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Rh₂(*R*-TPCP)₄-Catalyzed Enantioselective [3+2]-Cycloaddition between Nitrones and Vinyldiazoacetates

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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(triarylcyclopropane carboxylates) 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

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, we⁶ and others⁷ 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} The favored vinylogous reactivity was considered to be caused by the carbenoid being forced by the bulky catalyst Rh₂(*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 vinyl rhodium with retention of configuration.

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Supporting Information

Full experimental data for the compounds described in the paper 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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In this paper, we describe a novel [3+2] annulation between terminally substituted vinyl diazoacetates 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}

(eq. 1)

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*-butyl 2-diazo-5-phenylpent-4-enoate (**4a**) and nitrone **5a**. When sterically less crowded Rh₂(Oct)₄, Rh₂(*S*-DOSP)₄, Rh₂(*S*-PTAD)₄ and Rh₂(*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 Rh₂(*S*-biTISP)₂ afforded the formal [3+2]-cycloadduct **6** in 32% yield and 82% ee (Table 1, entry 5). The yield and enantioselectivity was further improved using a more sterically congested catalyst Rh₂(*S*-BTPCP)₄⁹ (Table 1, entry 6). Further optimization studies indicated pentane was the optimal solvent to conduct the reaction.

Considering the dramatic difference in outcome of the Rh₂(*S*-BTPCP)₄-catalyzed reactions compared to the reaction of the other dirhodium catalysts, we decided to prepare and evaluate a series of triarylcyclopropane carboxylate 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 triphenylcyclopropane carboxylate catalyst Rh₂(*R*-TPCP)₄ gave *ent*-**6** with 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.

Having developed the optimized conditions, the scope of the formal [3+2]-cycloaddition was examined (Table 4). The size of ester group did not have a significant impact on the level of enantioselectivity but the yield was highest with the *t*-butyl ester (compare *ent*-**6** with **7a-c**). Modification of the length of a linear alkyl at the vinyl terminus of the vinyl diazoacetate **4** had little effect on the asymmetric induction (**7d** and **7e**, both 94% ee), but a branched alkyl substituent such as an *iso*-propyl 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 vinyl diazoacetate, followed by vinylogous attack on the rhodium vinylcarbenoid **9** to form intermediate **10**. Then, cyclization by an iminium addition generates a new carbenoid **11**, which then undergoes a 1,3-hydride abstraction to form the zwitterion **12** followed by a proton transfer to form **13**. An alternative possibility would be 1,2-hydride migration followed by alkene isomerization. The formation of adduct **11** by a concerted cycloaddition reaction between nitron 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 described in Scheme 5. In the previous formal [3+3]-cycloaddition, rhodium-catalyzed decomposition of β -silyloxyvinyl diazoacetate **14** affords 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 nitron, a stable *trans*-rhodium-bonded vinyl nucleophile species **16** 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 vinyl diazoacetates provides a preference for further reaction to occur on the *s-trans* carbenoid **9**. Vinylogous attack by nitron affords a *cis*-rhodium-bonded vinyl species **10**, 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 triaryl cyclopropane carboxylate dirhodium catalysts. Application of the cyclopropane carboxylate dirhodium catalysts in new asymmetric transformations is ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
General reactivity of vinylcarbenoids

Scheme 2.
Vinylogous reactivity of rhodium carbenoids

Figure 1.
Structure of Chiral Dirhodium Catalysts

Scheme 3.
Derivatization *via* Reduction/Cyclization Process

Scheme 4.
Proposed Catalytic Cycle

Doyle's [3+3]-Annulation **Our [3+2]-Annulation** **Scheme 5.**

The [3+2] vs [3+3]-Cycloaddition Model

Table 1

Initial Optimization Results

entry	catalyst	solvent	yield (%) ^a	ee (%)
1	$\text{Rh}_2(\text{S-DOSP})_4$	pentane	<5	-
2	$\text{Rh}_2(\text{S-PTAD})_4$	pentane	<5	-
3	$\text{Rh}_2(\text{S-PTTL})_4$	pentane	<5	-
4	$\text{Rh}_2(\text{OOct})_4$	pentane	<5	-
5	$\text{Rh}_2(\text{S-bITISP})_2$	pentane	36	82
6	$\text{Rh}_2(\text{S-BTPCP})_4$	pentane	64	94
7	$\text{Rh}_2(\text{S-BTPCP})_4$	DCM	61	92
8	$\text{Rh}_2(\text{S-BTPCP})_4$	acetone	30	95
9	$\text{Rh}_2(\text{S-BTPCP})_4$	hexane	61	94

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

Design and Synthesis of New Dirhodium Catalysts

^b Prepared using Rh₂(S-DOSP)₄ as catalyst. Rh₂(S-BNPCP)₄ has the opposite configuration to that shown.

Table 3

New Dirhodium Catalysts Evaluation

entry	catalyst	x	yield (%)	ee (%)
1	$\text{Rh}_2(\text{R-NPCP})_4$	1	59	94
2	$\text{Rh}_2(\text{R-BPCP})_4$	1	58	94
3 ^a	$\text{Rh}_2(\text{S-BNPCP})_4$	1	52	94
4	$\text{Rh}_2(\text{R-TPCP})_4$	1	67	98
5	$\text{Rh}_2(\text{R-TPCP})_4$	2	77	98

^aProduct has the opposite stereochemistry to that shown.

Table 4

Substrate Scope