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Highly Stereoselective C−C Bond Formation by Rhodium-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement between Donor/Acceptor Carbenoids and Chiral Allylic Alcohols

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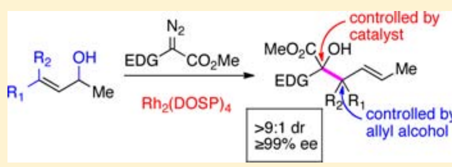
Supporting Information

ABSTRACT: The tandem ylide formation/[2,3]-sigmatropic rearrangement between donor/acceptor rhodium carbenoids and chiral allyl alcohols is a convergent C−C bond forming process, which generates two vicinal stereogenic centers. Any of the four possible stereoisomers can be selectively synthesized by appropriate combination of the chiral catalyst $Rh_2(DOSP)_4$ and the chiral alcohol.



1. INTRODUCTION

Chiral allylic alcohols are readily available and have been widely used as versatile building blocks in organic synthesis.[1] Recently we discovered an unexpected reaction between rhodium carbenoids and allylic alcohols.[2] Normally alcohols react with carbenoids to form O−H insertion products.[3−5] However, we found that the reaction between donor/acceptor-substituted carbenoids and racemic allylic alcohols bearing a 3,3-dimethyl functionality resulted in an enantioselective [2,3]-sigmatropic rearrangement.[2a,6] Homoallylic alcohols containing a single stereogenic center were formed in which the enantioselectivity was governed by the chirality of the catalyst rather than the chirality of the starting alcohol. As the resulting products can be used in extended domino sequences,[2b] we became interested in broadening the substrate scope and generality of the reaction. In particular, we wished to explore the possibility of generating products containing vicinal stereocenters in a stereoselective manner (Scheme 1). In this paper, we demonstrate that all four of the possible stereoisomers of the products can be selectively and predictably generated by using the appropriate combination of chiral allylic alcohol and chiral catalyst. The allylic stereocenter of the products is controlled by the chirality of the allylic alcohol and the alkene geometry, whereas the homoallylic stereocenter is dictated by the chirality of the catalyst.

Scheme 1. Rhodium(II)-Catalyzed [2,3]-Sigmatropic Rearrangement of Allyl Alcohols

2. RESULTS AND DISCUSSION

We began our investigations by studying the reaction of the stereoisomers of 3-penten-2-ol (**1**) with styryldiazoacetate **2**, catalyzed by either $Rh_2(R\text{-DOSP})_4$ or $Rh_2(S\text{-DOSP})_4$ (Table 1). The reactions of the four possible combinations of (*E*)-**1** and $Rh_2(DOSP)_4$ revealed that all the stereoisomers of the products **3** could be obtained in a stereoselective manner (>9:1 dr and >99% ee[7]) (entries 1−4). A comparison of entries 1 and 2 (and 3 and 4) demonstrated that the stereocenter at C_3 of the product was governed by the configuration of the allyl alcohol. In contrast, a comparison of entries 1 and 3 (and 2 and 4) demonstrated that the chiral catalyst controlled the configuration at C_2. The reactions of (*S,Z*)-**1** with $Rh_2(R\text{-DOSP})_4$ and $Rh_2(S\text{-DOSP})_4$ were also examined (entries 5 and 6). Significant matched and mismatched interactions between the chiral entities were displayed in these reactions.[8] The $Rh_2(R\text{-DOSP})_4$-catalyzed reaction of (*S,Z*)-**1** with **2** was very efficient, generating (2*S*,3*S*)-**3** in 69% yield and with 94:6 dr and >99% ee (entry 5). The stereochemical configuration of the product was the same as that of the product derived from the $Rh_2(R\text{-DOSP})_4$-catalyzed reaction of (*R,E*)-**1** (entry 4). However, the $Rh_2(S\text{-DOSP})_4$-catalyzed reaction of (*S,Z*)-**1** with **2** was a mismatched reaction. In this case a 3:1 mixture of diastereomers was produced in low overall yield (35% for the major diastereomer) (entry 6).

