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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.

Keywords

Carbenoid; cycloaddition; rhodium; cycloheptadienes; vinyldiazoacetate

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 cyclohexene **3** (Scheme 1).[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 longstanding problem but they involve multistep synthetic sequences.[3] Relatedly, our laboratory has developed a rhodium-catalyzed formal [4+3] cycloaddition between vinyldiazoacetates and dienes.[4,5] This reaction is also highly regioselective, as illustrated by the reaction of diene **1** with rhodium vinylcarbene intermediate **5** to generate the cycloheptadiene **6**, because it proceeds by a tandem cyclopropanation/Cope rearrangement (CPCR). In this paper 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, leading to the formation of cycloheptadiene **7**.

A representative example of the regular formal [4+3] cycloaddition of vinyldiazoacetates is the Rh_2(*S*-PTAD)$_4$-catalyzed reaction of 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

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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 reactions are highly regioselective, 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 siloxyvinyldiazoacetate **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** ratio, 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, 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 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 the regioisomeric [4+3] cycloadduct **13a** formed. In the reaction conducted in pentane, the ratio of **12a** to **13a** was 79:21, whereas when dichloromethane was used as solvent, the ratio improved to 30:70 (entries 3 and 4), but with poor enantiocontrol (5% ee).

Recently, we have discovered that sterically crowded tetrakis(triarylcyclopropanecarboxylate) dirhodium catalysts are very effective at enhancing vinylogous reactivity of rhodium vinylcarbenes.[8j] Therefore, we explored the effect of Rh_2(*S*-BTPCP)$_4$ on the reaction of **9** with 2-siloxydienes **11** (Table 2). The Rh_2(*S*-BTPCP)$_4$-catalyzed reaction resulted in the formation of a third product, alkynoate **14a,** in addition to the two [4+3] cycloadducts **12a** and **13a**. Compounds related to alkynoate **14a** had been observed in the reaction of vinylcarbenes with vinyl ethers and were shown to be derived from vinylogous attack on the vinylcarbenoid, followed by a 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 solvent (entry 1) but the enantioinduction (87% ee vs. 54% ee) was higher when pentane was used as solvent (entry 2). Further optimization studies revealed that the siloxy group migration to form the alkynoate **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**).

Having established optimized conditions for the formation of the regiosiomeric [4+3] cycloadducts, we explored the generality of this reaction with 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 followed by hydrolysis. The absolute configuration of the other cycloadducts are tentatively assigned by analogy. [10]

In general, vinylogous reactivity under rhodium(II) catalysis is most common when the vinyl terminus of the carbenoid is unsubstituted.[8] Rh_2(*S*-BTPCP)$_4$, however, is capable of inducing vinylogous reactivity on more highly substituted vinylcarbenes.[8j] Therefore, the Rh_2(*S*-BTPCP)$_4$-reaction of the methyl-substituted vinyldiazoacetate **17** was examined (Table 4). Mono- and bicyclic cycloadducts **18** containing stereogenic centers at C-3 and C-7 were formed with high levels of enantiocontrol (92-99% ee). Furthermore, even though the vinyldiazoacetate **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.

The study was then extended to the reaction of vinyldiazoacetate **9** with 1,4-disubstituted diene **19**, which would be expected to generate [4+3] cycloadducts **20** containing stereogenic centers at C-4 and C-7 (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 dienes **19** consisted of ∼9:1 mixture of (*Z,E*):(*E,E*) isomers. Consequently, we were pleasantly surprised to find that cycloadducts **20** were produced as single diastereoisomers with high levels of asymmetric induction (96% ee). The high diastereoselectivity is presumable caused by preferred reaction of the vinylcarbenoid on (*Z,E*)-**19** over (*E,E*)-**19**.

A final reaction was conducted between vinyldiazoacetate **17** and diene **19a**. Even though both **17** and **19** are composed of mixtures of *E/Z* isomers the Rh_2(*S*-BTPCP)$_4$,-catalyzed reaction smoothly formed cycloadduct **21**, containing three new stereogenic centers in 72% yield as a single diastereomer. Analysis of **21** by chiral HPLC was unsuccessful, but after treatment with DIBAL, the resulting cycloheptene **22** was determined to be 85% ee (reduction yield is unoptimized).

