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Combined C—H Functionalization/Cope Rearrangement with Vinyl Ethers as a Surrogate for the Vinylogous Mukaiyama Aldol Reaction

Yajing Lian and Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia, 30322

Abstract

Vinyl ethers selectively undergo the combined C—H functionalization/Cope rearrangement reaction (CHCR) *via* an *s-cis*/boat transition. With chiral dirhodium catalysts, products are generated in a highly diastereoselective and enantioselective fashion. This reaction can be considered as a surrogate to the traditional vinylogous Mukaiyama aldol reaction. Effective kinetic resolution has been achieved, leading to the recovery of a cyclic vinyl ether with axial chirality of high enantiomeric purity.

C—H functionalization has the potential to revolutionize the synthetic strategies used for making natural products and pharmaceutical targets.¹ Rhodium-catalyzed carbenoid C—H insertion is one of the most effective methods for stereoselective C—H functionalization.² Of particular interest is the possibility of using the C—H functionalization as a complementary disconnection strategy to the conventional transformations used in organic synthesis.¹ Intermolecular C—H functionalization by means of carbenoid-induced C—H insertion has been shown to be complementary to the aldol reaction,³ Mannich reaction,⁴ Claisen condensation,⁵ Michael addition⁶ and the Claisen rearrangement.^{3a} In this paper we describe how the combined C—H functionalization/Cope rearrangement (CHCR) can be applied as a surrogate to the vinylogous Mukaiyama aldol reaction.

The vinylogous Mukaiyama aldol reaction has been widely used in organic synthesis.⁷ It has the potential of generating highly functionalized products containing two newly-formed stereogenic centers. In recent years, several protocols have been developed to achieve this transformation in an enantioselective manner.⁸ Even with these advances, controlling both the diastereoselectivity and enantioselectivity of the vinylogous Mukaiyama aldol reaction is still a challenge. Recently, Panek reported a carbenoid approach to generate the typical *syn*-products of a vinylogous Mukaiyama aldol reaction through a two-steps sequence, a rhodium-catalyzed asymmetric Si—H insertion between vinyl diazoacetates and silanes followed by a Lewis acid-catalyzed crotylation (Scheme 1).⁹ The C—H functionalization approach described herein, complements the Panek approach, leading to a highly stereoselective method for the formation of the typical *anti*-products of the vinylogous Mukaiyama aldol.

The new methodology arises from the CHCR reaction between allylic C—H bonds and vinyl diazoacetates.¹⁰ This reaction typically generates products with two new stereocenters. With suitable substrate design, the reaction can proceed through either *s-cis*/chair^{10a-f} or *s-*

hmdavie@emory.edu.

Supporting Information Available: 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>.

cis/boat^{10g} transition states to generate independently the two possible diastereomers (eq **1** and **2**). Recent computational studies revealed that the reaction proceeds through a concerted, but highly asynchronous hydride transfer/C—C bond forming process and there is a potential energy surface bifurcation between the CHCR reaction and the competing direct C—H insertion reaction.¹¹ As a result, controlling reactions to undergo selectively a CHCR reaction over a direct C—H insertion is challenging. Only a few substrate systems to date favor a clean CHCR reaction, and the majority of these are cyclohexadiene and dihydronaphthalene derivatives.^{10a–b,10c–f} Therefore, a major challenge in this field is to broaden the scope of substrates that will selectively undergo the CHCR reaction.

(1)

(2)

Recently, we described that disubstituted cyclopentenyl derivatives smoothly undergo the CHCR reaction *via* a boat transition state.^{10g} Evaluation of the *s-cis*/boat transition state model¹¹ lead us to the realization that acyclic trisubstituted vinyl ethers might be ideal substrates for CHCR reaction because steric repulsion with the catalyst “wall” would be avoided in a *s-cis*/boat transition state (Scheme 2). If this is indeed the case the scope of the CHCR reaction will be greatly broadened because vinyl ethers are readily accessible from the corresponding ketones *via* the Wittig reaction.