The tandem ylide formation/[2,3]-sigmatropic rearrangement was examined with a series of donor/acceptor-substituted diazoacetates with a variety of aryl and alkenyl substituents. In all cases, the major diastereomer was produced with very high asymmetric induction (>99% ee), but the diastereoselectivity was variable. In the case of the aryldiazoacetates, **4a** and **4b**, the diastereoselectivity was ≥9:1 (Table 2, entries 1−2). The *p*-bromostyryl derivative **4c** (entry 3) was comparable to the unsubstituted phenyl system (Table 1, entry 1). The butenyl- and propenyl-substituted diazo compounds (**4d** and **4e**, respectively) underwent the rhodium-catalyzed transformation with high levels of asymmetric induction (entries 4 and 5). These results are consistent with previous examples of the high enantioselectivity exhibited in the $Rh_2(S\text{-DOSP})_4$ catalyzed

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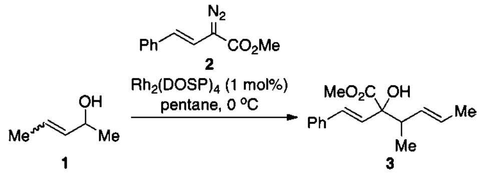
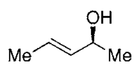
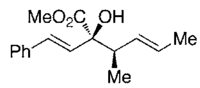
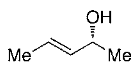
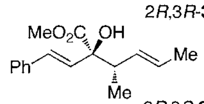
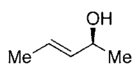
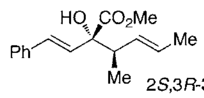
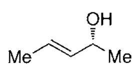
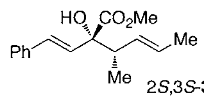
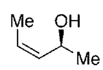
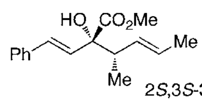
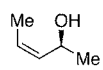
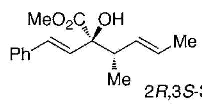
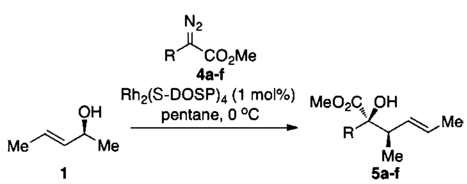
Table 1. Stereocontrolling Elements of the Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement[a]

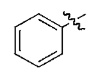
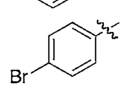
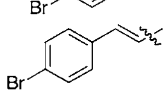
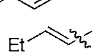
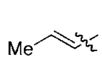
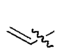


entry	Substrate	$Rh_2(DOSP)_4$	Product	Yield, %[b]	dr[c]	ee, %[d]
1	 S,E-**1**	S	 2R,3R-**3**	70	92:8	>99
2	 R,E-1	S	 2R,3S-**3**	64	91:9	>99
3	 S,E-1	R	 2S,3R-**3**	54	92:8	>99
4	 R,E-**1**	R	 2S,3S-**3**	78	95:5	>99
5	 S,Z-**1**	R	 2S,3S-**3**	69	94:6	>99
6	 S,Z-**1**	S	 2R,3S-**3**	35	75:25	>99

[a]Reaction conditions: To a pentane solution of the allyl alcohol (1 equiv) and Rh_2(S-DOSP)$_4$ (0.01 equiv) at 0 °C under an atmosphere of Ar was added a solution of the diazo compound (2.0 equiv) in pentane solution over 1.5 h. The reaction was stirred for 1 h further at 0 °C and then concentrated under reduced pressure. [b]Isolated yield of the major diastereomer. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by chiral HPLC.

Table 2. Reaction of (S,E)-1 with 4a–f[a]



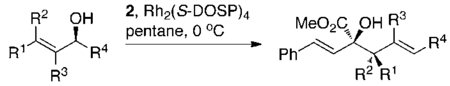
entry	comp'd	R	yield, %[b]	dr[c]	ee[d]
1	a		56	94 : 6	>99
2	b		66	90 : 10	>99
3	c		69	>95 : 5	>99
4	d		60	>95 : 5	>99
5	e		55	>95 : 5	>99
6	f		43	79 : 21	>99

[a]Same reaction conditions as described in Table 1. [b]Isolated yield of the major diastereomer. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by chiral HPLC.

