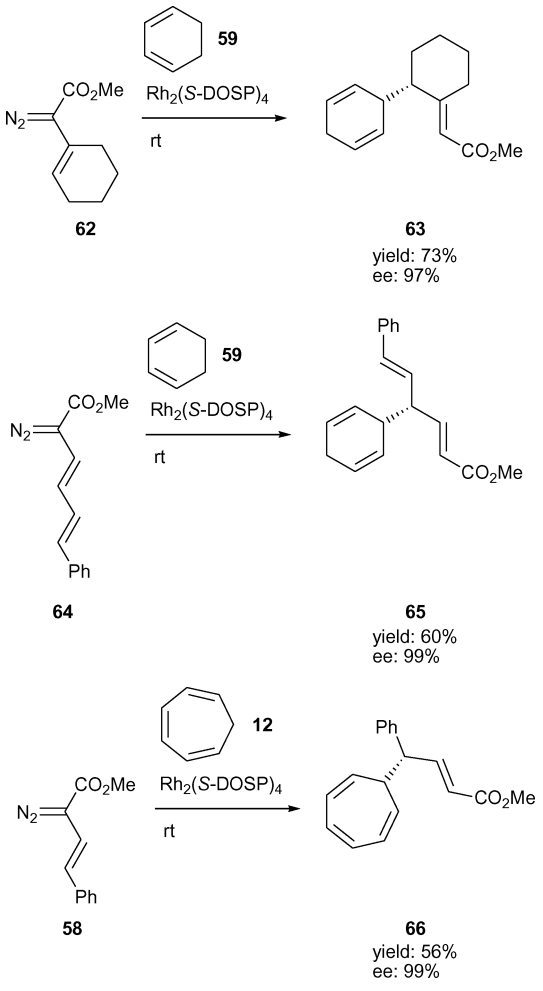
Table 9 C–H activation of 1,3-cyclohexene with phenylvinyldiazoacetate



58 60 61

Rh_2L_4	**60** : **61**
$Rh_2(S\text{-DOSP})_4$[a]	84 : 16
$Rh_2(OOct)_4$	26 : 74
$Rh_2(TFA)_4$	46 : 54

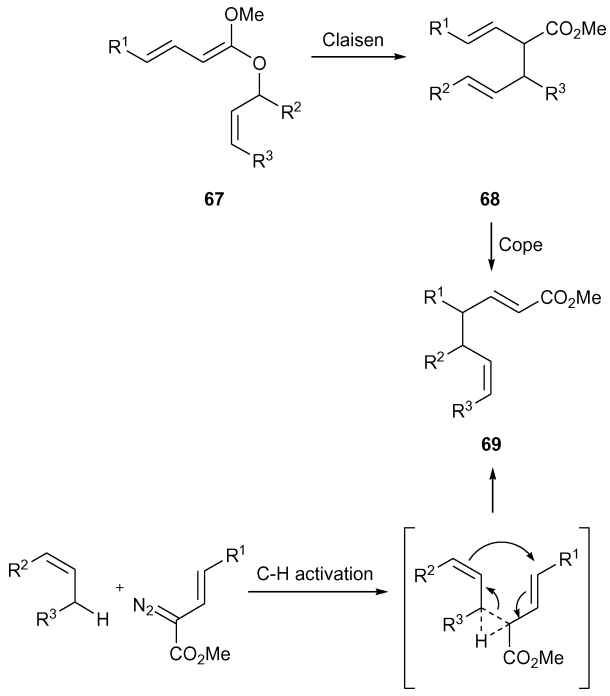
[a] ee **60**: 98%.



Scheme 11

Using classical synthesis, preparation of compounds **60**, **63**, **65** and **66** would be conceivable by a sequence employing a Claisen rearrangement followed by a Cope rearrangement (**67** → **68** → **69**, Scheme 12).[32] Thus, the carbenoid chemistry represents another promising disconnection strategy for synthesis.

