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Reversal of the Regiochemistry in the Rhodium-Catalyzed [4+3] Cycloaddition between Vinyldiazoacetates and Dienes**

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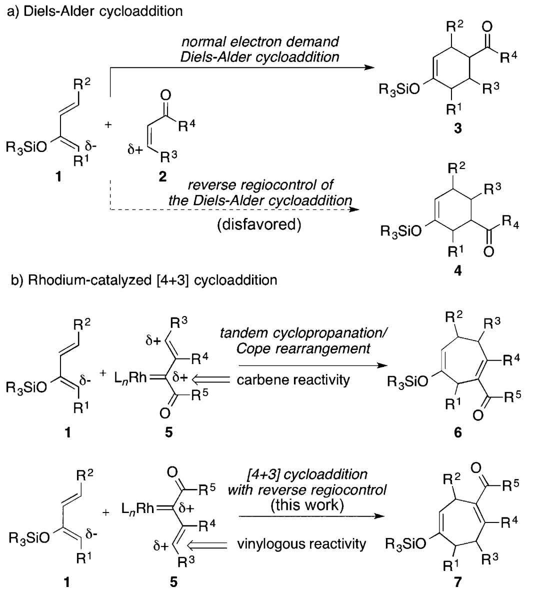
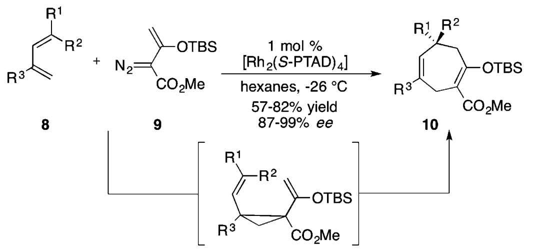
Abstract: *A regio-, diastereo-, and enantioselective [4+3] cycloaddition between vinylcarbenes and dienes has been achieved using the dirhodium tetracarboxylate catalyst [Rh_2(S-BTPCP)$_4$]. This methodology provides facile access to 1,4-cycloheptadienes that are regioisomers of those formed from the tandem cyclopropanation/Cope rearrangement reaction of vinylcarbenes with dienes.*

Cycloaddition reactions play a pivotal role in the synthetic design of complex natural products. The venerable Diels–Alder reaction is a notable example of the synthetic utility of cycloaddition strategies.[1] Excellent stereocontrol is routinely achieved, and with appropriate electronic bias in the diene **1** and dienophile **2**, high levels of regioselectivity are also obtained to form the cyclohexene **3** (Scheme 1 a).[2] The defined regiocontrol is a great advantage for the predictable use of the Diels–Alder reaction but it also presents a limitation as the reverse regioisomer **4** is not readily accessed. Limited methods have been developed to address this long-standing problem but they involve multistep synthetic sequences.[3] Relatedly, our laboratory has developed a rhodium-catalyzed formal [4+3] cycloaddition between vinyldiazoacetates and dienes (Scheme 1 b).[4,5] This reaction is also highly regioselective, as illustrated by the reaction of **1** with the rhodium vinylcarbene intermediate **5** to generate the cycloheptadiene **6**, because it proceeds by a tandem cyclopropanation/Cope rearrangement (CPCR). Herein we describe an alternative and mechanistically distinct [4+3] cycloaddition caused by initial attack of the diene at the vinylogous position of the vinylcarbene instead of at the carbene center. In this way, we achieve a regiochemical switch of the [4+3] cycloaddition, thus leading to the formation of the cycloheptadiene **7**.

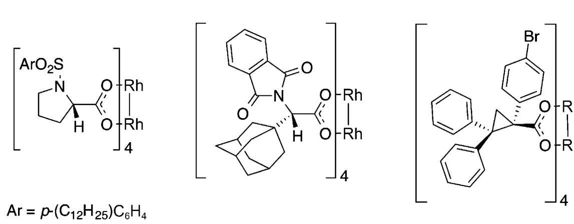


Scheme 1. Different cycloaddition approaches.

