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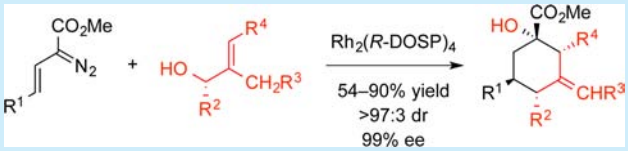
Stereoselective Synthesis of Highly Substituted Cyclohexanes by a Rhodium-Carbene Initiated Domino Sequence

Brendan T. Parr and Huw M. L. Davies*

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

Supporting Information

ABSTRACT: A stereoselective synthesis of cyclohexanes bearing four stereocenters from vinyldiazoacetates and allyl alcohols by a rhodium-carbene initiated domino reaction is described. The reaction cascade features a tandem ylide formation/[2,3]-sigmatropic rearrangement, oxy-Cope rearrangement, and type II carbonyl ene reaction, all of which proceed with a high degree of stereocontrol. The products are routinely isolated with excellent stereocontrol (>97:3 dr, 99% ee).

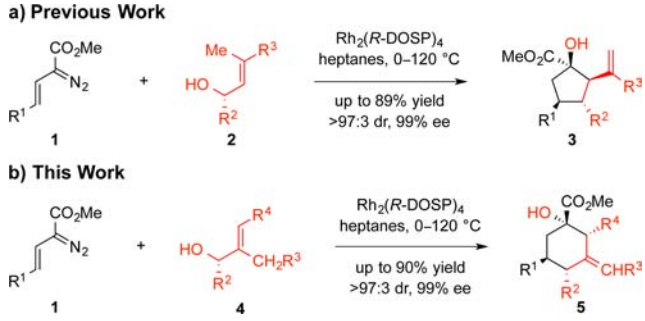


Convergent methods for the stereoselective synthesis of six-membered carbocycles are important strategies for the synthesis of complex targets. Although the venerable Diels–Alder [4 + 2]-cycloaddition reaction has remained state-of-the-art,[1−3] many novel annulations, including [3 + 3]- and [5 + 1]-cycloadditions[4,5] have enabled entry into distinct, cyclohexane derivatives. While it is doubtful any convergent annulation strategy can compete with the Diels–Alder reaction in terms of broad generality, the development of orthogonal approaches to the synthesis of a cyclohexane nucleus, which allow alternative substitution patterns and stereocontrol, is nonetheless desirable.

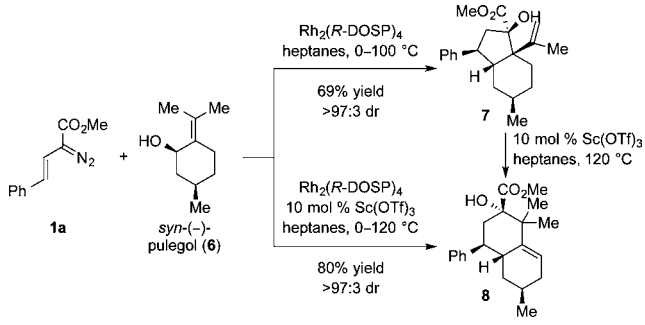
Donor/acceptor-substituted rhodium carbenes have a rich history of application toward the synthesis of medium-sized carbocycles.[6,7] For example, cyclopropanation of conjugated dienes by rhodium vinylcarbenes, followed by a Cope rearrangement of the transient *cis*-divinylcyclopropane is a powerful approach to the stereoselective construction of cycloheptadienes.[6] Also, vinylogous addition to rhodium-vinylcarbenes has proven an efficient approach to cyclopentene synthesis.[7a,c] In recent studies, we disclosed the synthesis of functionalized cyclopentanes **3** bearing four stereocenters by a complex reaction cascade involving interception of rhodium vinylcarbene intermediates derived from **1** with allyl alcohols **2** (Scheme 1a).[8] A range of vinyldiazoacetates and allyl alcohols were found to be suitable partners for the synthesis of cyclopentanes in exceptional yields and stereocontrol. Herein, we report that appropriate engineering of the alcohol partner, such as **4**, enables entry to cyclohexanes **5** bearing four stereocenters and an exocyclic olefin (Scheme 1b). Similar to our previously reported cyclopentane synthesis,[8] the cyclohexanes are formed as single stereoisomers in good yields through a one-pot domino reaction.