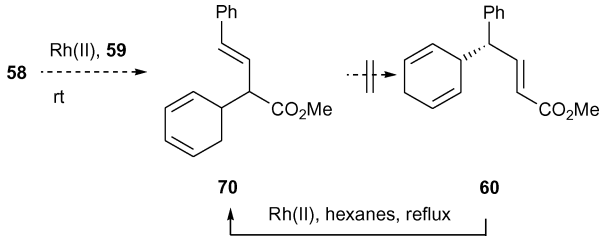
The most obvious mechanism for the reaction of vinyldiazoacetates with allylic sites would be a C–H insertion followed by a Cope rearrangement. This is not the case, however, because there is no thermodynamic driving force for the Cope rearrangement



67 68 69

Scheme 12

of the C–H insertion product **70** to **60**. Under the rhodium catalysed reaction conditions, both **70** and **60** are stable, while under forcing conditions **60** rearranges to **70** (Scheme 13). Based on this observation, an alternative mechanism involving a combined C–H activation–Cope rearrangement must be occurring because the direct allylic C–H insertion product **70** is not a viable intermediate to **60**.[32]



70 60

Scheme 13

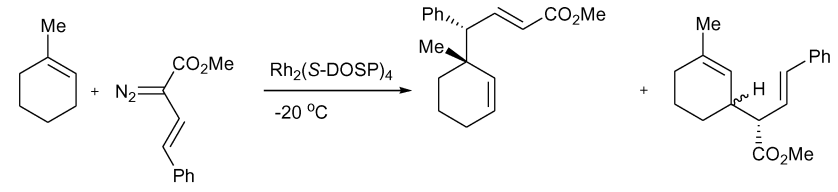
The combined C–H insertion–Cope rearrangement is both highly enantio- and diastereoselective. Reaction of phenylvinyldiazoacetate **58** with methylcyclohexene (**71**) at −20 °C afforded **72** virtually as one diastereomer in 98% ee (Scheme 14).[44] The minor product was the direct C–H insertion product **73**, which was formed as a mixture of diastereomers. The Rh_2(*S*-DOSP)$_4$ catalysed reaction of **58** with dihydropyranone **74** gave the C–H insertion–Cope product **75** in 87% yield, >98% de and 99% ee. Direct C–H insertion product **76** and cyclopropane **77** combined accounted for only 10% of the mass balance (Scheme 14).[44]

Cyclohexadiene **78**, obtained in 99% ee from a combined C–H activation–Cope reaction between 1,3-cyclohexadiene and 3,4-dichlorophenylvinyldiazoacetate, is an excellent precursor for the synthesis of the antidepressant drug (+)-sertraline (**81**). As shown in Scheme 15, key intermediate **80** could be synthesized with minimal racemization from **78**.[32]

Dihydronaphthalenes are exceptional substrates for the combined C–H activation–Cope rearrangement. From the reaction of 4-methyl-1,2-dihydronaphthalene (**82**) and ethylvinyldiazoacetate (**83**) the C–H insertion–Cope rearrangement product **84** could be isolated in >98% de and 98% ee. Upon heating in toluene, **84** underwent a retro-Cope rearrangement to form **85** (Scheme 16).[45] Complete stereocontrol occurs in the conversion of **84** to **85**, consistent with a chair transition state for the retro-Cope rearrangement.

In certain systems, the retro-Cope rearrangement is so favorable that the observed products are the apparent direct C–H insertion products. This is seen in the reaction of the dihydronaphthalene **82** with the phenylvinyldiazoacetate **58** (Scheme 17). The apparent direct C–H insertion product **87** is isolated in 92% yield, >98% de and 98% ee.[45] The reaction proceeds *via* the combined C–H insertion–Cope rearrangement to form **86** followed by an in situ retro-Cope rearrangement to form **87**.

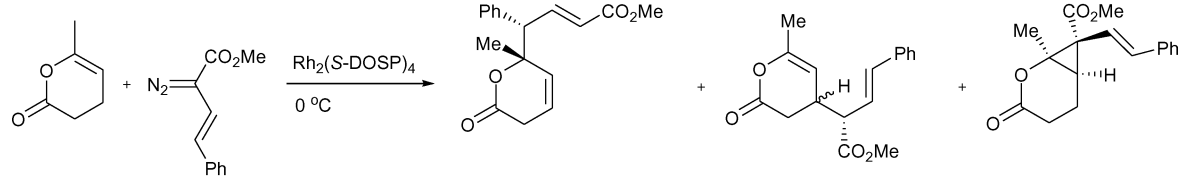
Other products rather than just dihydronaphthalene derivatives are accessible from this chemistry. The reaction with siloxydihydronaphthalene **88** generates the formal C–H insertion product **89** which is readily hydrolysed to ketone **90**. The overall transformation is intriguing because it would be



