Communication

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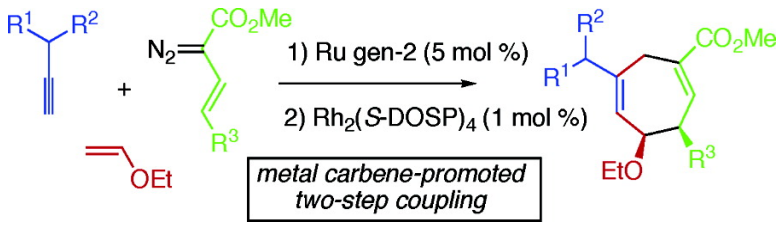

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Metal Carbene-Promoted Sequential Transformations for the Enantioselective Synthesis of Highly Functionalized Cycloheptadienes

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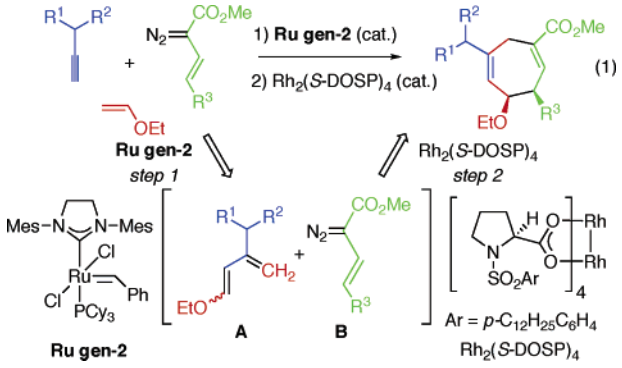
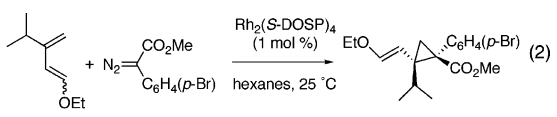
The development of sequential organometallic transformations[1] offers exciting opportunities for the rapid access to structurally complex targets. Ring synthesis through modular, complexity-building reactions in a catalytic and stereocontrolled manner is a tremendous challenge. In this communication, we describe a two-step, three-component coupling strategy between alkynes, vinyl ethers, and vinyldiazoacetates for the enantioselective synthesis of highly functionalized cycloheptadienes (eq 1).

Scheme 1. Two-Step Synthesis of Cycloheptadienes



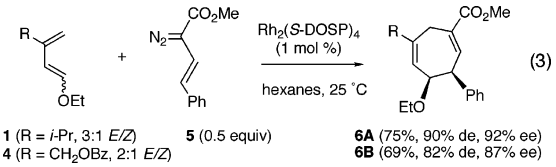
The three-component coupling of eq 1 involves two powerful metal carbene-promoted couplings, applied together in a two-step sequence. The first step is based on the enyne metathesis[2] between various alkynes and vinyl ethers to form 3-substituted-1-alkoxy-1,3-dienes **A**, developed by the Diver group (Scheme 1).[3] The reaction uses the second generation Grubbs' carbene complex (**Ru gen-2**),[4] tolerates a variety of heteroatom functionality on the alkyne, and provides a simple and rapid synthesis of electron-rich 1,3-dienes **A**. The second step of the sequence is the (Rh_2(*S*-DOSP)$_4$)-catalyzed [4 + 3] cycloaddition between vinyldiazoacetates **B** and dienes **A** to from cycloheptadienes, developed by the Davies group.[5] By combining the strengths of these two reactions, a stereoselective synthesis of cycloheptadienes is possible. The products can also be obtained in high enantiomeric purity even when starting with racemic alkynes and isomeric mixtures of dienes.

