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Vinyldiazolactone as a Vinylcarbene Precursor: Highly Selective C−H Insertion and Cyclopropanation Reactions

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Rhodium(II)-stabilized vinylcarbenes are valuable synthetic intermediates capable of undergoing a spectrum of transformations in a highly selective fashion.[1] Their versatility is illustrated in applications directed to the construction of complex molecular architectures.[2] However, limitations of this catalytic methodology have become apparent. Vinyldiazoacetates undergo a spontaneous [1,5]-cyclization to yield pyrazoles,[3] and this transformation has limited their applications with catalysts that are less reactive toward diazo decomposition than dirhodium tetracarboxylates. In addition, although *E*-styrylcarbenes readily undergo intermolecular addition and insertion reactions, the *Z*-vinylcarbene isomer produces the intramolecular aromatic substitution product exclusively,[4] and asymmetric intermolecular reactions of *Z*-vinylcarbenes have been observed only when the *Z*-substituent is alkyl.[5] In the course of our research with vinyldiazoacetates,[2c,d] we became intrigued by the possibility of utilizing vinyldiazolactones as carbene precursors. Restriction of the vinyldiazo moiety within a ring was expected to prevent the undesirable intramolecular processes that occur with acyclic vinyldiazoacetates and vinylcarbene intermediates. We report here the first synthesis of a vinyldiazolactone and its unexpected suitability for asymmetric induction in intermolecular insertion and addition reactions with a chiral dirhodium carboxamidate.

The synthesis of vinyldiazolactone **1** was accomplished in one step from commercially available 5,6-dihydro-2*H*-pyran-2-one using direct diazo transfer conditions that are reported in the preparation of select vinyldiazoacetates.[6] However, unlike vinyldiazoacetates, lactone **1** exhibited a long shelf life. Throughout this study, **1** was stored for several weeks at 4 °C and used without further purification.

Perhaps the most remarkable property of rhodium(II)-stabilized vinylcarbenes is their applicability toward intermolecular C−H insertion reactions.[7] Carbenes generated from vinyldiazoacetates and aryldiazoacetates in the asymmetric environment of Rh_2(DOSP)$_4$ (Figure 1) and related structures are unique in their ability to undergo insertion into unactivated C−H bonds with synthetically viable yields and enantioselectivities. To investigate the utility of **1** in intermolecular C−H insertion reactions, asymmetric dirhodium(II) carboxylate and carboxamidate catalysts were screened in the reaction of **1** with 1,4-cyclohexadiene (Table 1).

Surprisingly, Rh_2(*S*-DOSP)$_4$,[8] ordinarily the optimal catalyst for enantioselective C−H insertion reactions of vinyldiazoacetates,[7] was not suitable in this application. Not only was the enantiomeric excess of C−H insertion product **2a** negligible, but the propensity of this catalyst for C−H insertion relative to cyclopropanation was the lowest of all catalysts evaluated (Table 1, entry 2). The carboxamidate catalyst Rh_2(*S*-MEPY)$_4$,[9] which has seen some use in C−H insertion reactions but was found to be unsuitable for reactions with vinyldiazoacetates,[3] provided a greater chemoselectivity for **2a** than Rh_2(*S*-DOSP)$_4$, but enantiocontrol with this catalyst was low (Table 1, entry 3). With the azetidinone ligated

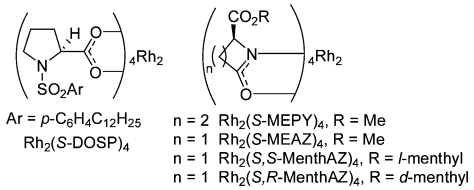
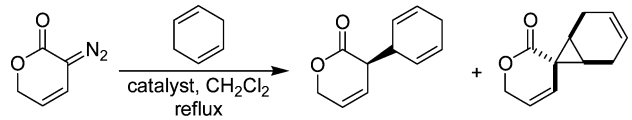


Figure 1. Asymmetric dirhodium catalysts.

Table 1. C−H Insertion of **1** into 1,4-Cyclohexadiene[a]



1 **2a** **2b**

entry	catalyst	**2a**/**b**[b]	yield (%)	ee (%)[c]
1	Rh_2(OAc)$_4$	2:3	53	
2[d]	Rh_2(*S*-DOSP)$_4$	1:9	56	18, *R*
3	Rh_2(*S*-MEPY)$_4$	4:1	47	8, *R*
4	Rh_2(*S*-MEAZ)$_4$	9:1	43	60, *R*
5	Rh_2(*S*,*S*-MenthAZ)$_4$	9:1	42	79, *R*
6	Rh_2(*S*,*R*-MenthAZ)$_4$	9:1	50	80, *R*

[a] Unless otherwise noted, to a solution of 5 equiv diene and 1.0 mol % of catalyst in refluxing CH_2Cl_2 (20 mL) under N_2 was added a solution of **1** (1.3 mmol) in CH_2Cl_2 (10 mL) over 8 h. [b] Determined by ^{1}H NMR spectroscopy prior to chromatography. [c] The ee (%) of **2a** determined by GC. [d] Reaction run at room temperature.

catalyst Rh_2(*S*-MEAZ)$_4$ (Table 1, entry 4),[10] however, promising selectivities were obtained. Optimization of the azetidinone catalyst structure led to the use of diastereomeric catalysts Rh_2(*S*,*S*-MenthAZ) and Rh_2(*S*,*R*-MenthAZ)$_4$,[11] the selectivities from which were high and comparable (Table 1, entries 5 and 6). Absolute stereochemistry of **2a** was determined by oxidative aromatization of the diene of **2a** followed by reduction of the olefin to provide the known compound α-phenyl-*δ*-valerolactone. Comparison of the optical rotation to that reported for (*R*)-α-phenyl-*δ*-valerolactone[12] allowed the assignment of absolute stereochemistry of **2a** as shown (Table 1). All of the dirhodium catalysts evaluated provided comparable isolated yields of **2a**,**b**.