71 58 72 73

yield: 53%
de: >98%
ee: 98%

ratio **72**:**73** = 4.5:1

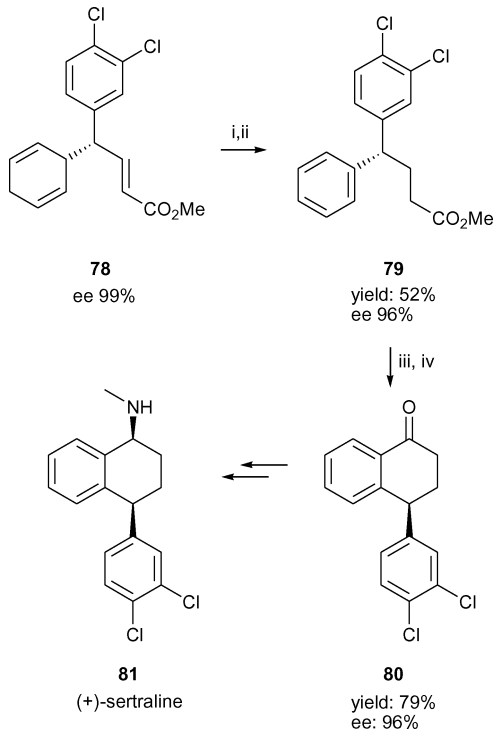


74 58 75 76 77

yield: 87%
de: >98%
ee: 99%

ratio **75**:**76**:**77** = 90:5:5

Scheme 14



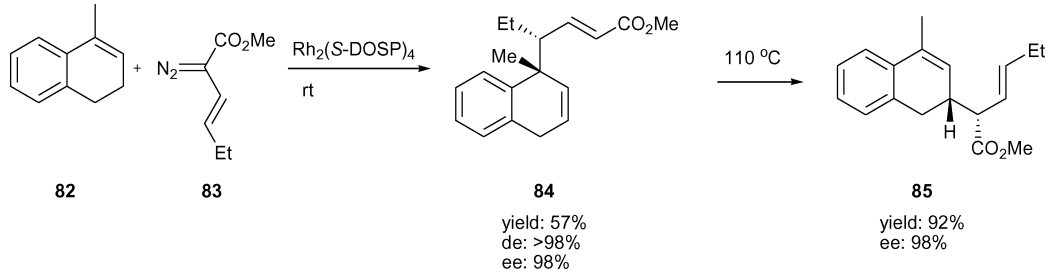
Scheme 15 (i) DDQ, C_6H_6; (ii) H_2, Pd/C; (iii) 6 M HCl; (iv) $ClSO_3H$.

the equivalent of a Michael addition to the keto tautomer of 1-naphthol, clearly an impractical transformation. *Via* this reaction cascade the rather elaborate formal Michael addition product **90** was accessible from the keto tautomer of 1-naphthol (**88**) in high yield, diastereoselectivity and enantioselectivity (Scheme 18).[45] Another pathway is possible with 4-acetoxy-1,2-dihydronaphthalene (**91**). The combined C–H activation/Cope rearrangement occurs to form **92**, which then aromatizes by elimination of acetic acid to form the naphthalene derivative **93** in an unexpected aromatization reaction (Scheme 19).