For the two step, three-component coupling to be successful, the rhodium vinylcarbenoid must undergo selective reactions to distinguish between the mixture of dienes derived from the enyne metathesis. Donor/acceptor substituted carbenoids are capable of chemoselective reactions and are highly discriminating as compared to the conventional carbenoids lacking a donor group.[6] The reaction of **1** with methyl *p*-bromophenyldiazoacetate (**2**) was used to begin exploring the chemoselectivity issues (eq 2). The reaction catalyzed



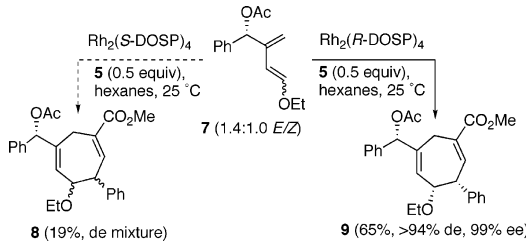
by Rh_2(*S*-DOSP)$_4$ (1 mol %) gave a promising result. A single cyclopropane **3** was formed in 71% yield, >94% de, and 95% ee. Thus, the rhodium carbenoid selectively reacted with (*E*)-**1** instead of (*Z*)-**1** even though the cyclopropanation was occurring at the other double bond of the diene.

After having determined that a chemoselective and stereoselective cyclopropanation was possible, the reaction of diene **1** with the vinyldiazoacetate **5** was examined (eq 3). The Rh_2(*S*-DOSP)$_4$-catalyzed reaction was very efficient, but the product now was the cycloheptadiene **6A**, which was formed in 75% yield, 90% de, and 92% ee. This suggests that the vinylcarbenoid did not fully distinguish between dienes (*Z*)-**1** and (*E*)-**1** in the initial cyclopropanation step, because the cycloheptadiene diastereomer formed is controlled by the alkene geometry.[5] The Rh_2(*S*-DOSP)$_4$ reaction of **5** was also applied to the benzoyl derivative **4** (eq 3). Again, a stereoselective reaction was obtained, forming **6B** in 69% yield, 82% de, and 87% ee.



The combined transformation would be even more powerful if it was possible to achieve kinetic resolution in addition to the alkene geometry discrimination. To explore this possibility, the reaction of **7** with **5** was next examined. It was anticipated that double diastereodifferentiation might be observed since the diene and catalyst each possess facial bias. The matched reaction catalyzed by Rh_2(*R*-DOSP)$_4$ resulted in the formation of **9** in 65% yield >94% de (right side, Scheme 2). In contrast, the mismatched reaction with Rh_2(*S*-DOSP)$_4$ was very ineffective, resulting in the formation of an undetermined 2:1 mixture of diastereomers **8** in 19% yield.

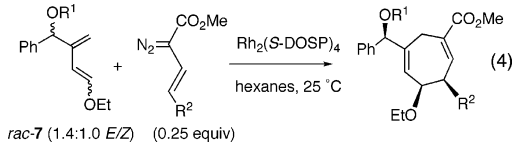
Scheme 2. Double Diastereodifferentiation



The above results indicate that the [4 + 3] cycloaddition could lead to effective kinetic resolution of the racemic dienes (Table 1). This led to the formation of cycloheptadienes *ent*-**9**, **10**, and **11** in 40−64% isolated yield with high enantioselection (85−99% ee), although the diastereoselectivity was considerably lower (50−82% de).

10.1021/ja045173t CCC: $30.25

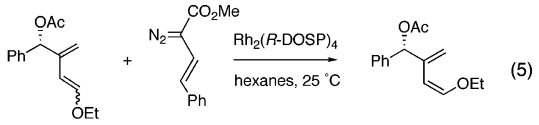
Table 1. Kinetic Resolution with Chiral Rh_2(*S*-DOSP)$_4$ Catalyst



rac-**7** (1.4:1.0 *E*/*Z*) (0.25 equiv)

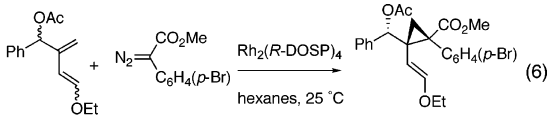
R^1	R^2	product	yield, %	de, %	ee, %
Ac	Ph	*ent*-**9**	64	50	99
Bz	Ph	**10**	40	82	95
Ac	CH=CHPh	**11**	54	50	85

The selectivity of the reaction of *E*-vinyl ether is so pronounced that under appropriate conditions it is possible to recover cleanly the *Z*-diene. As can be seen in the reaction of **7** with **5** (1.5 equiv), complete consumption of (*E*)-**7** can be achieved through cyclopropanation−Cope rearrangement, leaving (*Z*)-**7** which was recovered in 40% yield (eq 5).



