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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, United States

Supporting Information

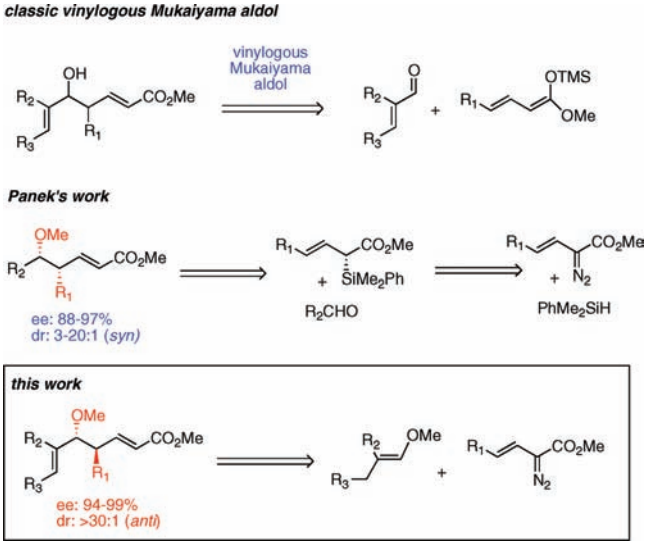
ABSTRACT: Vinyl ethers selectively undergo the combined C−H functionalization/Cope rearrangement reaction via an s-cis/boat transition state. With chiral dirhodium catalysts, products are generated in a highly diastereoselective and enantioselective fashion. This reaction can be considered as a surrogate 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.

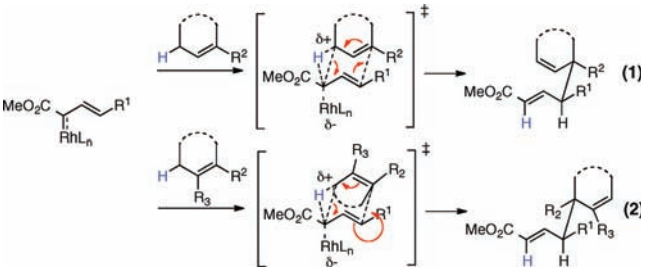
C−H functionalization has the potential to revolutionize the synthetic strategies used for making natural products and pharmaceutical targets.[1] Rhodium-catalyzed carbenoid C−H insertion is one of the most effective methods for stereoselective C−H functionalization.[2] Of particular interest is the possibility of using the C−H functionalization as a disconnection strategy that is complementary 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 addition,[6] and Claisen rearrangement.[3a] In this paper, we describe how the combined C−H functionalization/Cope rearrangement (CHCR) reaction 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 to generate 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 the enantioselectivity of the vinylogous Mukaiyama aldol reaction is still a challenge. Recently, Panek[9] reported a carbenoid approach for generating the typical syn products of a vinylogous Mukaiyama aldol reaction through a two-step sequence involving a rhodium-catalyzed asymmetric Si−H insertion between vinyldiazoacetates and silanes followed by a Lewis acid-catalyzed crotylation (Scheme 1). 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 reaction.

The new methodology arises from the CHCR reaction between allylic C−H bonds and vinyldiazoacetates.[10] This reaction typically generates products with two new stereocenters. With suitable substrate design, the reaction can proceed through either an s-cis/chair[10a−f] or an s-cis/boat[10g] transition state to generate independently the two possible diastereomers (eqs 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 the reaction to select the CHCR pathway over the 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−f] Therefore, a major challenge in this field is to broaden the scope of substrates that selectively undergo the CHCR reaction.

Scheme 1. Carbenoid Approaches to Vinylogous Aldols





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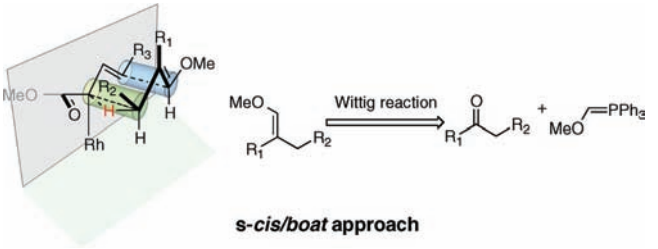
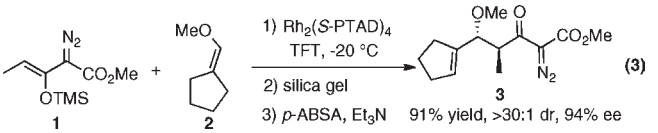
Scheme 2. Rationalization of Substrate Scope Design