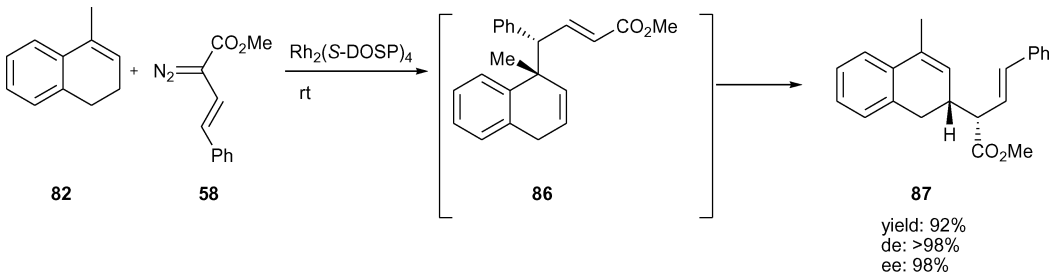
Scheme 20 shows a predictive model developed to rationalize the consistently observed high diastereo- and enantioselectivities in the combined C–H activation–Cope and the combined C–H activation–Cope–retro-Cope reaction.[45] In this model, the catalyst is assumed to exist in a D_2-symmetric conformation and can be simplified as having two blocking groups arranged as in **94**.[46] A front approach of the substrate over the vinyl group of the carbenoid is required in order to allow for the C–H insertion–Cope rearrangement to occur with a defined stereochemistry. A retro-Cope rearrangement *via* a chair like transition state finally generates **96** in the observed configuration.[45]

The combined C–H activation–Cope rearrangement installs two defined stereocenters in one catalytic reaction step. This methodology has the potential to be of general utility in the construction of diterpenes such as erogorgiaene (**97**), pseudopterosin aglycone (**98**) and colombiasin A (**99**) isolated from the West Indian sea whip *Pseudopterogorgia elisabethae* (Fig. 2).[47,48] These compounds have found some interest in recent years as antimycobacterial substances.[47,48]

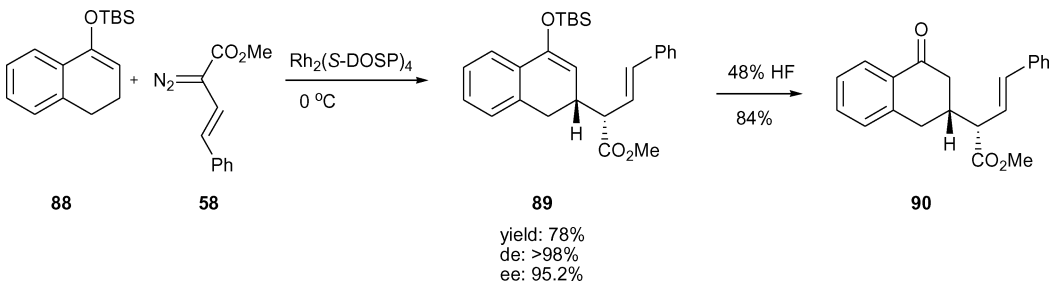
The control of three stereocenters remote from any functional group has proven to be challenging in the synthesis of members of this class of natural products.[49–55] Parallel kinetic resolution[56,57] of a racemic mixture of (±)-dihydronaphthalene **100** with vinyldiazoacetate **101** catalysed by $Rh_2(R\text{-DOSP})_4$, is a very direct method to control the setup of all three stereocenters. The C–H insertion–Cope product **103** was formed in 90% ee with all three stereocenters in the same relative configuration as found



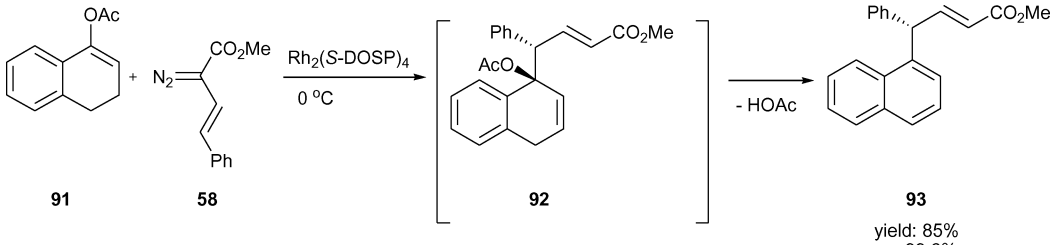
Scheme 16 Combined C–H activation–Cope rearrangement followed by a retro-Cope rearrangement.