The discovery of the cyclohexane forming reaction pathway was made during our previous investigations into cyclopentane synthesis with *syn*-(−)-pulegol (**6**).[8a,9] Formation of the fused cyclopentane **7** occurs upon heating of the crude product resulting from the Rh-catalyzed reaction of **6** and styryldiazoacetate **1a** (Scheme 2).[8a] We found, however, under more vigorous reaction conditions, the fused cyclohexane **8** was formed as the sole product. Moreover, exposure of the fused cyclopentane **7** to Lewis acid and elevated temperatures resulted in smooth conversion of **7** to the fused cyclohexane **8** in quantitative yield. In both instances, **8** was generated as a single diastereoisomer. The relative and absolute stereochemical configuration of **8** was confirmed by X-ray crystallo-

Scheme 1. One-Pot Cyclopentane (a) and Cyclohexane (b) Syntheses



Scheme 2. Discovery of Cyclohexane Formation



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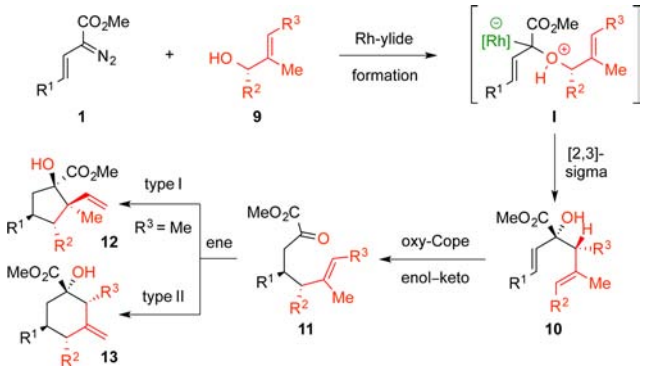
graphic analysis.[10] An intriguing observation was the relative inversion of the hydroxyester stereocenter in **8** compared to **7**.

A reasonable mechanism for the formation of cyclohexane products is the cascade sequence outlined in Scheme 3.[8] Ylide

Scheme 3. Mechanistic Rationale for Cyclohexane (13) Formation

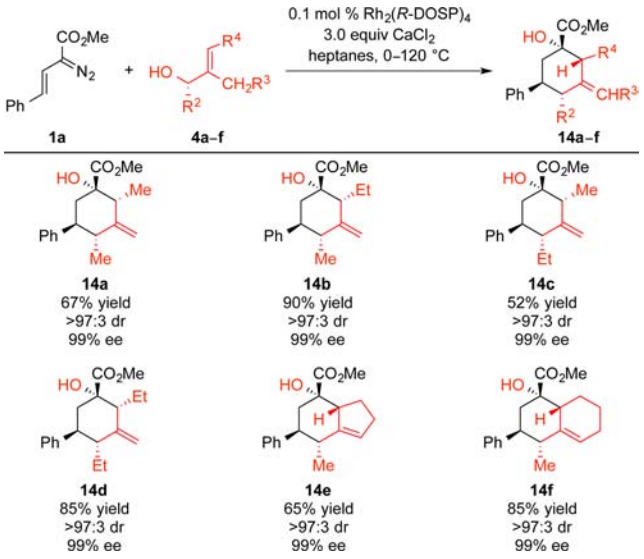


formation (**I**) from diazoacetate **1a** derived rhodium carbene and allyl alcohol **9** with tandem [2,3]-sigmatropic rearrangement is a transformation established in several recent studies by our group.[9,11] The 3-hydroxy-1,5-hexadiene **10** participates in a thermal oxy-Cope rearrangement via a chairlike transition state.[8] Upon enol−keto tautomerization, the α-ketoester **11** is generated. In our previous studies, the R^3 substituent of the allyl alcohol would contain at least one C−H bond available to participate in an intramolecular ene reaction.[8] For example, if the alcohol C(3)-substituent was methyl, a type I hetero-ene cyclization event[12] would forge the cyclopentane **12** bearing a vinyl substituent and vicinal quaternary carbon stereocenters.[8]