A representative example of the regular formal [4+3] cycloaddition of vinyldiazoacetates is the [Rh_2(S-PTAD)$_4$]-catalyzed reaction of the 2-siloxyvinyldiazoacetate **9** with various dienes (**8**; Scheme 2).[5a] Some of the most significant chiral catalysts for the reactions of vinyldiazoacetates are illustrated in Figure 1.[6] The [Rh_2(S-PTAD)$_4$]-catalyzed reaction proceeds with high asymmetric induction and has been used as a key reaction for the synthesis of several natural products.[5a,b] In all of the published examples to date, the



Scheme 2. [Rh_2(S-PTAD)$_4$]-catalyzed tandem cyclopropanation/Cope rearrangement. TBS = *tert*-butyldimethylsilyl.



Ar = *p*-($C_{12}H_{25}$)C_6H_4
[Rh_2(S-DOSP)$_4$] [Rh_2(S-PTAD)$_4$] [Rh_2(S-BTPCP)$_4$]

Figure 1. Representative chiral dirhodium catalysts.

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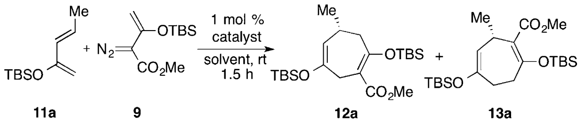
reactions are highly regioselective, thus proceeding by an initial cyclopropanation of the electronically most favorable and sterically most accessible double bond.

The possibility of reversing the regiochemistry of the CPCR [4+3] cycloaddition was discovered during a study of the reaction of **9** with 2-*tert*-butyldimethylsiloxybutadiene (**11a**) catalyzed by [Rh$_2$(*S*-PTAD)$_4$] (Table 1, entry 1). The major product was the typical CPCR cycloadduct **12a** but a small amount of the regiosiomeric [4+3] cycloadduct **13a** was also formed (**12a**/**13a** = 94:6). We rationalized that the formation of the regioisomeric [4+3] cycloadduct **13a** was most likely caused by a competing reaction of the diene occurring at the vinylogous position of the carbenoid, thus generating a zwitterionic intermediate, which then cyclizes to **13a**.[7–9] Previous studies have shown that vinylogous reactivity is favored in polar solvents.[7] Indeed, when the reaction was repeated using dichloromethane as the solvent, the ratio of **12a** to **13a** improved to 87:13, and the regiosiomeric [4+3] cycloadduct **13a** was produced in 71% *ee*. Another major chiral catalyst for vinyldiazoacetate reactions is the proline-derived dirhodium catalyst [Rh$_2$(*S*-DOSP)$_4$] (see Figure 1). The [Rh$_2$(*S*-DOSP)$_4$]-catalyzed reaction of **9** with **11a** increased the amount of **13a** formed. In the reaction conducted in *n*-pentane, the ratio of **12a** to **13a** was 79:21, whereas when dichloromethane was used as solvent, the ratio improved to 30:70 (Table 1, entries 3 and 4), but with poor enantiocontrol (5% *ee*).

Table 1: First observation of [4+3] cycloadduct **13a.**



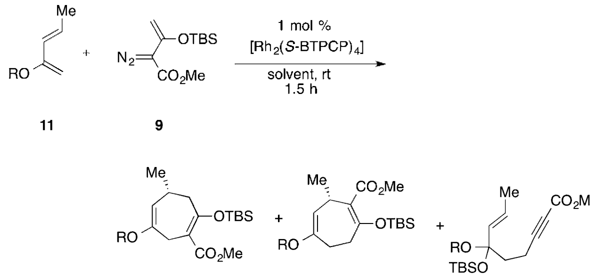
11a **9** **12a** **13a**

Entry	Solvent	Catalyst	**12a**/**13a**[a]	Yield [%]	**13a** *ee* [%][d]
1	*n*-pentane	[Rh$_2$(*S*-PTAD)$_4$]	94:6	55[b]	−73
2	CH$_2$Cl$_2$	[Rh$_2$(*S*-PTAD)$_4$]	87:13	43[c]	−71
3	*n*-pentane	[Rh$_2$(*S*-DOSP)$_4$]	79:21	62[c]	33
4	CH$_2$Cl$_2$	[Rh$_2$(*S*-DOSP)$_4$]	30:70	61[c]	5

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of the isolated **12a**. [c] Combined yield of **12a** and **13a**. [d] A negative sign indicates the enantiomer of **13a**.

