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Rh_2(*R*-TPCP)$_4$-Catalyzed Enantioselective [3+2]-Cycloaddition between Nitrones and Vinyldiazoacetates

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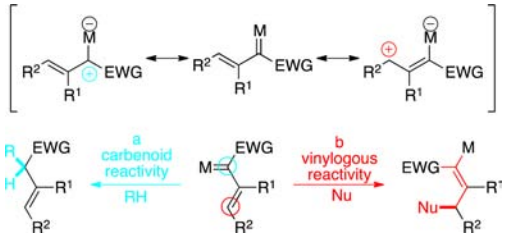
Supporting Information

ABSTRACT: Rhodium-catalyzed reaction of vinyldiazoacetates with nitrones results in a formal [3+2]-cycloaddition to generate 2,5-dihydroisoxazoles with high levels of asymmetric induction. The cascade reaction begins with a vinylogous addition event, followed by an iminium addition ring-closure/hydride migration/alkene isomerization cascade. Dirhodium tetrakis(triarylcyclopropanecarboxylates) are the optimum catalysts for this process.

Donor/acceptor-substituted rhodium carbenoids are useful intermediates for a wide range of stereoselective synthetic methods.[1,2] Among the donor/acceptor carbenoids studied, vinylcarbenoids have emerged as particularly useful reagents. In addition to the standard carbenoid reactions,[3] the vinylcarbenoids can participate in a diverse array of more elaborate transformations,[4] such as the tandem cyclopropanation/Cope rearrangement,[4a] the combined C−H functionalization/Cope rearrangement,[4b] and the ylide formation/[2,3]-sigmatropic rearrangement/oxy-Cope rearrangement/ene reaction cascade sequence.[4c] Furthermore, vinylcarbenoids possess electrophilic character at the vinylogous position, a feature recognized by us during our early studies on donor/acceptor carbenoids (Scheme 1).[5]

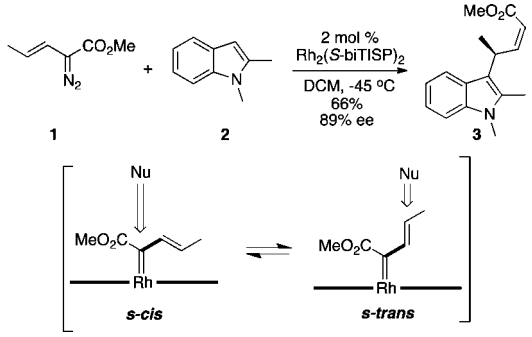
Scheme 1. General Reactivity of Vinylcarbenoids



In the early studies, the vinylogous reactivity of rhodium carbenoids was observed only when the vinylogous position of the carbenoid is unsubstituted.[5] Other factors found to favor vinylogous reactivity were electron-deficient dirhodium catalysts, polar solvents, and bulky esters on the carbenoid. Recently, we[6] and others[7] have studied this unusual vinylogous reactivity in a variety of transformations, using a combination of experimental and theoretical studies to gain a better understanding of this chemistry.[8] We have found that dimolybdenum, diruthenium, and especially silver catalysts enhance vinylogous reactivity.[6a−c] Another major breakthrough was the discovery that chiral bulky dirhodium catalysts could enhance vinylogous reactivity, especially if the trapping nucleophile is also sterically demanding.[6d]

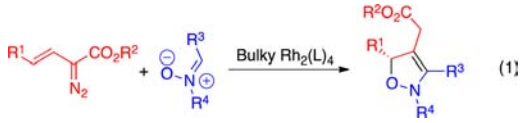
Scheme 2 illustrates an application of a bulky dirhodium catalyst for the enantioselective functionalization of indoles.[8b]

Scheme 2. Vinylogous Reactivity of Rhodium Carbenoids



The favored vinylogous reactivity was considered to be caused by the carbenoid being forced by the bulky catalyst Rh_2(*S*-biTISP)$_2$ to react in the *s-trans* configuration, which blocks normal carbenoid reactivity and favors vinylogous reactivity. The *cis*-olefin configuration of **3** is consistent with attack occurring on the *s-trans* configuration of the carbenoid followed by protonation of the vinylrhodium with retention of configuration.

In this paper, we describe a novel [3+2]-annulation between terminally substituted vinyldiazoacetates and nitrones (eq 1).