Alternatively, the presence of a C(2)-methyl group on the alcohol renders a different "ene" component and an alternative termination pathway. Thus, cyclization via a type II heteroene reaction[12,13] would yield the cyclohexane **13** bearing an exocyclic olefin. We hypothesized that the driving force for the formation of **13** rather than **12** is alleviation of the strain derived from severe eclipsing interactions of vicinal quaternary carbon centers in a cyclopentane ring. Under equilibrating conditions, the cyclopentane formed in Scheme 2 would undergo a retro ene reaction followed by the type II carbonyl-ene reaction to generate the fused cyclohexane product.

We pursued the validity of the mechanism proposed in Scheme 3, by investigating the reactivity of various allyl alcohols bearing C(2) C−H substituents (**4a−f**) combined with the rhodium vinylcarbene derived from Rh_2(*R*-DOSP)$_4$-catalyzed decomposition of **1a**, as shown in Scheme 4. In the presence of calcium chloride, these reactions were efficiently catalyzed with only 0.1 mol % of Rh_2(*R*-DOSP)$_4$. Using the simple pentenol **4a**, which differs from substrates used in our cyclopentane synthesis only in the presence of a methyl group at the internal position of the alkene, gave rise to the cyclohexane **14a** in good yield and excellent stereoselectivity (67% yield, >97:3 dr, 99% ee). Variations in the substitution of the alcohol at either the terminal (**4b**), carbinol (**4c**), or both (**4d**) positions were all well tolerated. The corresponding cyclohexanes (**14b−d**) were forged in high yields (52−90%) and as single stereoisomers. In addition, the internal methyl group of the alcohol could be fused with the terminal position of the alkene in a cyclopentene or cyclohexene ring (**4e** and **f**, respectively). The fused

Scheme 4. Scope of chiral alcohol 4[a−c]

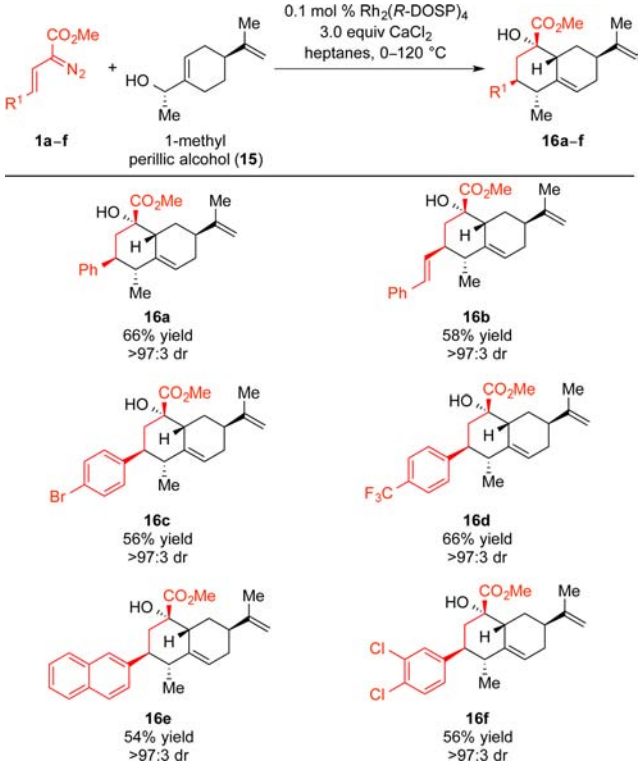


[a]Isolated yields of **14**. [b] Diastereomeric ratios determined by ^{1}H NMR analysis of crude reaction residues. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase.

cyclohexanes, **14e** and **14f**, were formed in good yields (65% and 85%, respectively) and with high levels of stereoselectivity.