A reasonable mechanism for the [4+3] cycloadditions is shown in Scheme 4. Rh_2(*S*-BTPCP)$_4$ has been shown to be a sterically hindered catalyst that 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 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 subsequent 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 adopt preferentially 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 **26 –27 – 28**. This 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*-BTPCP)$_4$ was used as catalyst in hydrocarbon solvents. By an appropriate choice of diene and vinyldiazoacetate, cloheptadienes with up to three new stereogenic centers can be generated with excellent stereocontrol.

Experimental Section

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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10. For x-ray crystallographic data for the derivative of **16a**, see the Supporting Information. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre under deposition number CCDC 979611.
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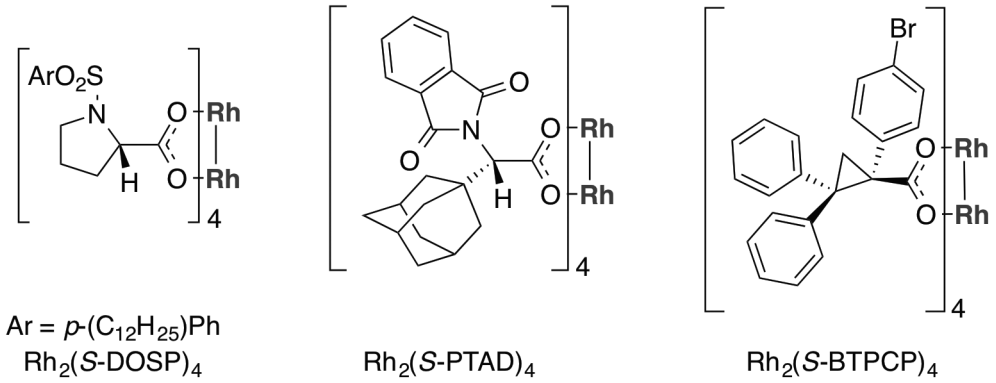
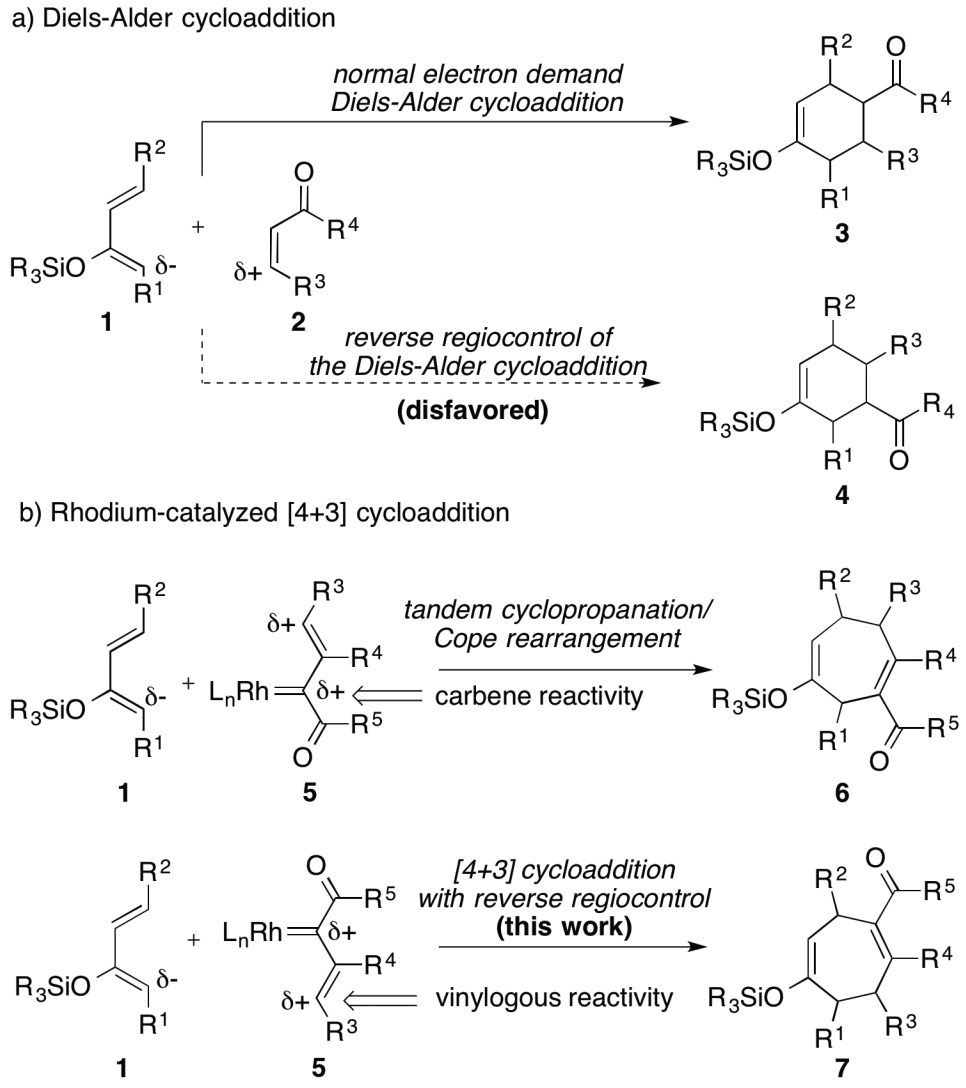
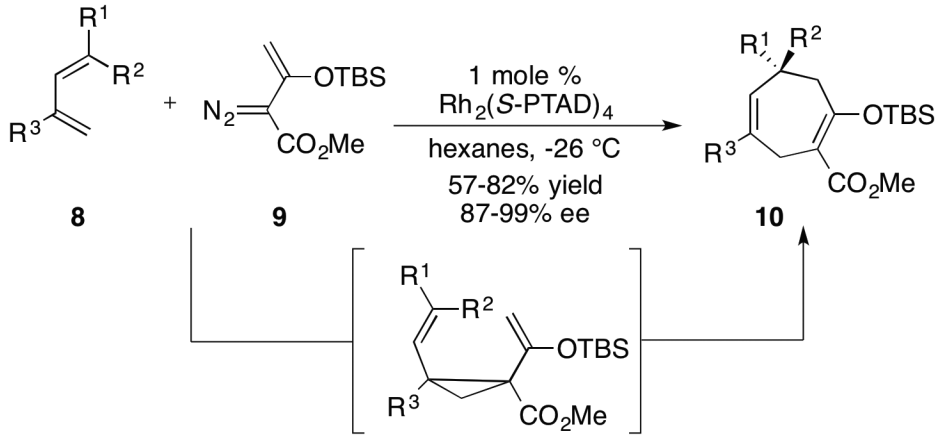