These studies demonstrate the important role of bulky dirhodium catalysts and contrast with previous studies on the reaction of vinylcarbenoids with nitrones, which resulted in [3+3]-cycloadditions.[7a]

At the onset of this project, we expected that a bulky catalyst would be required to enhance the vinylogous reactivity. Therefore, we decided to explore the effect of different dirhodium catalysts (Figure 1) on the reaction of (*E*)-*tert*-

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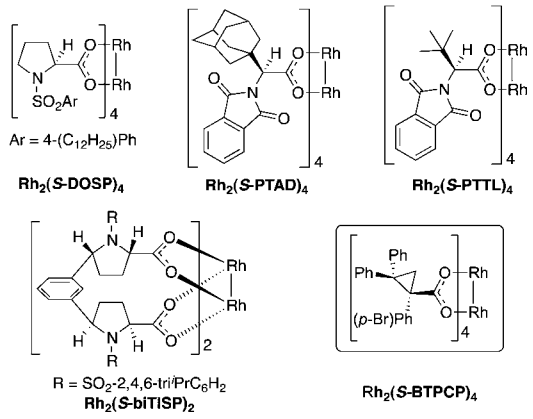
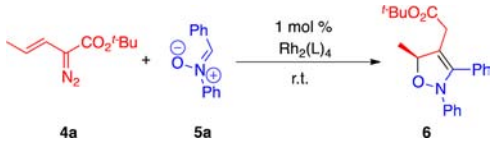


Figure 1. Structure of chiral dirhodium catalysts.

butyl 2-diazo-5-phenylpent-4-enoate **4a** and nitrone **5a**. When sterically less crowded $Rh_2(OOct)_4$, Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-PTAD)$_4$, and Rh_2(*S*-PTTL)$_4$ were used as catalysts, diazo compound **4a** was not fully decomposed, and the nitrone starting material was recovered. In contrast, the sterically bulky catalyst Rh_2(*S*-biTISP)$_2$ afforded the formal [3+2]-cycloadduct **6** in 36% yield and 82% ee (Table 1, entry 5). The yield and

Table 1. Initial Optimization Results



4a 5a 6

entry	catalyst	solvent	yield (%)[a]	ee (%)
1	Rh_2(*S*-DOSP)$_4$	pentane	<5	
2	Rh_2(*S*-PTAD)$_4$	pentane	<5	
3	Rh_2(*S*-PTTL)$_4$	pentane	<5	
4	$Rh_2(OOct)_4$	pentane	<5	
5	Rh_2(*S*-biTISP)$_2$	pentane	36	82
6	**Rh_2(*S*-BTPCP)$_4$**	**pentane**	**64**	**94**
7	Rh_2(*S*-BTPCP)$_4$	DCM	61	92
8	Rh_2(*S*-BTPCP)$_4$	acetone	30	95
9	Rh_2(*S*-BTPCP)$_4$	hexane	61	94

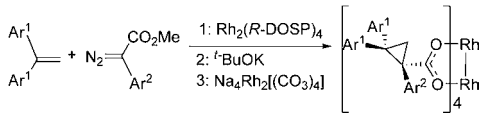
[a]Isolated yield, <5% means **6** was not observed from ^{1}H NMR analysis of the crude mixture prior to flash chromatography.

enantioselectivity were further improved using a more sterically congested catalyst, Rh_2(*S*-BTPCP)$_4$ (Table 1, entry 6).[9] Further optimization studies indicated pentane was the optimal solvent for the reaction.

Considering the dramatic difference in outcome of the Rh_2(*S*-BTPCP)$_4$-catalyzed reactions compared to those with the other dirhodium catalysts, we decided to prepare and evaluate a series of triarylcyclopropanecarboxylate catalysts (Table 2). These catalysts were prepared in three steps in good yields (47−68%), using a highly enantioselective cyclopropanation as the key step.[9a]

The newly designed dirhodium carboxylate catalysts were evaluated in the standard reaction (Table 3). All of these catalysts provided the desired product with high levels of enantioselectivity (94−98% ee). Increasing the size of the aryl that has either *gem*- or *cis*-relationship to the carboxylate did not enhance the enantioselectivity. The unsubstituted triphenylcyclopropanecarboxylate catalyst Rh_2(*R*-TPCP)$_4$ gave *ent*-**6** with

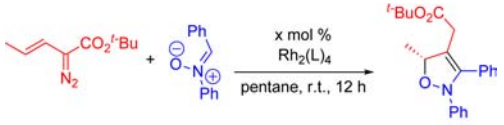
Table 2. Design and Synthesis of New Dirhodium Catalysts



entry	catalyst	Ar^1	Ar^2	yield (%)[a]
1	Rh_2(*R*-NPCP)$_4$	Ph	2-Nap	58
2	Rh_2(*R*-BPCP)$_4$	Ph	4-PhC_6H_4-	65
3[b]	Rh_2(*S*-BNPCP)$_4$	2-Nap	4-BrC_6H_4-	47
4	Rh_2(*R*-TPCP)$_4$	Ph	Ph	68

[a]Yield refers to the isolated yield in the ligand exchange to form the catalyst. [b]Prepared using Rh_2(*S*-DOSP)$_4$ as catalyst. The configuration of Rh_2(*S*-BNPCP)$_4$ is opposite to that shown.