In order to test the hypothesis presented above, the Rh₂(*S*-PTAD)₄-catalyzed decomposition of siloxyvinyl diazoacetate **1** with vinyl ether **2** was examined. Rh₂(*S*-PTAD)₄ is known to be an effective catalyst for the enantioselective reaction of siloxyvinyl diazoacetates such as **1**, and when the reaction was conducted at −20 °C with 1 mol % of catalyst, followed by desilylation and diazotization, the diazoacetate **3** was formed as a single diastereomer in 91% overall yield with 94% ee over three steps. The siloxyvinyl diazoacetate **1** is one of the best vinylcarbenoid precursors with regard to favoring the CHCR-reaction over a direct C—H insertion, but the formation of **3** in 91% yield is much higher than the yields obtained in the previous study using cyclopentene substrates.^{10g}

(3)

On the basis of the promising result with **1**, we then focused on whether this reaction can be applied to a range of vinyl ethers and vinyldiazoacetates. Previous studies have shown that $\text{Rh}_2(\text{S-DOSP})_4$ is the optimum chiral catalyst for asymmetric reactions with *trans*-vinyldiazoacetates (Figure 1).¹² The $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of *trans*-phenyl vinyldiazoacetate **8** with vinyl ether **2** generated the CHCR product **13** as a single diastereomer in good yield with extremely high asymmetric induction (entry **1**, Table 1). This transformation was then successfully applied to a variety of *trans*-vinyldiazoacetates and vinyl ethers as summarized in Table 1. In all cases, a single diastereomer of the CHCR product was produced in good yields (67–89%) and with excellent enantioselectivity, in the majority cases greater than 98% ee. Traces of the direct C—H insertion products were observed in the crude reaction mixtures in some cases, but the amounts were never more than 10% of the total C—H functionalization products. The absolute configuration of product **14** was unambiguously assigned by X-ray crystallography.¹³ The stereo-chemical outcome is consistent with the CHCR reaction proceeding *via* a boat transition state. The stereochemical configuration of the other CHCR products **13**, **15–21** were tentatively assigned on the assumption that all the substrates reacted through a similar transition state and trajectory of approach.

The CHCR reaction with acyclic ether **7** deserves further comment. In previous studies, effective CHCR reactions were limited to cyclic substrates as otherwise a significant amount of competing direct C-H insertion products occurred.¹⁴ The ether **7** represents nice examples of effective CHCR reactions occurring in acyclic systems. The geometry of the newly formed trisubstituted double bonds in **21** is consistent with the hypothesis that the reaction is proceeding through an *s-cis*/boat transition state (Scheme 3).¹¹ The resulting geometry of the enoate is characteristic of whether the reaction is occurring on the *s-cis* vinylcarbenoid (to form the *E*-enoate) or on the *s-trans* vinylcarbenoid (to form the *Z*-enoate).¹⁴ The *anti* diastereoselectivity is indicative of a boat transition state¹¹ and the geometry of the trisubstituted double is set through positioning of the methyl group away from the rhodium “wall” in the transition state.

The reactions of donor/acceptor carbenoids are very sensitive to steric and electronic effects^{2b} and this is also the case with the CHCR reaction. These controlling influences were readily seen in the reaction of **8** with the isomeric mixture of **22a** and **22b** (eq 4). Each isomer has two possible allylic sites for C—H functionalization, yet product **23** was formed as the major product in 60% yield. Less than 10% of other CHCR products were observed. The methoxy group blocks attacks at the allylic site *cis* to it,^{2a} which means the methyl site (H_2) in **22a** and the methylene site (H_4) in **22b** are not prone to C—H functionalization. The CHCR reaction is initiated by a hydride transfer event.¹¹ Thus, the methylene site (H_1) in **22a** is more reactive than the primary methyl group (H_3) in **22b** because the methylene site would be better at stabilizing positive charge build-up in the transition state. Once again the C—H functionalization is highly stereoselective as **23** was formed with >30: 1 dr and 94% ee.