Figure 1.
Representative chiral dirhodium catalysts.

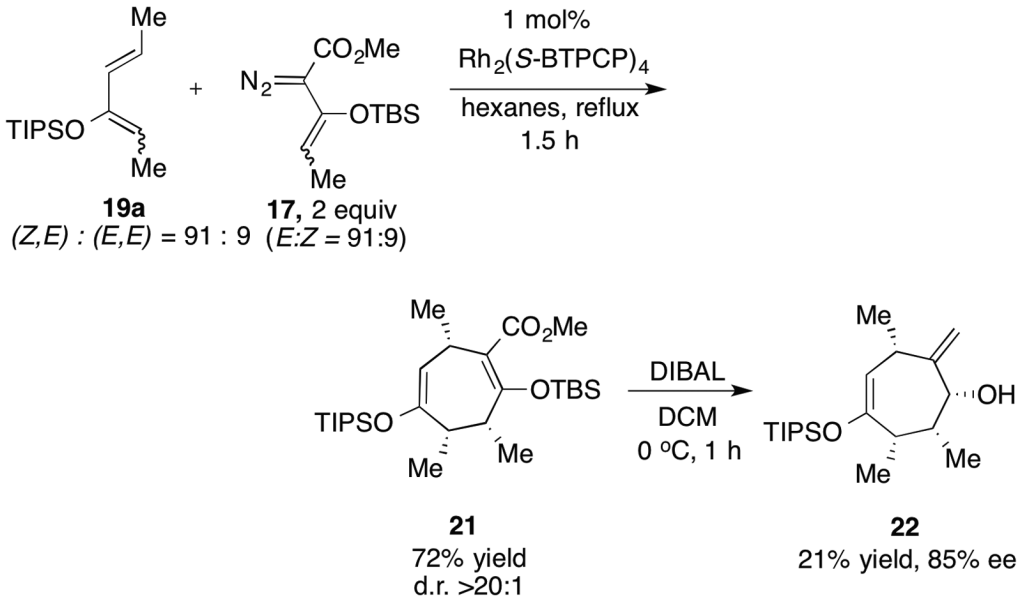


Scheme 1.
Different cycloaddition approaches.

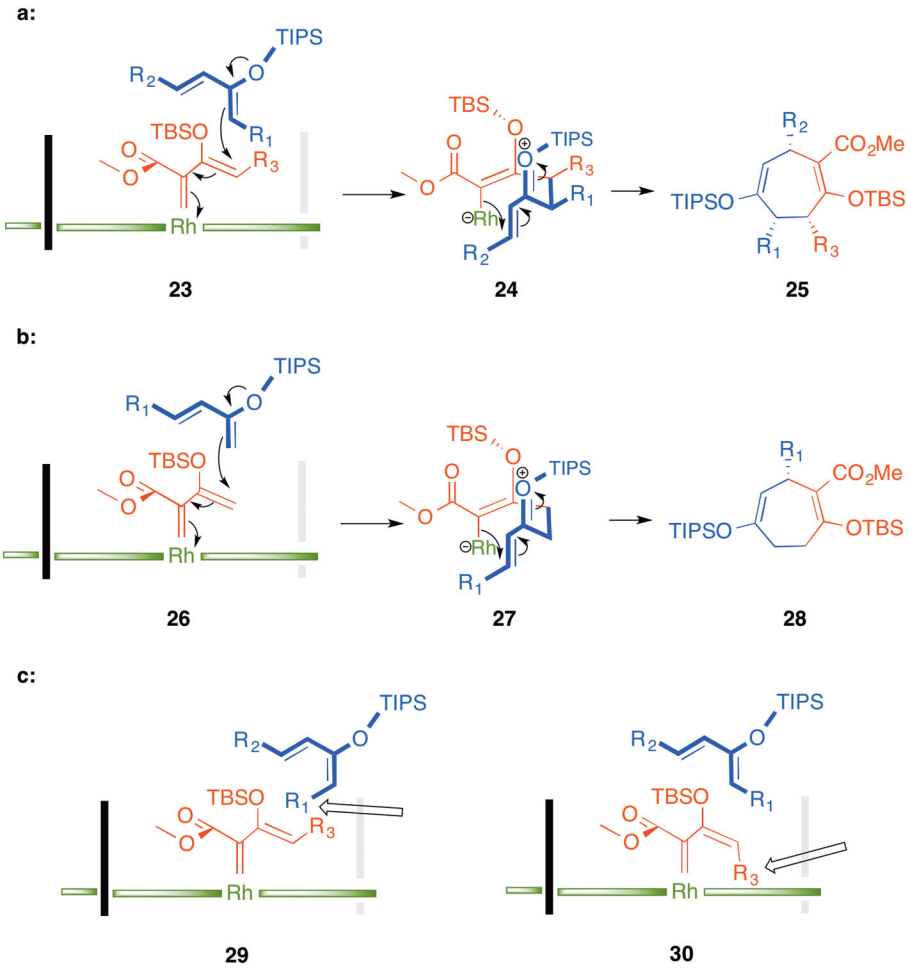


Scheme 2.

Rh_2(*S*-PTAD)$_4$-catalyzed tandem cyclopropanation/Cope rearrangement.



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

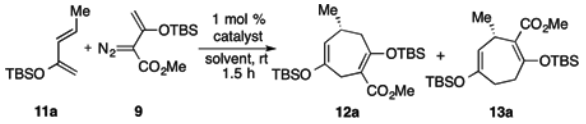


Scheme 4.