7 (1.4:1.0 *E*/*Z*) **5** (1.5 equiv) (*Z*)-**7** (40%)

To determine the absolute stereochemistry of these reactions, the Rh_2(*R*-DOSP)$_4$-catalyzed reaction of **7** with **2** was examined (eq 6). This resulted in the formation of the cyclopropane **12** in 58% yield, >94% de, and 92% ee. In this case, the presence of the aryl group serves two purposes. First, it precludes Cope rearrangement, permitting assignment of facial selectivity in the cyclopropanation step. Second, the presence of the heavy atom allows the assignment of absolute stereochemistry by crystal structure determination. Recrystallization of **12** enriched the material to >99% ee whose X-ray crystal structure revealed that it was the drawn stereoisomer **12**. The assigned stereochemistry of the cycloheptadienes is based on the well-precedented analogous enantioinduction for the cyclopropanation with vinyldiazoacetates,[7] followed by a divinylcyclopropane rearrangement occurring through a boat transition state.[5]



rac-**7** (1.4:1.0 *E*/*Z*) **2** (0.5 equiv) **12** (58%, >94% de, 91% ee)

The chemoselectivity of the carbenoid transformations can be rationalized as illustrated in Figure 1. The diene *E*-**7** is more reactive that the *Z*-isomer, and this is more pronounced as the size of the 3-substituent increases. With large 3-substituents, the *E*-diene would exist predominantly in the *s-cis* conformation (eq 7). In the corresponding *Z*-isomer, the *Z*-substituent would be twisted from planarity due to steric repulsion (favoring the right side of eq 8). The resulting twist out of conjugation will limit the electron-donating influence of the ethoxy group on the double bond undergoing cyclopropanation. The highly diastereoselective [4 + 3] cycloaddition occurs by a tandem cyclopropanation/Cope rearrangement. The Rh_2(*R*-DOSP)$_4$-catalyzed cyclopropanation is well established to be highly diastereoselective and enantioselective, and thus the formation of the necessary *cis*-divinylcyclopropane intermediate **C** is well-precedented.[5] In the case of *E*-**7**, 1,3-allylic strain

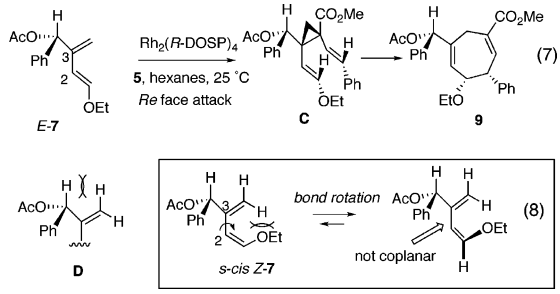


Figure 1. Model for stereoselectivity

would also be expected to have a significant effect on face selectivity in the cyclopropanation (see **D**).[8] Assuming that attack over the phenyl group is disfavored both for the (*S*)-substrate and for the (*R*)-catalyst, then selective cyclopropanation of the *re* face will occur, leading to a strongly matched reaction. Once the divinylcyclopropane **C** has been formed in a stereoselective manner, the cycloheptadiene **9** will inevitably be formed stereoselectively because the Cope rearrangement of divinylcyclopropanes proceeds through a well-defined boat transition state.

These studies demonstrate that a highly stereoselective three-component ring synthesis can be accomplished by conjoining two powerful metal carbene-mediated transformations. Furthermore, the highly discriminating Rh_2(DOSP)$_4$ catalyst selects diene topology and can differentiate propargylic stereochemistry in an effective kinetic resolution. By applying these reactions in sequence, highly stereoselective synthesis of complex cycloheptadienes can be achieved.

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Supporting Information Available: Full experimental data for the compounds described in this paper, ^{1}H and ^{13}C spectra of selected compounds, and X-ray crystallographic data for **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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