Recently, we discovered that the sterically crowded tetrakis(triarylcyclopropanecarboxylate) dirhodium catalysts are very effective at enhancing vinylogous reactivity of rhodium vinylcarbenes.[8i] Therefore, we explored the effect of [Rh$_2$(*S*-BTPCP)$_4$] on the reaction of **9** with the 2-siloxydienes **11** (Table 2). The [Rh$_2$(*S*-BTPCP)$_4$]-catalyzed reaction resulted in the formation of a third product, the alkynoate **14a**, in addition to **12a** and **13a**. Compounds related to **14a** had been observed in the reaction of vinylcarbenes with vinyl ethers and were shown to be derived from vinylogous attack on the vinylcarbenoid and subsequent siloxy-group transfer.[8c] The [Rh$_2$(*S*-BTPCP)$_4$]-catalyzed reaction, however, was promising because the amount of the standard cycloadduct **12a** was considerably reduced (entries 1 and 2). The desired cycloadduct **13a** was the dominant product when dichloromethane was used as the solvent (entry 1) but the enantioinduction (87% *ee* versus 54% *ee*) was higher when *n*-pentane was used as solvent (entry 2). Further optimization studies revealed that the siloxy group migration to form **14** was sensitive to the size of the siloxy group on the diene. The OTMS derivative **11b** gave more of the alkynoate product **14b**, but when the more sterically demanding OTIPS derivative **11c** was used, only traces of the alkynoate **14c** was observed. Furthermore, the size of the siloxy group also influenced carbenoid versus vinylogous reactivity, as the ratio of **12c** to the desired regioisomer **13c** improved to 5:95. Furthermore, the bulkier silyl groups resulted in improved levels of enantioselectivity for the reaction (70% *ee* for the TMS derivative **13b**, 87% *ee* for the TBS derivative **13a**, and 96% *ee* for the TIPS derivative **13c**).

Table 2: Optimization studies for the formation of **13**.



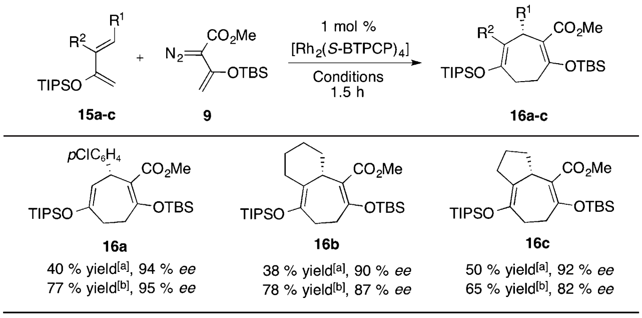
11 **9** **12** **13** **14**

Entry	**11**	R	Solvent	**12**/**13**/**14**[a]	Yield [%][e]	*ee* [%][c]
1	**11a**	TBS	CH$_2$Cl$_2$	9:70:26	37,[b] 16[d]	54
2	**11a**	TBS	*n*-pentane	4:29:62	23,[b] 42[d]	87
3	**11b**	TMS	*n*-pentane	14:18:68	16,[b] 45[d]	70
4	**11c**	TIPS	*n*-pentane	5:95:trace	59[c]	96

[a] Determined by ^{1}H NMR analyis of the crude reaction mixture. [b] Combined yield of **12** and **13**. [c] Adduct **13**. [d] Yield of isolated **14**. [e] Yield of isolated product. TIPS = triisopropylsilyl, TMS = trimethylsilyl.