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

Table 1

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



entry	solvent	catalyst	ratio[a] 12a : 13a	yield, %	ee of 13a, %[d]
1	pentane	Rh_2(*S*-PTAD)$_4$	94 :6	55[b]	-73
2	CH_2Cl_2	Rh_2(*S*-PTAD)$_4$	87 :13	43[c]	-71
3	pentane	Rh_2(*S*-DOSP)$_4$	79 : 21	62[c]	33
4	CH_2Cl_2	Rh_2(*S*-DOSP)$_4$	30 : 70	61[c]	5

[a] Determined by ^{1}H NMR of crude reaction mixture,

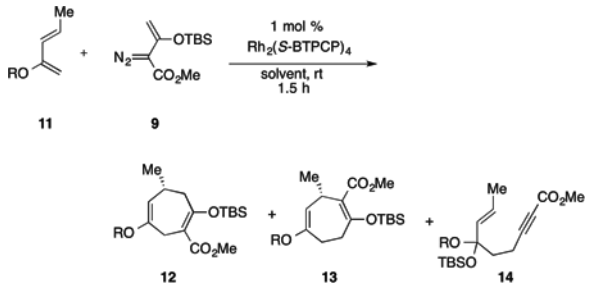
[b] isolated yield of **12a**,

[c] combined yield of **12a** and **13a**.

[d] negative sign indicates the opposite enantiomer of **13a**.

Table 2

Optimization studies for the formation of **13**.



entry	compound	R	solvent	ratio[a] 12 : 13 : 14	yield, % [e]	% ee[c]
1	a	TBS	CH_2Cl_2	9 : 70 : 26	37[b], 16[d]	54
2	a	TBS	pentane	4 : 29 : 62	23[b], 42[d]	87
3	b	TMS	pentane	14 : 18 : 68	16[b], 45[d]	70
4	c	TIPS	pentane	5 : 95 : trace	59[c]	96

[a] Determined by ^{1}H NMR of crude reaction mixture,

[b] combined yield of **12** and **13**,

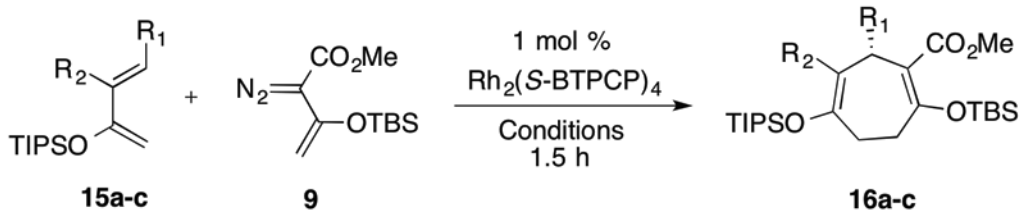
[c] adduct **13**.

[d] isolated yield of **14**.

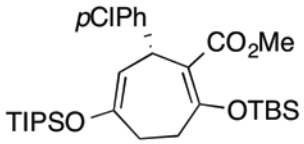
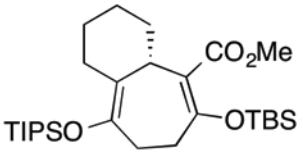
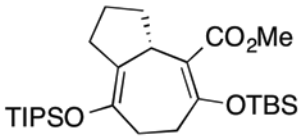
[e] isolated yield.

Table 3

Reactions of 2-OTIPS-1,3-dienes 15 with 9



15a-c **9** **16a-c**

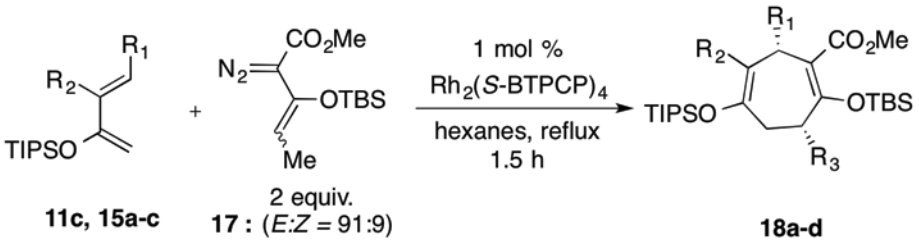
16a	**16b**	**16c**
		
40 % yield[a], 94 % ee 77 % yield[b], 95 % ee	38 % yield[a], 90 % ee 78 % yield[b], 87 % ee	50 % yield[a], 92 % ee 65 % yield[b], 82 % ee

[a] 5 equiv. of diene, pentane, rt.

