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# Synthesis of Complex Hexacyclic Compounds via a Tandem Rh(II)-Catalyzed Double-Cyclopropanation/Cope Rearrangement/Diels–Alder Reaction

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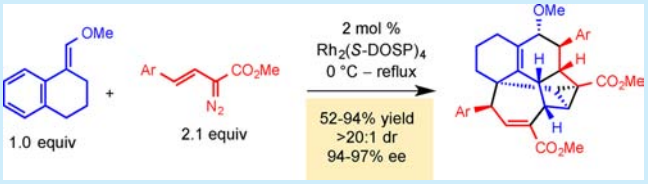
Supporting Information

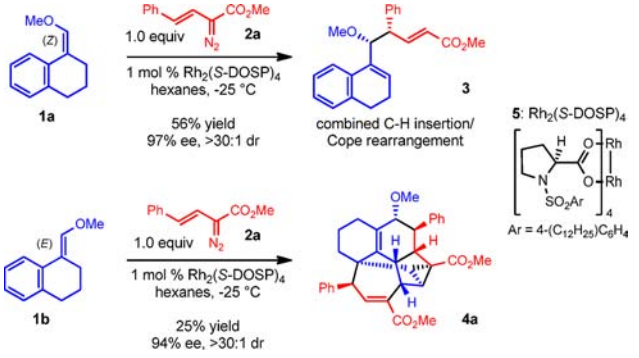
**ABSTRACT:** Treatment of (*E*)-1-(methoxymethylene)-1,2,3,4-tetrahydronaphthalene with styryl diazoacetates in the presence of catalytic amounts of the dirhodium complex $Rh_2$(*S*-DOSP)$_4$ provides a highly enantioenriched hexacyclic product with 10 new stereogenic centers. The transformation proceeds by a cascade sequence starting with a double cyclopropanation of a benzene ring, followed by a Cope rearrangement of a divinylcyclopropane and then an intramolecular Diels–Alder cycloaddition.




The rhodium(II)-catalyzed reaction of diazo compounds generates highly reactive carbenoid intermediates under very mild conditions. The energy released on formation of dinitrogen can be harnessed to generate unstable, high energy products that are often capable of initiating a cascade sequence of reactions.[1,2] We have developed a number of such cascade sequences from vinyl diazoacetates, including the stereoselective synthesis of cycloheptadienes via the tandem cyclopropanation/Cope rearrangement[3] and the combined C–H functionalization/Cope rearrangement/retro-Cope rearrangement.[4] Recently, we also developed an enantioselective six-step cascade sequence that provides cyclopentanes containing four new stereogenic centers from the union of allylic alcohols and vinyl diazoacetates.[5] In this paper, we describe our discovery of a novel complexity-generating cascade sequence involving a tandem double-aromatic cyclopropanation/Cope rearrangement/Diels–Alder reaction, which generates highly enantioenriched hexacyclic products with 10 new stereogenic centers in a single transformation.

During the course of a recent study of the Rh(II)-catalyzed combined C–H functionalization/Cope rearrangement (CHCR) of enol ethers,[6] our group synthesized the $\alpha$-tetralone-derived enol ethers **1a** and **1b** (Scheme 1). Treatment of the less hindered *Z*-enol ether, **1a**, with vinyl diazoacetate **2a** and 1 mol % of the $Rh_2$(*S*-DOSP)$_4$ catalyst (**5**) under standard CHCR conditions, provides enoate **3** in excellent yield with high levels of diastereo- and enantioselectivity.[6] Owing to the results of our previous studies of the CHCR of geo-isomeric enol ethers,[6] we had expected that the more hindered *E*-enol ether **1b** would fail to undergo the CHCR and suspected that this compound would undergo C–H insertion at the electronically activated benzylic methylene site.[7] However, to our surprise, treatment of **1b** with vinyl diazoacetate **2a** under the same reaction conditions provides the complex polycyclic product **4a** in modest yield as a single diastereoisomer and 94% ee.

**Scheme 1. Divergent Reactivity of Enol Ethers 1a and 1b**[a–c]




[a]Reaction conditions: 1 equiv of substrate (0.25 mmol), 1.2 equiv of **2a** added dropwise over 3 h, 1 mol % of $Rh_2$(*S*-DOSP)$_4$, hexanes, −25 °C. [b]Isolated yields reported. [c]Enantiomeric exccess determined by HPLC analysis after purification.