We recently reported that disubstituted cyclopentenyl derivatives smoothly undergo the CHCR reaction via a boat transition state.[10g] Evaluation of the s-cis/boat transition state model[11] led us to the realization that acyclic trisubstituted vinyl ethers might be ideal substrates for the CHCR reaction because steric repulsion with the catalyst "wall" would be avoided in an s-cis/boat transition state (Scheme 2). If this were indeed the case, the scope of the CHCR reaction would 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 Rh_2(*S*-PTAD)$_4$-catalyzed reaction of siloxyvinyldiazoacetate **1** with vinyl ether **2** (eq 3) was examined. Rh_2(*S*-PTAD)$_4$ is known to be an effective catalyst for the enantioselective reaction of siloxyvinyldiazoacetates such as **1**, and when the reaction was conducted at −20 °C with 1 mol % catalyst, followed by desilylation and diazotization, diazoacetoacetate **3** was formed as a single diastereomer in 91% overall yield with 94% ee over three steps. **1** is one of the best vinylcarbenoid precursors with regard to favoring the CHCR reaction over the direct C−H insertion, but the 91% yield of **3** is much higher than the yields obtained in the previous study using cyclopentene substrates.[10g]



On the basis of the promising result with **1**, we then focused on whether this reaction could be applied to a range of vinyl ethers and vinyldiazoacetates. Previous studies have shown that Rh_2(*S*-DOSP)$_4$ (Figure 1) is the optimum chiral catalyst for asymmetric reactions with *trans*-vinyldiazoacetates.[12] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of *trans*-styryldiazoacetate **8** with vinyl ether **2** generated the CHCR product **13** as a single diastereomer in good yield with extremely high asymmetric induction (Table 1, entry 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 yield (67−89%) 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 amount of C−H functionalization products. The absolute configuration of product **14** was unambiguously assigned by X-ray crystallography.[13] The stereochemical outcome is consistent with the CHCR reaction proceeding via a boat transition state. The stereochemical configurations of the other CHCR products (**13** and **15**−**21**) were tentatively assigned on the assumption that all of the substrates reacted through a similar transition state and trajectory of approach.

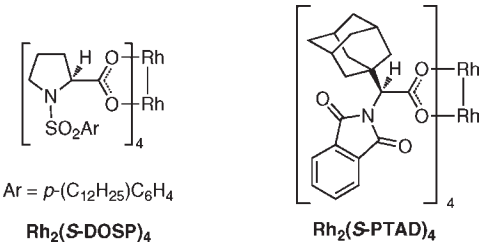
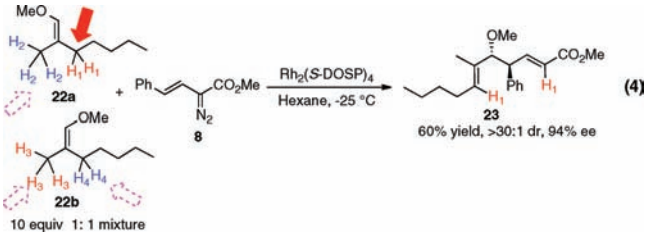


Figure 1. Structures of Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTAD)$_4$.

The CHCR reaction with acyclic ether **7** deserves further comment. In previous studies, effective CHCR reactions were limited to cyclic substrates, as otherwise, significant amounts of products from the competing direct C−H insertion were obtained.[14] Ether **7** represents a nice example of an effective CHCR reaction occurring in an acyclic system. The geometry of the newly formed trisubstituted double bonds in **21** is consistent with the hypothesis that the reaction proceeds through an s-cis/boat transition state (Scheme 3).[11] The resulting geometry of the enoate is characteristic of whether the reaction occurs on the s-cis vinylcarbenoid [to form the (*E*)-enoate] or the s-trans vinylcarbenoid [to form the (*Z*)-enoate].[14] The anti diastereoselectivity is indicative of a boat transition state,[11] and the geometry of the trisubstituted double bond 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 an 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. Yields of <10% for the other CHCR products were observed. The methoxy group blocks attacks at the allylic site cis to it,[2a] which means that 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 buildup of positive charge in the transition state. Once again, the C−H functionalization was highly stereoselective, as **23** was formed with >30:1 dr and 94% ee.



There have been a few reported examples of substrates capable of undergoing two carbenoid reactions, resulting in the rapid generation of synthetic complexity.[15] We recognized that if the CHCR reaction were to be 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 Rh_2(*S*-DOSP)$_4$-catalyzed reaction of ether **24** with an excess of *trans*-styryldiazoacetate **8** was

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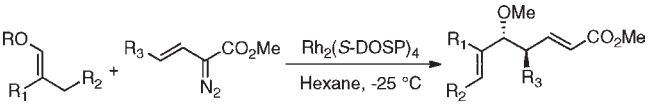
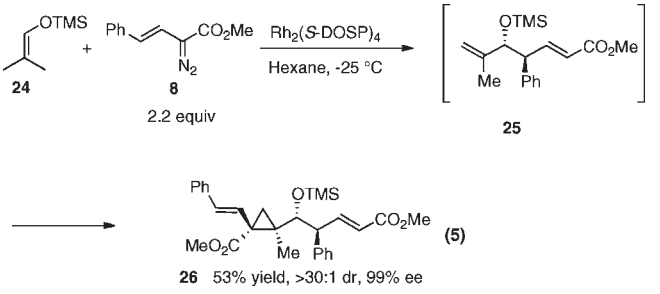
Table 1. Substrate Scope in the Reaction of Vinyl Ethers with Vinyldiazoacetates