Having established optimized reaction conditions for the formation of the regiosiomeric [4+3] cycloadducts, we explored the generality of this reaction with the representative 2-siloxydienes **15** (Table 3). Both 4-substituted and 3,4-disubstituted 2-OTIPS-1,3-dienes afforded the [4+3] cycloadducts **16** with good regiocontrol and moderate yields. In general, the products **16** were formed in higher yields at elevated temperatures with the diene as the limiting reagent (38–50% yield versus 65–78% yield), but the levels of asymmetric induction were generally higher at ambient temperatures with the vinyldiazoacetate **9** as the limiting agent (90–94% *ee* versus 82–95% *ee*). The [4+3] cycloaddition is restricted to moderately electron-rich dienes. Highly electron-rich dienes such as the triisopropylsilyl variant of the Danishefsky's diene results in the formation of a complex mixture of products, whereas less electron-rich dienes such as the *p*-nitro derivative of **15a** fail to react. The absolute configuration of **16a** was determined by X-ray crystallography of a derivative prepared by DIBAL reduction and subsequent hydrolysis. The absolute configuration of the other cycloadducts are tentatively assigned by analogy.[10]

Table 3: Reactions of the dienes **15** with **9**.



16a: 40 % yield[a], 94 % *ee*; 77 % yield[b], 95 % *ee*

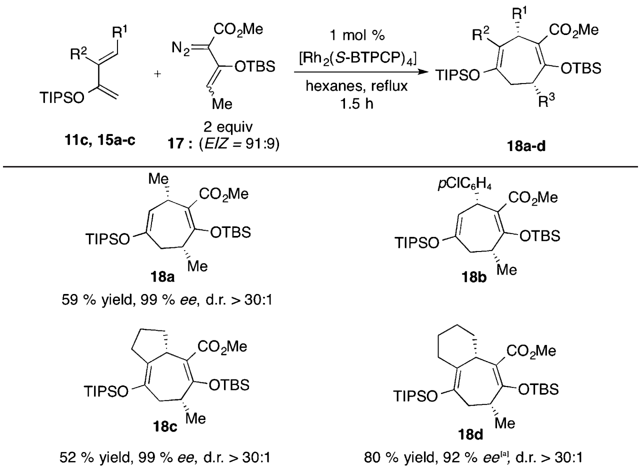
16b: 38 % yield[a], 90 % *ee*; 78 % yield[b], 87 % *ee*

16c: 50 % yield[a], 92 % *ee*; 65 % yield[b], 82 % *ee*

[a] 5 equiv of diene, *n*-pentane, RT. [b] 2 equiv of **9**, hexanes, reflux. Yield is that of the product isolated after silica gel chromatography.

In general, vinylogous reactivity under rhodium(II) catalysis is most common when the vinyl terminus of the carbenoid is unsubstituted.[8] $[\mathrm{Rh_2}(S\text{-BTPCP})_4]$, however, is capable of inducing vinylogous reactivity on more highly substituted vinylcarbenes.[8j] Therefore, the $[\mathrm{Rh_2}(S\text{-BTPCP})_4]$ reaction of the methyl-substituted vinyldiazoacetate **17** was examined (Table 4). The mono- and bicyclic cycloadducts **18** containing stereogenic centers at C3 and C7 were formed with high levels of enantiocontrol (92–99 % *ee*). Furthermore, even though **17** consists of a mixture of *E*,*Z* isomers, only the *cis* diastereomers of **18** were formed. These results suggest that only one geometrical isomer of the rhodium vinylcarbene is capable of undergoing the [4+3] cycloaddition.

Table 4: Diastereoselective formal [4+3] cycloaddition.



18a: 59 % yield, 99 % *ee*, d.r. > 30:1

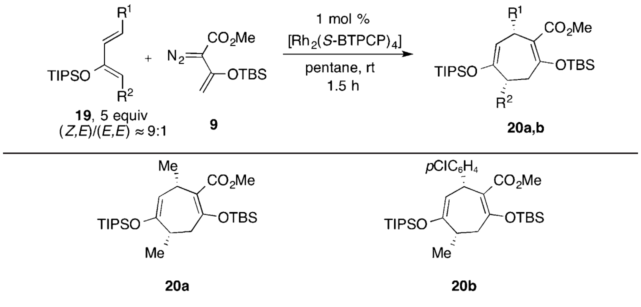
18c: 52 % yield, 99 % *ee*, d.r. > 30:1

18d: 80 % yield, 92 % *ee*[a], d.r. > 30:1

[a] The *ee* value of the corresponding allylic alcohol. Yield refers to that of product isolated after silica gel chromatography. Enantiomeric excess was determined by HPLC using a chiral stationary phase.