Notably, this transformation generates six new bonds, four new rings, and 10 new stereogenic centers (including two all-carbon quaternary stereogenic centers) in a single transformation. Considering the remarkable complexity generating nature of this transformation, we decided to explore the scope and generality of the transformation. No evidence for the formation of CHCR or C–H insertion products was observed. As this transformation requires incorporation of two molecules of vinyl diazoacetate **2a** into the enol ether **1b**, the yield of **4** is substantially improved by increasing the equivalency of vinyl diazoacetate as well as by elevating the reaction temperature and increasing the catalyst loading to 2 mol %. In addition, improved yields were observed for faster addition times of the vinyl diazoacetate to the reaction (addition over 15 min as

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opposed to 3 h) due to a reduction in the formation of undesired pyrazole byproduct.[8] Under these improved reaction conditions, polycyclic compound **4a** is obtained in 76% yield and 94% ee as a single diastereoisomer (Figure 1, entry 1).

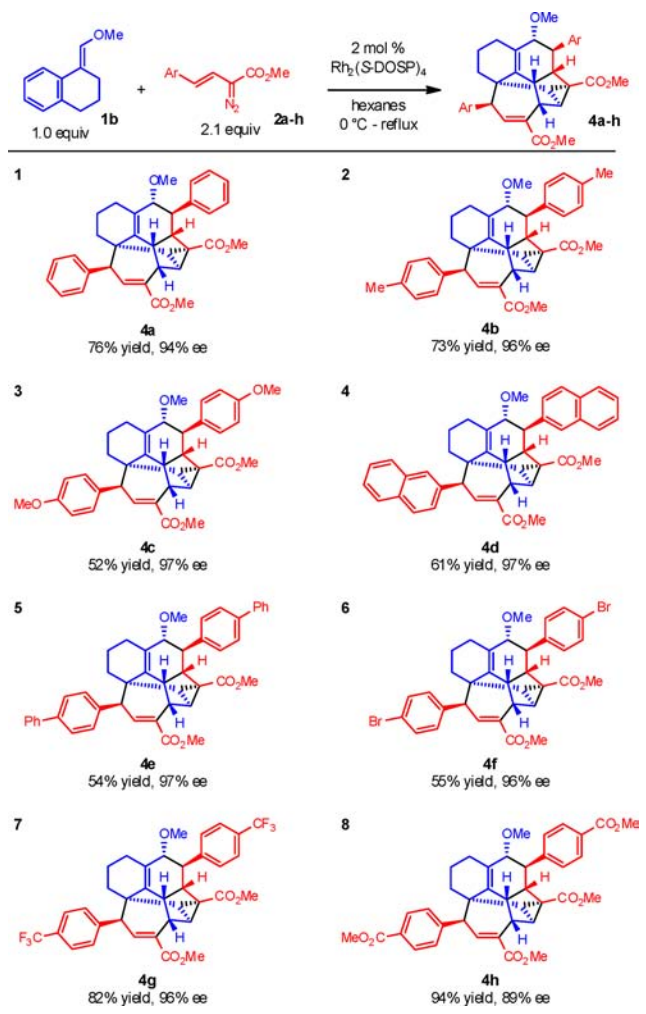



**Figure 1.** Scope of vinyl diazoacetates in polycyclic formation. Reaction conditions: 2.1 equiv of **2a** added dropwise over 15 min at 0 °C to **1b** and 2 mol % $Rh_2$(*S*-DOSP)$_4$ in hexanes at 0 °C followed warming to rt for 30 min and then heating under reflux for 2 h. Isolated yields reported. Enantiomeric excess determined by HPLC analysis after purification.

Having developed optimized reaction conditions for the synthesis of **4a**, we subsequently explored the scope of this reaction with respect to the diazo coupling partner. As shown in Figure 1, a variety of styryl diazoacetates react effectively to provide the corresponding hexacyclic products in good to excellent yield (52−94%) with uniformly high levels of asymmetric induction (94−97% ee). However, higher yields are generally achieved for more electron-deficient diazo substrates (82−94% yield, Figure 1, entries 6−8), which experience a slower rate of competitive pyrazolization.