entry	ethers		R_3		product[a]		yield (%)	ee (%)
1	MeO	2	Ph	8	OMe, CO_2Me, R_3	13	78	99
2			2-Naph	9		14	88	99
3			*p*-OMePh	10		15	77	98
4			Et	11		16	87	98
5			Me	12		17	67	93
6	MeO	4	Ph	8	OMe, CO_2Me, Ph	18	88	99
7	TBSO	5	Ph	8	OTBS, CO_2Me, Ph	19	75	98
8	MeO	6	Ph	8	OMe, CO_2Me, Ph	20	89	99
9	MeO	7	Ph	8	OMe, Et, CO_2Me, Ph	21	74	99

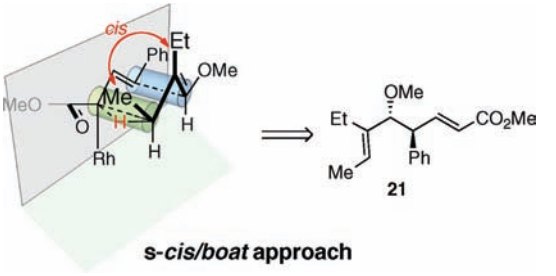
[a] The diastereoselective ratio was >30:1 in all reactions.

examined. This resulted in the formation of product **26** containing four newly formed contiguous stereocenters, two of which are quaternary. **26** was formed in 53% yield as a single diastereomer with 99% ee. The relative configuration of the cyclopropane in **26** was determined by nuclear Overhauser effect (NOE) analysis, 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 cyclopropanation reactions occurred in a highly stereoselective fashion, as only one diastereomer of the product was observed. The reaction represents the first example of initiation of the CHCR reaction by attack at a methyl C−H bond.

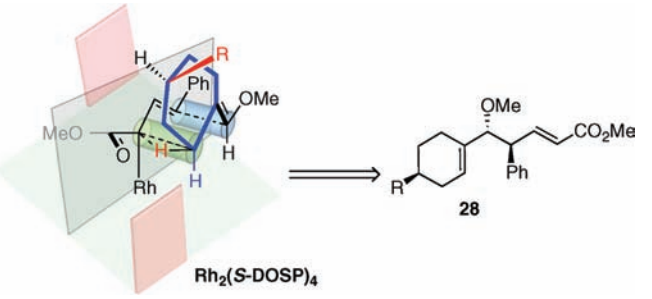


Donor/acceptor carbenoids have been shown to be capable of kinetic resolution, desymmetrization, and enantiomer differentiation.[10a,b,g,17] To explore the possibility of kinetic resolution in the CHCR reaction, the reaction between phenyl-substituted substrate **27a** and 0.6 equiv of diazo compound **8** in the presence of Rh_2(*S*-DOSP)$_4$ was examined (eq 6). This generated the CHCR product **28a** as a single diastereomer with 99% ee in good isolated yield (94% based on one enantiomer of

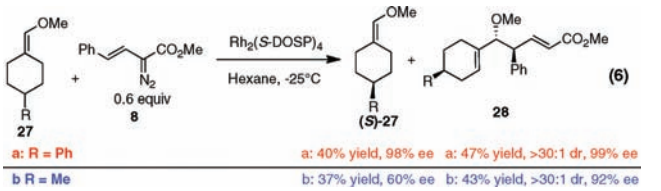
Scheme 3. Transition State Analysis with an Acyclic Substrate



Scheme 4. Proposed Transition State for the Kinetic Resolution



ether **27a**) (eq 6). The unreactive vinyl ether **27a** was recovered in 40% isolated yield with 98% ee. Thus, the Rh_2(*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 with 92% ee, and the recovered vinyl ether **27b** was obtained with 60% ee. This kinetic resolution approach provides a convenient way of making enantiopure cyclic vinyl ethers with axial chirality. The asymmetric synthesis of this type of compound is typically challenging, and the only successful previous approach required the use of chiral Wittig reagents as stoichiometric reagents.[18] The absolute and relative configurations of products **28a** and **28b** were unambiguously assigned by X-ray crystallography[13] and found to be consistent with the CHCR reaction proceeding though an s-cis/boat transition state.[11]



A reasonable mechanism that would be consistent with the kinetic resolution is shown in Scheme 4. The Rh_2(*S*-DOSP)$_4$ is proposed to adopt a D_2-symmetric structure, and the substrate would approach only from the front face.[12] The CHCR reaction would proceed through a boat transition state as shown.[11] The R group in the substrate would 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

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of the substrate reacts, leading to products with high stereochemical control. When the R group is methyl, the steric interference is not as dramatic, which 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 having 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-, diastereo-, and enantioselective.

■ ASSOCIATED CONTENT

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.

■ AUTHOR INFORMATION

Corresponding Author
hmdavie@emory.edu

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