The study was then extended to the reaction of **9** with the 1,4-disubstituted diene **19**, which would be expected to generate the [4+3] cycloadducts **20** containing stereogenic centers at C4 and C7 (Table 5). The additional terminal substituent on the diene was expected to be a challenge to the [4+3] cycloaddition because it would add steric interference at the position of initial bond formation and the dienes **19** consisted of about a 9:1 mixture of *Z*,*E* to *E*,*E* isomers. Consequently, we were pleasantly surprised to find that the cycloadducts **20** were produced as single diastereomers with high levels of asymmetric induction (96 % *ee*). The high diastereoselectivity is presumably caused by preferred reaction of the vinylcarbenoid with (*Z*,*E*)-**19** rather than with (*E*,*E*)-**19**.

Table 5: Diastereoselective formal [4+3] cycloaddition.

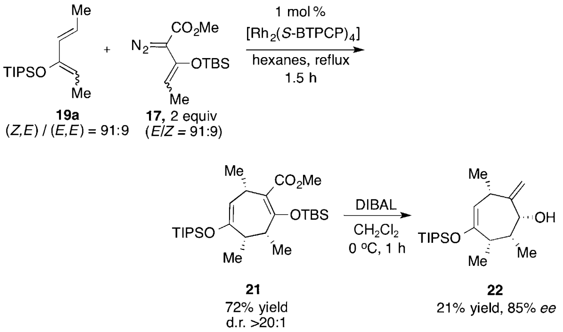


20a: 68% yield, 96% *ee*, d.r. > 30:1

20b: 71% yield, 96% *ee*, d.r. > 30:1

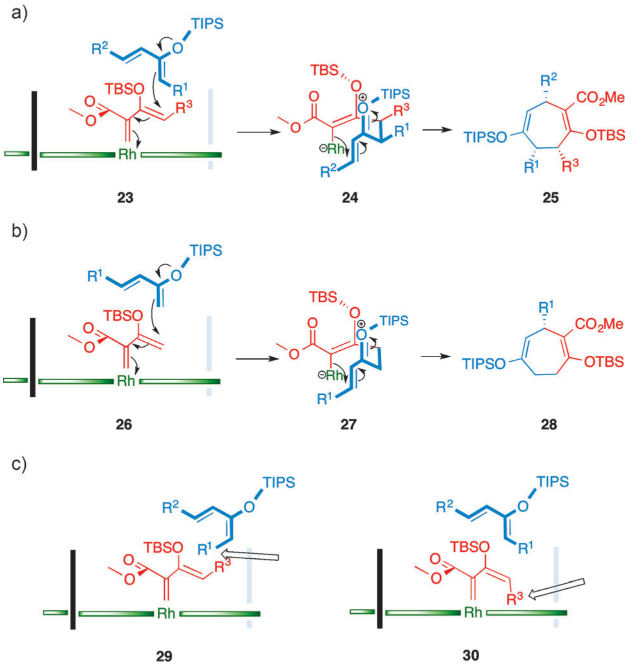
[a] Yield is that of the isolated product after silica gel chromatography. Enantiomeric excess was determined by HPLC using a chiral stationary phase.

A final reaction was conducted between **17** and **19a** (Scheme 3). Even though both **17** and **19a** are composed of mixtures of *E*/*Z* isomers, the $[\mathrm{Rh_2}(S\text{-BTPCP})_4]$-catalyzed reaction smoothly formed the cycloadduct **21**, containing three new stereogenic centers, in 72 % yield as a single diastereomer. Analysis of **21** by HPLC using a chiral stationary phase was unsuccessful, but after treatment with DIBAL, the resulting cycloheptene **22** was determined to have an *ee* value of 85 % (reduction yield is not optimized).