Table 3. New Dirhodium Catalysts Evaluation



4a 5a *ent*-**6**

entry	catalyst	x	yield (%)	ee (%)
1	Rh_2(*R*-NPCP)$_4$	1	59	94
2	Rh_2(*R*-BPCP)$_4$	1	58	94
3[a]	Rh_2(*S*-BNPCP)$_4$	1	52	94
4	Rh_2(*R*-TPCP)$_4$	1	67	98
5	**Rh_2(*R*-TPCP)$_4$**	**2**	**77**	**98**

[a]Product stereochemistry is opposite to that shown.

the highest level of enantioselectivity (98% ee, entry 4). The isolated yield was further improved when the catalyst loading was 2 mol % (entry 5). These studies once again underscore the importance of bulky dirhodium catalysts in vinylogous reactivity of vinylcarbenoids.

Once we had developed the optimized conditions, we examined the scope of the formal [3+2]-cycloaddition (Table 4). The size of the ester group did not have a significant impact on the level of enantioselectivity, but the yield was highest with the *tert*-butyl ester (compare *ent*-**6** with **7a**−**c**). Modification of the length of a linear alkyl at the vinyl terminus of the vinyldiazoacetate **4** had little effect on the asymmetric induction (**7d** and **7e**, both 94% ee), but a branched alkyl substituent such as an isopropyl group eroded the enantioselectivity (**7f**, 66% ee). The reaction can be conducted with a variety of nitrones, as illustrated by the range of products **7g**−**o** formed. The level of asymmetric induction was high for the aryl nitrones (85−97% ee) but much lower for the cinnamyl nitrone (**7l**, 42% ee).

To confirm the absolute configuration of the products, *ent*-**6** was transformed to the bicyclic product **8** in 66% yield (dr = 1.5/1, Scheme 3), which was confirmed by single-crystal X-ray analysis (see Supporting Information). The configuration of the other 2,5-dihydroisoxazole products is tentitively assigned by analogy.

A catalytic cycle is proposed to rationalize the mechanism of the formal [3+2]-cycloaddition (Scheme 4). It begins with rhodium-catalyzed decomposition of substituted vinyldiazoacetate, followed by vinylogous attack on the rhodium vinylcarbenoid **9** to form intermediate **10**. Cyclization by an iminium addition then generates a new carbenoid **11**, which undergoes a 1,3-hydride abstraction to form the zwitterion **12** followed by a proton transfer to form **13**. An alternative

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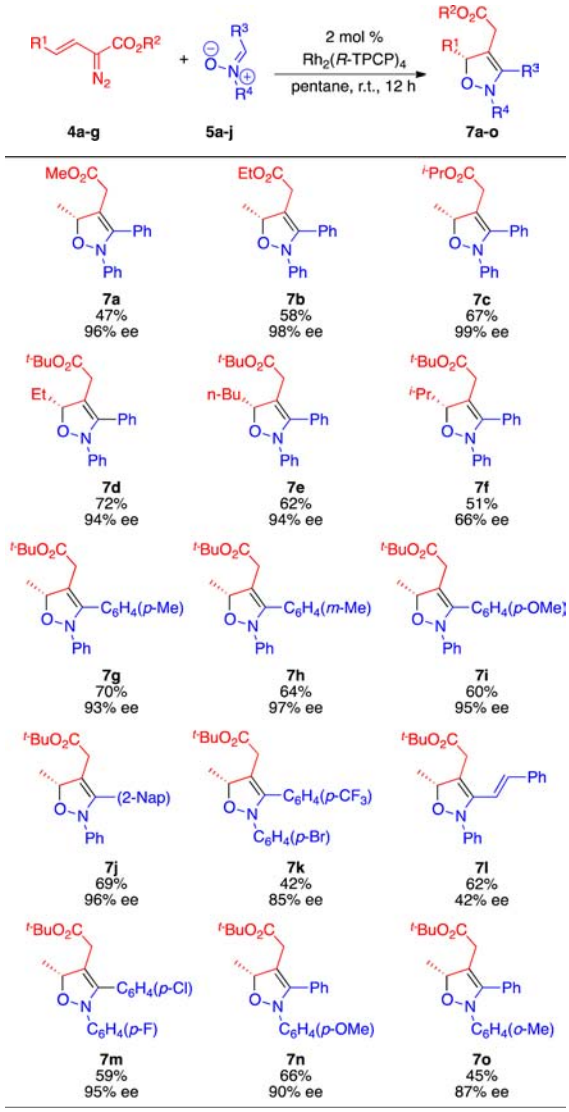
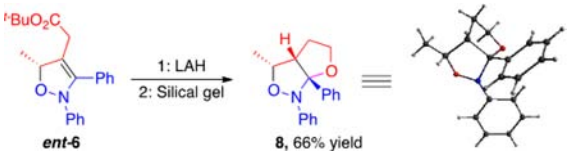
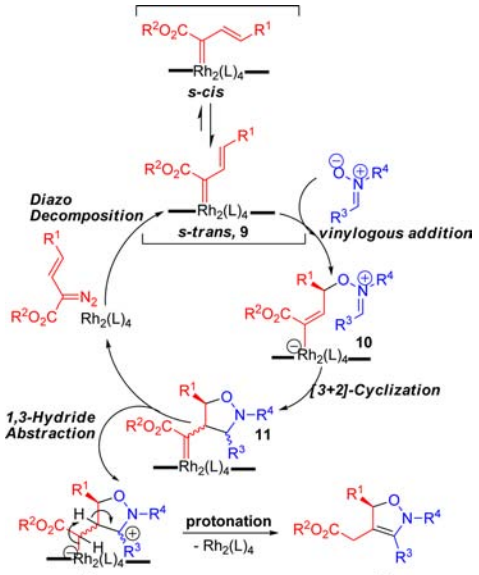
Table 4. Substrate Scope