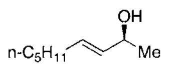
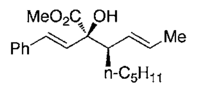
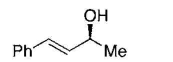
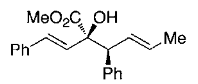
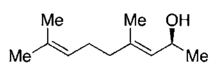
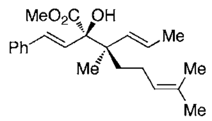
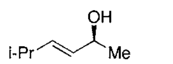
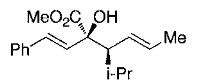
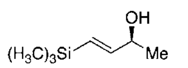
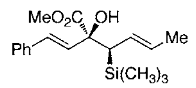
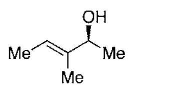
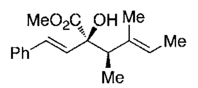
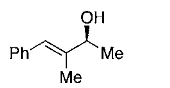
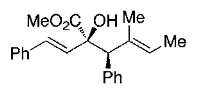
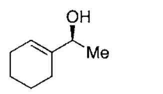
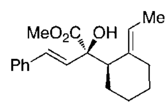
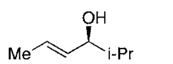
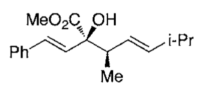
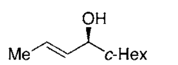
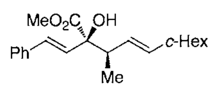
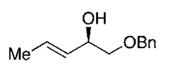
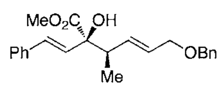
reactions of diazoacetates **4a–e**.[2] In entry 6, the unsubstituted vinyldiazoacetate **4f** was obtained in modest yield (43%) and with poor diastereoselectivity (79:21 dr). It is well established that Rh_2(S-DOSP)$_4$-catalyzed cyclopropanations with **4f** proceed with moderate enantiocontrol[8,9] and the moderate diastereoselectivity observed in entry 6 is consistent with a low level of stereocontrol by Rh_2(S-DOSP)$_4$ in this case.

The tolerance of the reaction to various substituents on the alcohols was then studied, and these results are summarized in Table 3. In general, extended aliphatic and aryl substituents at the C_3 position of the alcohol **6** were well tolerated (entries 1–2) including the 3,3-disubstituted substrate (entry 3). This substrate exemplified the utility of the metal-carbenoid transformation, facilitating the high yielding preparation of a product bearing two contiguous quaternary stereogenic centers with high levels of enantio- and diastereoselectivity. Allyl alcohols with relatively bulky substituents, such as isopropyl and trimethylsilyl (**6d** and **6e**), also afforded the corresponding rearrangement products, but the yields were modest (60% and 42%, respectively). An array of alcohols bearing C_2-substitution (**6f–h**) were evaluated, and they were also amenable to this transformation (entries 6–8). It was expected that, in the metal-bound oxonium-ylide intermediate formed, any functionality at C_2 would be oriented away from the catalyst and, thus, would have little consequence on the reactivity. Finally, the effect of various functional groups at the carbinol position was explored in entries 9–11, and in all cases the desired products

Table 3. Scope of the Allyl Alcohol 6[a]



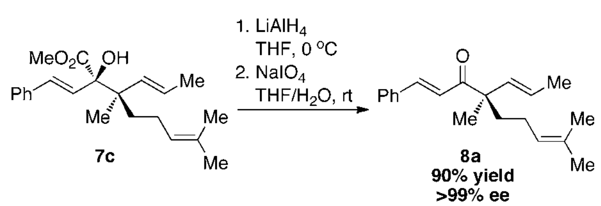
6a-j 7a-j

entry	comp'd	6	7	yield, %[b]	dr[c]	ee, %[d]
1	a			83	>95 : 5	>99
2	b			71	>95 : 5	>99
3	c			82	>95 : 5	>99
4	d			60	>95 : 5	>99
5	e			42	>95 : 5	99
6	f			61	>95 : 5	>99
7	g			68	>95 : 5	>99
8	h			77	>95 : 5	>99
9	i			75	>95 : 5	>99
10	j			86	>95 : 5	>99
11	k			70	>95 : 5	>99

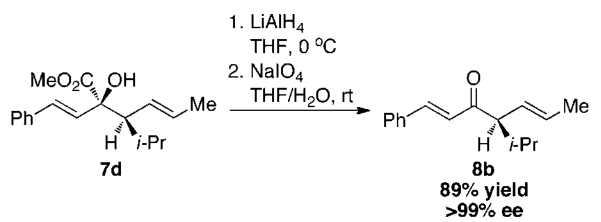
[a]Same reaction conditions as described in Table 1. [b]Isolated yield of the major diastereomer. [c]Determined by ^1H NMR analysis of the crude reaction mixture. [d]Determined by chiral HPLC.

were formed. Of particular significance is the reaction of the monobenzyl-protected 1,2-diol **6k**, which was capable of selective reaction at the allylic alcohol over the benzyl ether functionality.