The structure and absolute configuration of this novel hexacylic product were confirmed by X-ray crystallography of **4e** (Figure 2). The complex polycyclic compound features a cagelike architecture, the strained nature of which can be observed in the central tetrasubstituted alkene, which is twisted from planarity by approximately 18°. The absolute configuration of the other polycyclic compounds (**4**) is assigned by analogy.[9]

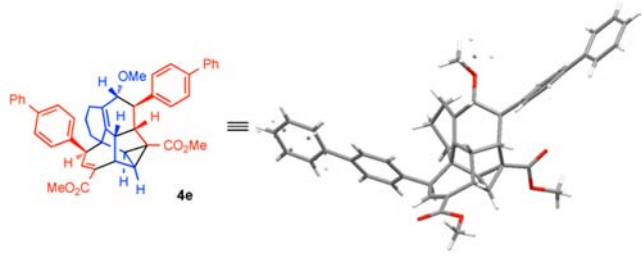
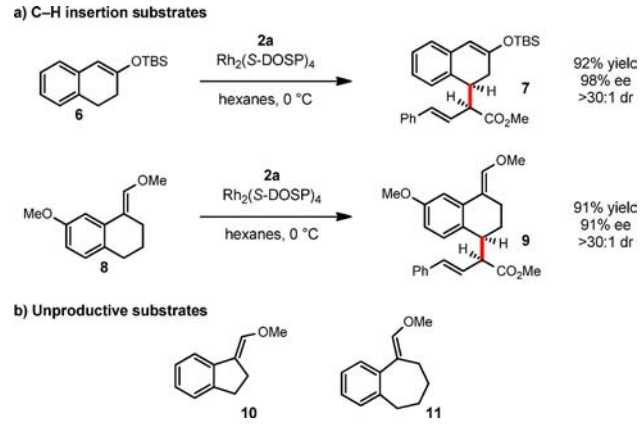



**Figure 2.** Crystal structure of **4e** establishes the relative and absolute configuration of polycyclic products.

We subsequently explored the arene substrate scope of this transformation (Scheme 2). We were interested in examining

**Scheme 2. Attempted Cascade Reactions of Other Aryl Substrates**




the reactivity of the $\beta$-tetralone-derived enol ether **6** as it is electronically similar to **1b**. We anticipated that this compound would be a substrate for the double cyclopropanation/Cope rearrangement, providing a product that would be unable to undergo the final Diels−Alder reaction. However, this aryl substrate undergoes a simple, but highly enantioselective, C−H insertion at the activated benzylic methylene to provide diene **7**.[10] Substitution of the aryl ring completely blocks cyclopropanation of the arene. In the case of the 7-methoxytetralone-derived enol ether, **8**, C−H insertion occurs at the activated benzylic position. Perhaps more surprisingly, compound **10** gave mixture of products and **11** failed to react under these reaction conditions. To date, we have found the *E*-enol ether **1b** to be a privileged substrate for the formation of this hexacyclic product.