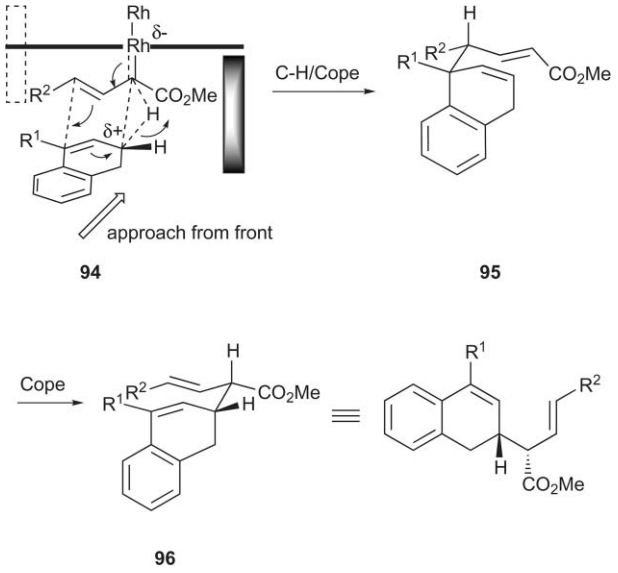
Scheme 17 Combined C–H activation–Cope–retro-Cope rearrangement.



Scheme 18



Scheme 19



Scheme 20 Predictive model for C–H insertion–Cope rearrangement.

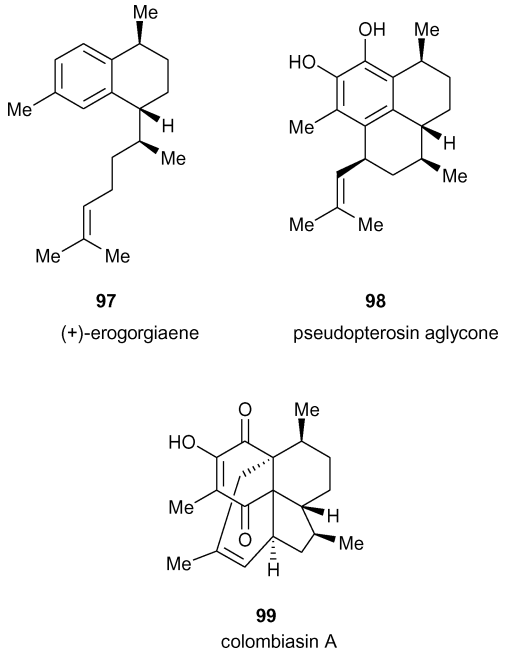
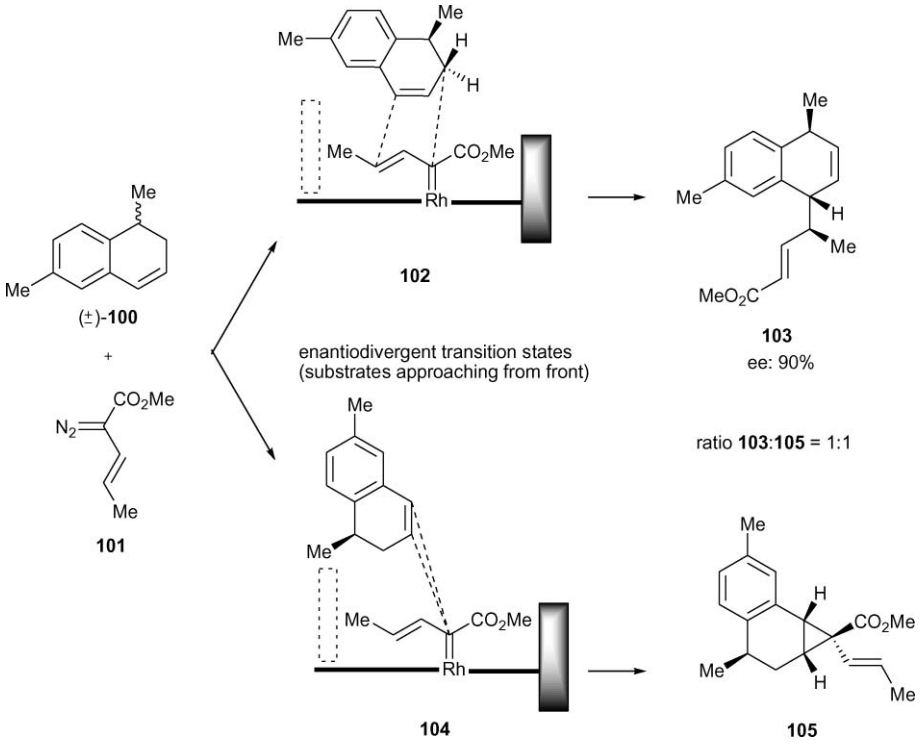