Encouraged by the results of this C−H insertion study, we turned our attention to asymmetric cyclopropanation of **1** (Table 2). Reactions occurred cleanly and in high yield with notable diastereoselectivities. As with the previously described C−H insertion, azetidinone ligated dirhodium catalysts are the optimal catalysts for the cyclopropanation of styrene [Rh_2(*S*-DOSP)$_4$, **3a** = 60% yield, 14% ee, dr > 20:1; Rh_2(*S*-MEPY)$_4$, **3a** = 69% yield, 10% ee, dr > 20:1; Rh_2(*S*,*R*-MenthAZ)$_4$, **3a** = 74% yield, 84% ee, dr > 20:1]. Other cyclopropanation reactions catalyzed by Rh_2(*S*,*R*-MenthAZ)$_4$ provided enantioselectivities ranging from 73 to 86% ee, with the *E*-cyclopropane as the dominant or exclusive diastereomer.

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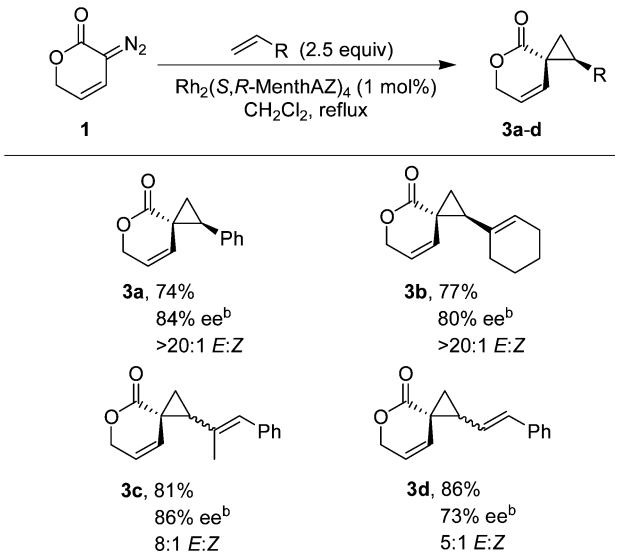
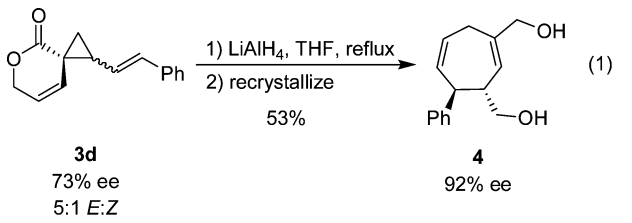
Table 2. Asymmetric Cyclopropanation of Selected Alkenes with **1**[a]



[a] To olefin (2.5 equiv) and catalyst (1.0 mol %) in refluxing CH_2Cl_2 (20 mL) under N_2 was added a solution of **2** (1.3 mmol) in CH_2Cl_2 (10 mL) over 8 h. *E*/*Z* ratio determined by ^{1}H NMR prior to chromatography. Reported yields obtained upon isolation via silica gel chromatography. [b] *E*-cyclopropane.

Extensive studies of vinyldiazoacetates by Davies have demonstrated that upon formation of *cis*-divinylcyclopropanes a Cope rearrangement occurs to provide hydroazulenes.[13] Construction of seven-membered carbocycles is important in natural product synthesis, and the development of stereoselective strategies toward these targets remains an ongoing challenge.[14] However, unlike the transient *cis*-divinylcyclopropanes formed from vinyldiazoacetates, conformational restrictions on spirocyclic cyclopropanes **3b**,**c** prevent subsequent Cope rearrangement and allow isolation of the cyclopropane products without rearrangement. Cleavage of the lactone overcomes this restriction and allows the dienes to access the necessary conformation for rearrangement.

Cope rearrangement product **4** was obtained upon reduction of lactone *E*-**3d** with $LiAlH_4$ in refluxing THF (eq 1). Recrystallization provided a facile means of separating **4** from the cyclopropanediol arising from *Z*-**3d** and, concomitantly, the enantiomeric excess of **4** was enriched to 92%.[15] Thus, in two steps the hydroazulene **4** is conveniently accessed in high enantiomeric excess from the diastereomeric mixture of **3d**. The relative stereochemistry of **4** was confirmed by X-ray diffraction.



Vinyldiazolactone **1** is an effective and stable vinylcarbene precursor. Over the course of this study comparisons were made of the reactivity of **1**, which had been stored for several weeks, with that of freshly purified **1**; no significant diminution in yield or selectivity was observed, emphasizing the operational convenience of **1** as a vinylcarbene precursor. The striking differential in selectivity between dirhodium(II) carboxylates and carboxamidates was unexpected but is probably a result of conformational influences in the reacting carbenes.[8,16] The spirocyclic structure of **3b**−**d** allows the isolation of unrearranged divinylcyclopropanes, and reduction of divinylcyclopropane lactones (i.e., **3d**) provides a convenient route to hydroazulenes such as **4**. The stereochemistry for substitution at the 3,4-position of **4** is opposite that which would be obtained from reactions of *E*-substituted vinyldiazoacetates. Future research will be focused on evaluating the scope of cyclic vinyldiazo compounds as carbene precursors and providing a better understanding of the unique selectivities obtained with azetidinone ligated dirhodium catalysts.

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Supporting Information Available: Experimental details, characterization data, synthesis of **1**, absolute stereochemical assignment of **2a**, and X-ray crystal structure of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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