(4)

A few examples have been reported of substrates capable of undergoing two carbenoid reactions, resulting in the rapid generation of synthetic complexity.¹⁵ We recognized that if the CHCR reaction was initiated at a primary methyl site of a vinyl ether such as **24**, then the resulting 1,2-disubstituted alkene **25** would be sterically accessible for a subsequent cyclopropanation (eq 5). In order to test this possibility, the $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of ether **24** with excess of *trans*-styryldiazoacetate **8** was examined. This resulted in the formation of **26**, containing four newly formed contiguous stereo-centers, two of which are quaternary. **26** was formed in 53% yield as a single diastereomer in 99% ee. The relative configuration of the cyclopropane in **26** was determined by nOe, while the absolute configuration of **26** was tentatively assigned on the basis of the expected *s-cis*/boat transition state model and the predictive transition state model for the cyclopropanation.¹⁶ This reaction indicated that both the CHCR and the cyclopropanation reactions occurred in a highly stereoselective fashion as only one diastereomer of the product was observed. The reaction represents the first example of the CHCR reaction being initiated by attack at a methyl C—H bond.

(5)

Donor/acceptor carbenoids have been shown to be capable of kinetic resolution, desymmetrization and enantiomer differ-differentiation.^{10a–b,10g,17} In order to explore the possibility of kinetic resolution in the CHCR reaction, the reaction between phenyl-substituted substrate **27a** and 0.6 equiv of diazo compound **8** in the presence of $\text{Rh}_2(\text{S-DOSP})_4$ was examined (eq 6). This generated the CHCR product **28a** as a single diastereomer in 99% ee in good isolated yield (94% yield based on one enantiomer of ether **27a**) (eq 6). The unreactive vinyl ether **27a** was recovered in 40% isolated yield with 98% ee. Thus, the $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction between **27a** and **8** displays a very high level of kinetic resolution. A similar kinetic resolution was achieved with the methyl-substituted substrate **27b**, but the stereoselectivity was not as pronounced. The CHCR product **28b** was produced in 92% ee, and the recovered vinyl ether **27b** was obtained in 60% ee. This kinetic resolution approach provides a convenient way of making enantio-pure cyclic vinyl ethers with axial chirality. The asymmetric synthesis of this type of compounds is typically challenging and the only successful previous approach required the use of chiral Wittig reagents as stoichiometric reagents.¹⁸ The absolute and relative configuration of products **28a** and **28b** were unambiguously assigned by X-ray crystallography¹³ and are consistent with the CHCR reaction proceeding through a *s-cis*/boat transition state.¹¹

A reasonable mechanism that would be consistent with the kinetic resolution is shown in Scheme 4. The $\text{Rh}_2(\text{S-DOSP})_4$ is proposed to adopt a D_2 -symmetry and the substrate would only approach from the front face.¹² The CHCR reaction proceeds through a boat transition state as shown.¹¹ The R group in the substrate will need to point away from the carbenoid to avoid steric interference. This controlling element must be severe for **27a** when R = phenyl, as only one enantiomer of the substrate reacts, leading to products with high stereochemical control. When the R group is methyl, the steric interference is not as dramatic and this would account for the moderate kinetic resolution with **27b**.

In conclusion, vinyl ethers have been demonstrated to be excellent substrates for the CHCR reaction. The reaction proceeds through an *s-cis* boat transition state, leading to the formation of products of defined stereochemistry that might typically be approached by the vinylogous Mukaiyama aldol reaction. These studies demonstrate that asymmetric C—H functionalization by the CHCR reaction can compete with a classic strategic reaction for organic synthesis. Furthermore, the studies underscore the subtle steric and electronic influences that allow the CHCR reaction to be highly regio, di-astereo- and enantioselective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Structures of $\text{Rh}_2(\text{S-DOSP})_4$ and $\text{Rh}_2(\text{S-PTAD})_4$.

classic vinylogous Mukaiyama aldol **Panek's work** **this work** **Scheme 1.**

Two carbenoid approaches to vinylogous aldol products

Scheme 2.
Rationalization of substrate scope design

Scheme 3.
Transition state analysis with acyclic substrate

Scheme 4.
Proposed transition state for the kinetic resolution

Table 1

Substrate Scope between vinyl ethers and vinyl diazoacetates

entry	ethers	R ₃	product ^a	yield (%)	ee (%)
1		Ph		78	99
2		2-Naph		88	99
3		2-p-OMePh		77	98
4		Et		87	98
5		Me		67	93
6		Ph		88	99
7		Ph		75	98
8		Ph		89	99
9		Ph		74	99

^aThe diastereoselective ratio is greater than 30:1 in all reactions