Fig. 2 Diterpenes from *Pseudopterogorgia elisabethae*.

in erogorgiaene (**97**) (Scheme 21).[58] In this reaction the (*R*)-**100** isomer was converted to cyclopropanation product **105**. A 1 : 1 mixture of the C–H activation product **103** and cyclopropane **105** (and a trace of a diastereomeric cyclopropane) was formed in a combined yield of 73%. Conversion of **103** to (+)-erogorgiaene (**97**) was achieved in four more steps. Based on (*R*)-**100** the final natural product was isolated in 45% overall yield, highlighting the efficiency of this kinetic resolution process.[58]

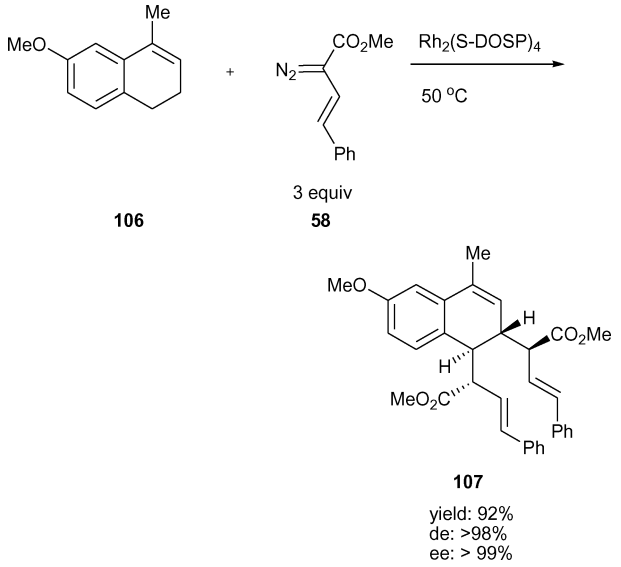
An explanation for the parallel kinetic resolution is shown in Scheme 21. Only (*S*)-**100** can undergo a matched C–H



Scheme 21 Parallel kinetic resolution *via* combined C–H insertion–Cope rearrangement.

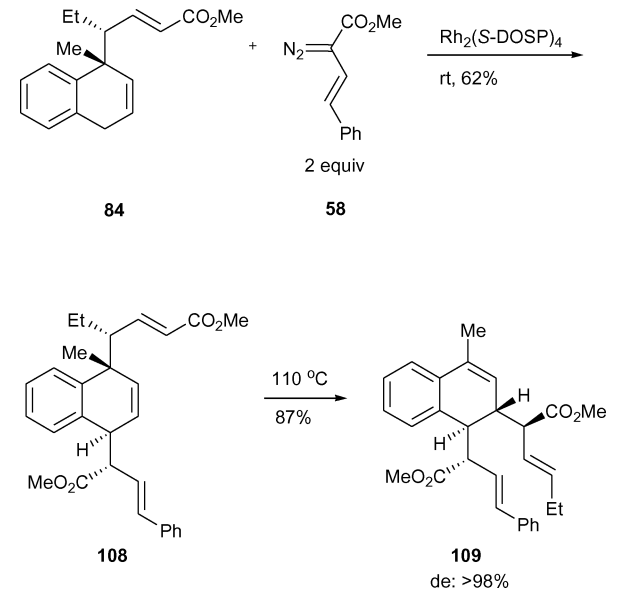
activation–Cope reaction with Rh_2(*R*-DOSP)$_4$, whereas (*R*)-**100** would have to approach the catalyst in a very unfavourable trajectory in which the methyl group at the asymmetric carbon atom points towards the catalyst in order to form the C–H activation–Cope product (transition state **102** *vs.* **104**).[58] Furthermore, only (*S*)-**100** can undergo a matched cyclopropanation to form **105** *via* transition state **104**.