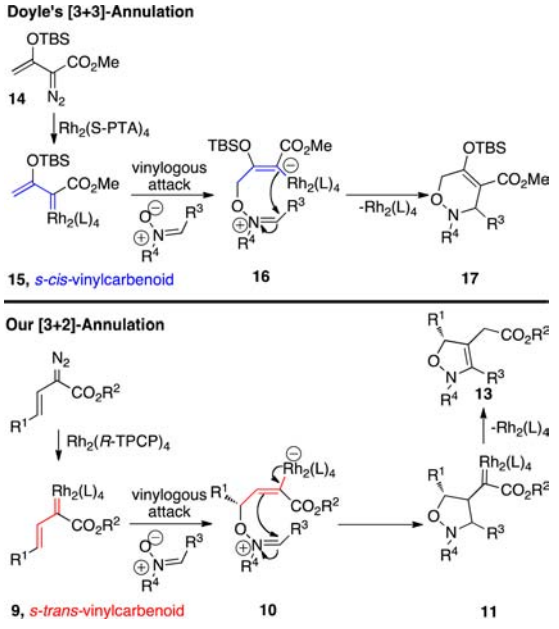
Scheme 3. Derivatization via Reduction/Cyclization Process



Scheme 4. Proposed Catalytic Cycle



Scheme 5. [3+2]- vs [3+3]-Cycloaddition Models



possibility would be 1,2-hydride migration followed by alkene isomerization. The formation of adduct **11** by a concerted cycloaddition reaction between nitrone and *s-trans*-(*E*)-methyl vinylcarbenoid intermediate **9**[10] is considered to be unlikely because of the well-known high reactivity of rhodium carbenoid intermediates, though such mechanisms do occur with the more stable Fisher carbene complexes.[11]

A tentative model that rationalizes the observed product divergence from the previously reported [3+3]-annulation is descried in Scheme 5. In the previous formal [3+3]-cycloaddition, rhodium-catalyzed decomposition of *β*-silyloxyvinyldiazoacetate **14** afforded a preferred *s-cis* carbenoid **15** to minimize the steric interaction between the internal OTBS group and the "wall" of rhodium catalyst. Upon vinylogous attack by nitrone, a configurationally stable vinyl rhodium **16**, *cis* orientated to the iminium is formed, which has the correct geometry to cyclize to the formal [3+3]-annulation product **17**. In our system, however, the bulky rhodium-catalyzed decomposition of terminally substituted vinyldiazoacetates provides a preference for further reaction to occur on the *s-trans* carbenoid **9**. Vinylogous attack by nitrone affords a vinyl rhodium **10**, *trans* orientated to the iminium, which can only undergo the [3+2]-annulation.

In conclusion, we have demonstrated a highly asymmetric vinylogous addition of nitrones to terminally substituted vinyl diazoacetates for the synthesis of 2,5-dihydroisoxazole derivatives. This study once again underscores the unusual reactivity of the triarylcyclopropanecarboxylate dirhodium catalysts. Application of the cyclopropanecarboxylate dirhodium catalysts in new asymmetric transformations is ongoing.

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■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) In a previous study on the rhodium-catalyzed reaction of methyl 2-diazo-3-butenoate with nitrones,[7d] the reaction was considered to be initiated by a concerted or stepwise [3+2]-cycloaddition between the nitrone and the rhodium vinylcarbene, drawn in the *s-cis* conformation. It is more likely that this reaction involves vinylogous attack of the nitrone on the *s-trans* conformation of the rhodium vinylcarbene, analogous to the mechanism proposed herein.

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