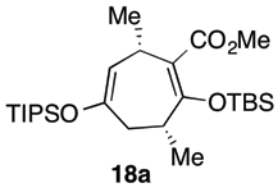
[b] 2 equiv. of **9**, hexanes, reflux. Yield refers to isolated yield after silica gel chromatography.

Table 4

Diastereoselective Formal [4+3] Cycloaddition.

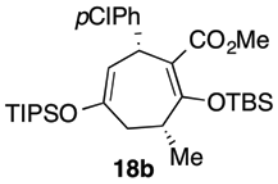


11c, 15a-c 2 equiv. **17 :** (*E*:*Z* = 91:9) **18a-d**

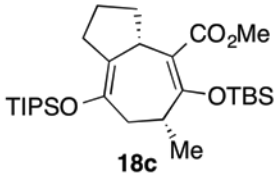


18a

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

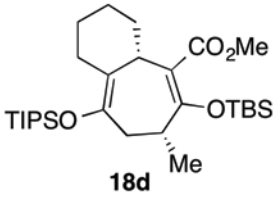


18b



18c

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



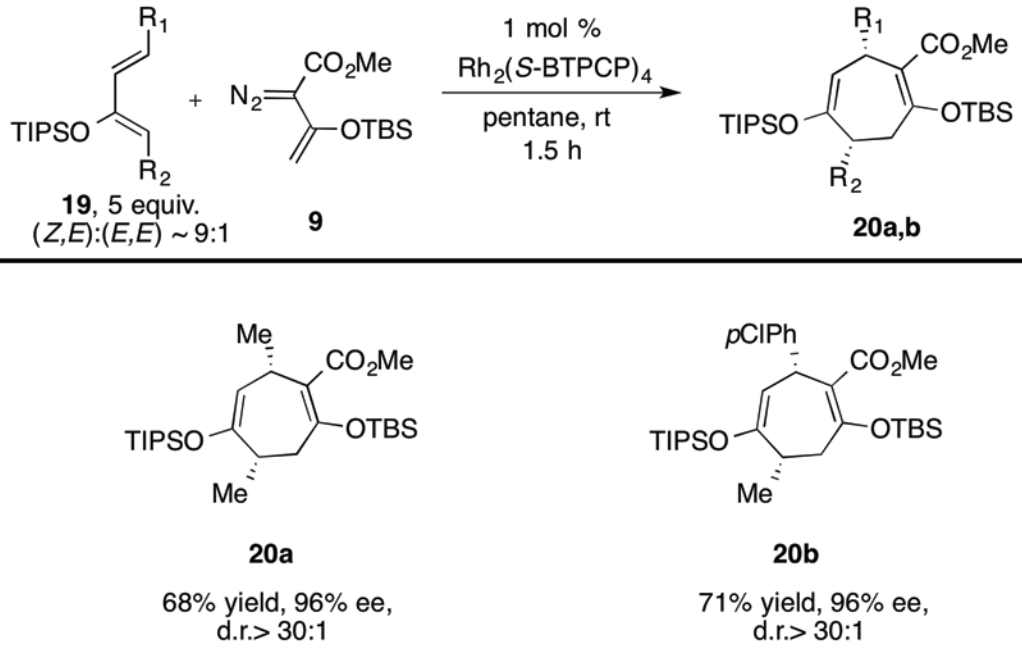
18d

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

[a]%ee of corresponding allylic alcohol. Yield refers to isolated yield after silica gel chromatography. Enantiomeric excess was determined by chiral HPLC.

Table 5

Diastereoselective Formal [4+3] Cycloaddition.



[a] Yield refers to isolated yield after silica gel chromatography. Enantiomeric excess was determined by chiral HPLC