Only a few examples of double C–H insertion using donor–acceptor-substituted carbenoids have been described.[27,59] Recently, it was found, that electronically rich dihydronaphthalenes like the 6-methoxy derivative **106** are excellent substrates for double C–H insertion reactions.[60] Using 3 equivalents of **58**, compound **107** could be isolated in 92% yield and in excellent diastereoselectivity (>98% de) as well as enantioselectivity (99% ee) (Scheme 22). In this reaction four defined stereocenters are installed in one step.[60]

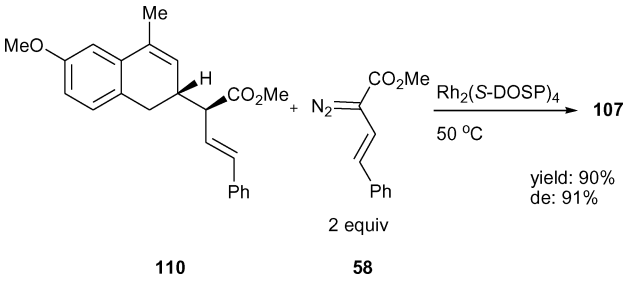


Scheme 22 Double C–H activation of 1,2-dihydro-6-methoxy-4-methyl-naphthalene.

The mechanism of the apparent double C–H activation is quite complex and involves a combined C–H activation–Cope rearrangement–retro-Cope rearrangement. The timing of the sequence is not clear, however, the second C–H activation can effectively be performed on either a C–H activation–Cope rearrangement product **84** (Scheme 23) or on a formal C–H activation product **110**. (Scheme 24).[60]

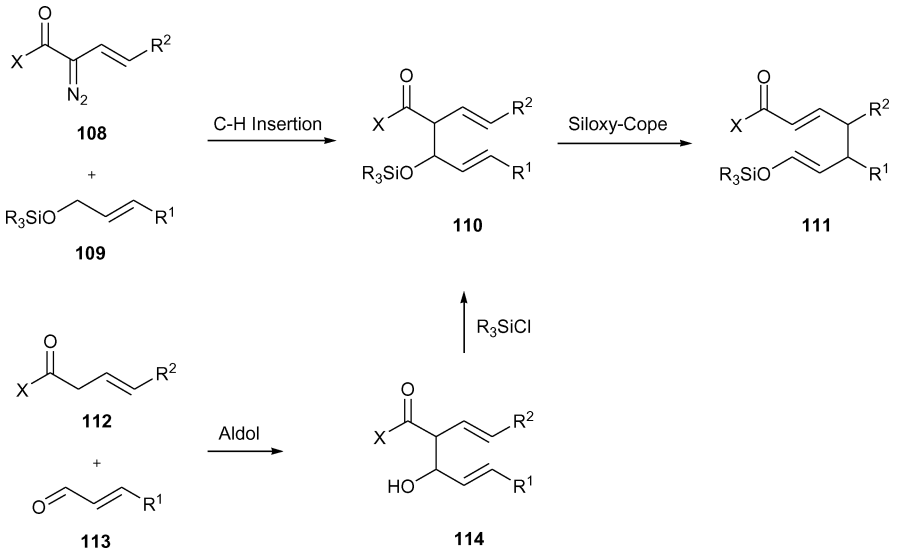


Scheme 23



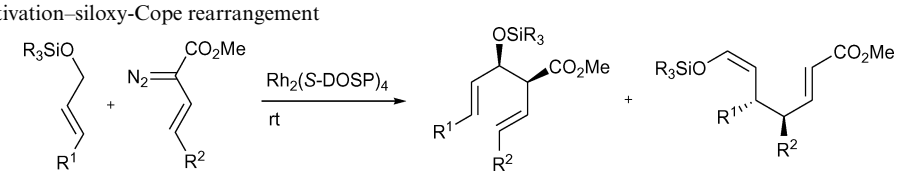
Scheme 24

One of the challenges of the combined C–H activation/Cope rearrangement is to use substrates that do not undergo a competing direct C–H activation, which is usually the thermodynamic product (see Scheme 13). One way to circumvent this problem would be to use allyl silyl ethers **109** as substrates. In this case, the C–H activation product **110** would not be the thermodynamically favored product because it would be capable of undergoing a siloxy-Cope rearrangement to **111**. Again, from a strategic perspective, this would be useful because it would be complementary to a sequential approach employing an enantioselective aldol condensation (**112** + **113** → **114**) followed by a siloxy Cope rearrangement of **110** to **111** (Scheme 25).