Our proposed mechanism for this cascade sequence is shown in Scheme 3. An enantio- and diastereoselective double cyclopropanation of enol ether **1b** would provide bis-cyclopropane **13**. After the initial cyclopropanation to form cyclohexadiene **12**, a second and more rapid cyclopropanation from the unhindered face would provide **13**. Thus, the absolute configuration of the product is set during the first cyclopropanation step. The stereoselective double cyclopropanation of aromatic rings by donor/acceptor carbenoids has been observed previously.[11] A subsequent divinylcyclopropane rearrangement[3] of **13** would form tetracycle **14**. The bis-cyclopropane **13** contains two divinylcyclopropanes. We attribute the regioselectivity of the divinylcyclopropane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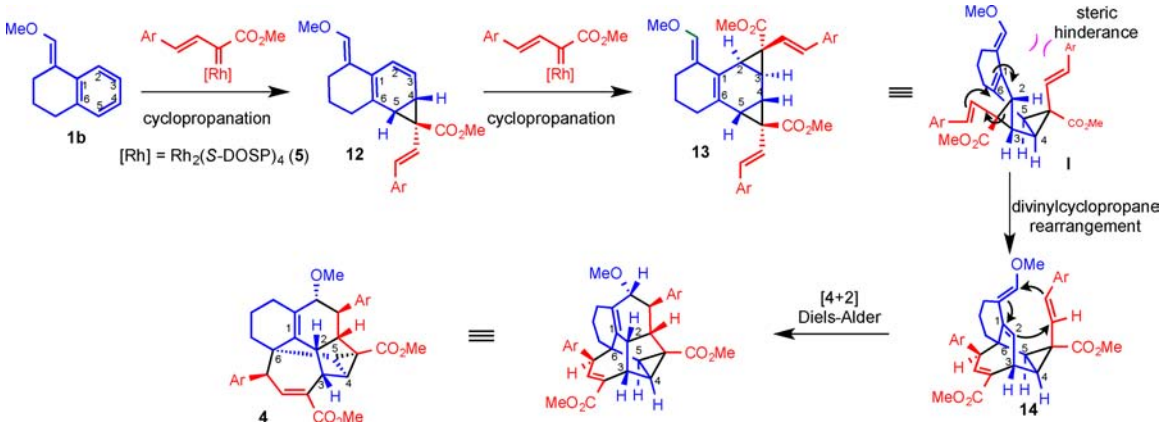
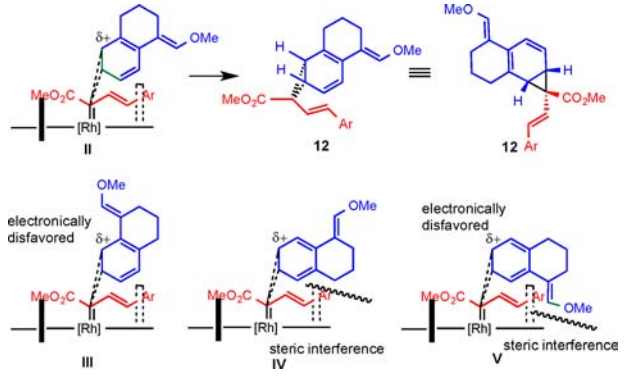
**Scheme 3. Proposed Mechanism of Polycyclic Compound Formation**




rearrangement to a steric interaction between the aryl group of the unreactive styrene and the methoxy enol ether in the boat-like transition state **I** that would be required for this rearrangement. Finally, a proximity-induced Diels–Alder reaction in **14** would yield the hexacyclic compound **4**.[12]

The successful formation of **4** requires the initial cyclopropanation to be highly site-, diastereo-, and enantioselective. It is well-established that vinyl diazoacetates undergo highly diastereoselective cyclopropanations, and $Rh_2(S\text{-DOSP})_4$ is an exceptional chiral catalyst for these types of transformations.[8a,13] The site selectivity can be understood by considering the well-explored transition-state models for asymmetric cyclopropanation of electron-rich alkenes by $Rh_2(S\text{-DOSP})_4$ (Scheme 4).[8a,13,14] The cyclopropanation is a concerted

**Scheme 4. Stereochemical Analysis of the First Cyclopropanation Step**




asynchronous process in which there is buildup of positive charge on one of the alkene carbons during the cyclopropanation.[14] The rhodium carbenes of donor/acceptor carbenes are sterically demanding and preferentially initiate the cyclopropanation at the least substituted carbon of the alkene.[14] As it is well-established that cyclopropanation of a 1,4-disubstituted benzene ring does not occur,[7,11] we assume the site for greater initial bond formation during the cyclopropanation would not be adjacent to a ring substituent. Four possible orientations (**II**–**V**) would fit this criterion, although only transition state **II** would avoid steric interference with the "wall" of the catalyst and is electronically favored for delocalization of the positive charge build up into the methoxy group. A reaction proceeding through transition state **II** would generate **12**, which on further reaction would generate **4** with the observed absolute configuration.

In conclusion, we have discovered a novel and high complexity-generating reaction of styryl diazoacetates and the α-tetralone-derived enol ether **1b** that features an enantioselective double-cyclopropanation/Cope rearrangement/Diels–Alder cascade. The formation of polycyclic compound **4** demonstrates the capacity of reactive Rh(II) carbenoid intermediates to form strained and high energy products. Although this reaction has a broad scope with respect to the styryldiazo component, the arene scope is extremely limited, only succeeding with enol ether **1b**. These studies demonstrate the subtle controlling factors of the substrate on the chemoselectivity of donor/acceptor rhodium carbene reactions.

## ■ 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.

## ■ ACKNOWLEDGMENTS

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(10) The relative and absolute stereochemistry of **7** was assigned by X-ray crystallography and extended to compound **9** by analogy (see the Supporting Information). This crystal structure has been deposited with the Cambridge Database (CCDC no. 1015313).
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