Scheme 3. Reaction of **17** with **19a**.

A reasonable mechanism for the [4+3] cycloadditions is shown in Scheme 4. $[\mathrm{Rh_2}(S\text{-BTPCP})_4]$ has been shown to be a sterically hindered catalyst which blocks the *re* face of the carbene,[6c] and preferentially reacts at the vinylogous position when electron-rich trapping agents are used. The regioisomeric [4+3] cycloaddition involves initial attack at the vinylogous position of the vinylcarbene, as illustrated in **23**, to generate the zwitterionic intermediate **24**. A similar type of zwitterionic intermediate has been proposed for the [3+2] cycloaddition between vinylcarbenes and dienes.[8d] The high diastereoselectivity of this reaction suggests that the subse-



Scheme 4. Proposed mechanism for the [4+3] cycloaddition: a) General model. b) Model of the reaction of the unsubstituted vinyldiazoacetate **9** with dienes **15a–c**. c) Explanation for high diastereocontrol when the diene or vinyldiazoacetates are not pure geometrical isomers.

quent cyclization to the cycloheptadiene **25** is faster than bond rotation. Zwitterionic intermediates have been shown to be likely in several types of stereoselective reactions of rhodium vinylcarbenes,[8] so the concept of rapid cyclization of zwitterionic intermediates without epimerization is well established. Both the diene and the vinylcarbenoid would need to react through an *s-cis* conformation for ring closure to occur without bond rotation. Rhodium 2-siloxyvinylcarbenes have been shown to preferentially adopt an *s-cis* conformation[11] and the 2-siloxy group would likely favor the *s-cis* conformation of the diene. The face selectivity of attack of the diene on the rhodium carbene determines the absolute configuration of the final product, even when no stereocenters are present in the zwitterionic intermediate **27**, as illustrated in the conversion sequence **26**→**27**→**28**. This situation would be the case for the examples shown in Table 3. Even though the exact trajectory of approach of the dienes is not known, the proposed mechanism can be used to rationalize why highly diastereoselective reactions are possible even when the vinylcarbene and the diene are mixtures of geometrical isomers. An *E*,*E* diene would have R^1 in an unfavorable position pointing towards the vinylcarbene (see structure **29**), whereas a *Z* vinylcarbene would unlikely form because R^3 would be pointing towards the catalyst surface (see structure **30**).

In summary, an asymmetric [4+3] cycloaddition between rhodium vinylcarbenes and dienes has been developed. The reaction proceeds with the opposite regiochemistry to the traditional tandem cyclopropanation/Cope rearrangement. An efficient asymmetric cycloaddition was achieved when $[Rh_2(S\text{-BTPCP})_4]$ was used as catalyst in hydrocarbon solvents. By an appropriate choice of diene and vinyldiazoacetate, cycloheptadienes with up to three new stereogenic centers can be generated with excellent stereocontrol.

Experimental Section

Representative procedure for the synthesis of **13c**: (*E*)-Triisopropyl(penta-1,3-dien-2-yloxy)silane (1.51 mmol, 5.00 equiv), *n*-pentane (3.5 mL), and $[Rh_2(S\text{-BTPCP})_4]$ (5.3 mg, 0.0030 mmol, 0.010 equiv) were added to a round-bottom flask. A solution of methyl 3-[(*tert*-butyldimethylsilyl)oxy]-2-diazobut-3-enoate (77.0 mg, 0.30 mmol, 1.00 equiv) in *n*-pentane (3.5 mL) was added by syringe pump over 1 h. Once the addition was complete, the reaction was stirred at 23 °C for 0.5 h. The reaction was stopped by concentration under reduced pressure and purified by flash chromatography on silica gel (*n*-pentane/diethyl ether 98:2) to provide pure products.

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[10] For X-ray crystallographic data for the derivative of **16a**, see the Supporting Information. CCDC 979611 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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