Scheme 25

Table 10 C–H activation–siloxy-Cope rearrangement



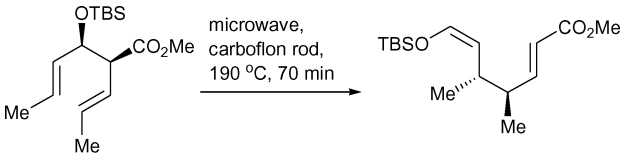
109a-e **115a-e** **116a-e**

	R_3Si	R^1	R^2	Yield [%][a]	**115** : **116**	De **115** (%)	Ee **115** (%)	De **116** (%)	Ee **116** (%)
a	TBS	Me	Ph	85	1.0 : 1.0	> 98	88	> 98	89
b	TBS	(*E*)-CH_3CH_2=CH–	Ph	69	1.0 : 2.5	> 98	91	> 98	92
c	TBS	C_6H_5	Ph	94	1.0 : 1.4	> 98	91	> 98	91
d	TBS	Me	Me	48	1.0 : 1.2	> 98	81	> 98	82
e	TMS	Me	Ph	82	1.0 : 1.3	> 98	90	> 98	91[b]

[a] combined yield. [b] Determined for the corresponding free aldehyde.

The C–H activation of allyl silyl ethers **109** with various vinyldiazoacetates leads to a mixture of the direct C–H activation products **115a–e** and the combined C–H activation–Cope rearrangement products **116a–e**. Both sets of products are formed with very high diastereoselectivity (>98% de) and similar enantioselectivity (81–92% ee) (Table 10).[61] Both sets of products are stable under the reaction conditions.

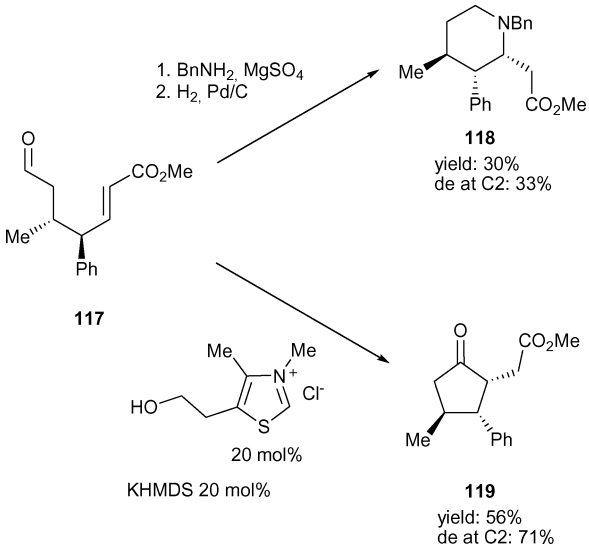
Unlike the previously described C–H activation–Cope reaction the C–H activation–siloxy-Cope rearrangement offers the possibility to drive the reaction to completion by heating, *i.e.* to convert the direct C–H activation products **115** completely to **116** *via* a thermal [3,3]-sigmatropic reaction. This conversion is most advantageously achieved under microwave conditions which afforded **116d** in 52% yield without loss of stereochemistry (Scheme 26).[61]



115d **116d**
yield: 52%
de: >98%
ee: 82%

Scheme 26 Microwave induced siloxy-Cope rearrangement.

The C–H activation–siloxy-Cope rearrangement offers opportunities for the rapid synthesis of a range of compounds. For example, deprotection of **116e** afforded aldehyde **117** which could be used as a building block in the synthesis of piperidine **118** or cyclopentenone **119** (Scheme 27).[61]



118
yield: 30%
de at C2: 33%

117

119
yield: 56%
de at C2: 71%

Scheme 27

Conclusion and perspective

Allylic C–H activation with donor–acceptor-substituted carbenoids displays unique chemo- and stereoselectivity in reactions catalysed by rhodium(II) prolinate Rh_2(*S*-DOSP)$_4$. The synthetic potential of this approach has been exploited in various examples ranging from the synthesis of elaborate organic intermediates for medicinal chemistry to total synthesis of natural products. Allylic C–H activation of donor–acceptor carbenoids has thereby been proven to be a reliable and handy complement to known asymmetric methods and furthermore gives the opportunity for novel asymmetric disconnection approaches unprecedented in the arsenal of conventional organic synthesis methodology.

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