The synthetic utility of the rhodium-catalyzed sigmatropic rearrangement with the chiral alcohols lies in the ability to generate two adjacent stereogenic centers in a controlled and predictable manner. A distinctive feature of the transformation is the generation of a quaternary hydroxyl carbonyl moiety bearing a vicinal stereocenter, which is a structural feature embedded in a number of natural products.[10] We also decided to demonstrate the broader synthetic potential of the reaction by illustrating a two-step conversion of the products to enones, containing a chiral center α to the carbonyl (eqs 1 and 2). Enones containing quaternary (**8a**) and tertiary (**8b**) stereocenters α to the carbonyl were readily prepared in excellent yields. A particularly appealing feature of this approach to chiral enones is the likelihood that a chiral catalyst would not be



(1)



(2)

required because the stereogenic center α to the carbonyl is controlled by the chirality of the starting alcohol.

Due to the uniformly high levels of asymmetric induction for the tandem ylide formation/[2,3]-sigmatropic rearrangement, we sought a general transition-state model which would rationalize the observed stereochemical results.[6] It has been well established that the Rh_2(*S*-DOSP)$_4$-catalyzed reactions of vinyldiazoacetates result in attack at the *Re* face of the vinylcarbenoid.[11] The [2,3]-sigmatropic rearrangement would be expected to proceed through an envelope-like transition state, in which $A_{1,3}$-strain is minimized.[12] A reasonable model, which takes into account the established stereochemical understanding of these reactions, is shown in Figure 1. *Re*

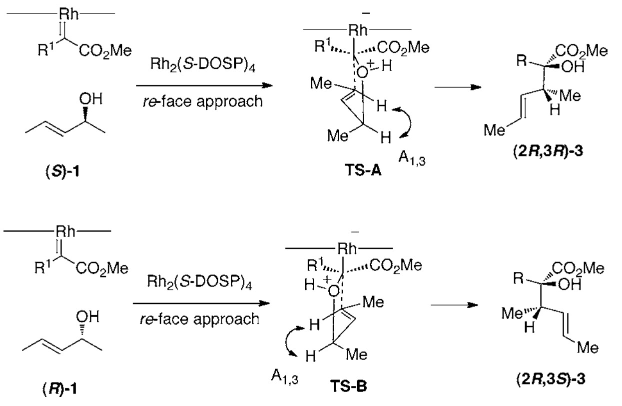


Figure 1. Transition-state analysis for the formation of **3**.

face attack of the carbenoid by (*S,E*)-**1** would generate an intermediate that would preferentially undergo a 2,3-sigmatropic rearrangement through TS-A, in which the $A_{1,3}$ strain is minimized. This transition state would lead to the formation of the observed (2*R*,3*R*) isomer. Likewise, the reaction of (*R,E*)-**1** would proceed through TS-B, which would generate the (2*R*,3*S*) isomer. The *Re* face attack on the carbenoid controls the stereochemistry at C_2 in the product, and at least in the case of (*E*)-**1**, the carbenoid-induced stereogenic center does not have a significant influence on the stereochemistry of the [2,3]-sigmatropic rearrangement.

3. CONCLUSION

In summary, the tandem ylide formation/[2,3]-sigmatropic rearrangement between donor/acceptor rhodium carbenoids and chiral allyl alcohols is a convergent C−C bond forming process, which generates two vicinal stereogenic centers. Any of the four possible stereoisomers can be selectively synthesized by the appropriate combination of the chiral catalyst Rh_2(DOSP)$_4$ and the chiral alcohol. Only traces of O−H insertion products are observed in these reactions, which further illustrates the difference in reactivity of donor/acceptor carbenoids compared to conventional carbenoids, lacking a donor group.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details and spectral data. 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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