Our next series of experiments explored the scope of vinyldiazoacetate **1** when partnered with another monoterpenoid substrate 1-methyl perilic alcohol (**15**) (Scheme 5). In contrast to the endocyclic allyl alcohol *syn*-(−)-pulegol (**6**), **15**

Scheme 5. Scope of Diazoacetate 1[a,b]



[a]Isolated yields of **16**. [b] Diastereometric ratios determined by ^{1}H NMR analysis of crude reaction residues.

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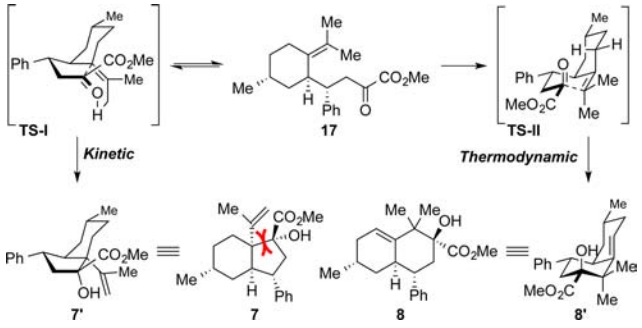
contains an exocyclic allyl alcohol moiety, which was expected to generate a regioisomeric fused cyclohexane product. Reactions of phenyl (**1a**) and styryl (**1b**) substituted vinyldiazoacetate both proceeded in good yield to afford a single stereoisomer of the bicyclic products (**16a** and **b**, respectively) containing five stereocenters. A *para*-substituent on the arene had minimal implications on reaction efficacy, as the 4-Br (**1c**) and 4-CF_3 (**1d**) substituted phenyldiazoacetates afforded comparable yields of annulated cyclohexanes, again as single diastereoisomers. A disubstituted arene was also compatible with the cyclohexane synthesis. The 2-naphthyl (**1e**) and 3,4-Cl_2 (**1f**) donors provided moderate yields (54% and 56%, respectively) and excellent stereoselectivities (>97:3 dr). The relative and absolute stereochemical configurations of the fused cyclohexane **16d** were confirmed by X-ray crystallographic analysis, and this configuration was assigned to the series of products by analogy.[10]

Having established the relative and absolute configuration of several of the cyclohexanes synthesized, we considered a stereochemical rationale for the opposite configuration of the hydroxyester stereocenter in the fused cyclohexanes **8** versus the fused cyclopentanes **7**. The analysis is graphically represented in Scheme 6. An envelope-like transition state

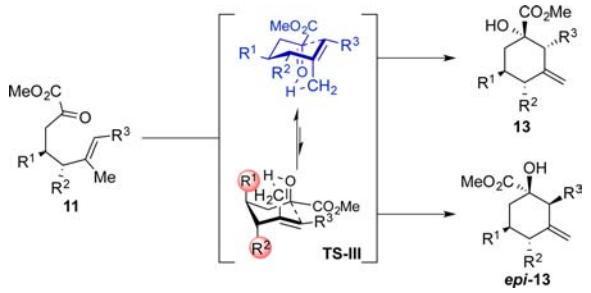
Scheme 6. Stereochemical Rationale for the Ene Cyclizations of *syn*-(−)-Pulegol Derivatives



such as **TS-1**, with the phenyl group occupying a pseudoequatorial position, is consistent with our previous observations for the formation of cyclopentanes. The α-ketone and alkene are oriented *syn* to achieve requisite orbital overlap,[8,12−16] on the convex face of the ensuing transition state to the bicyclic product **7**. Alternatively, a chairlike transition state en route to **8**, such as **TS-II**, could be rendered, where the ring junction as well as phenyl and carbomethoxy substituents are all oriented in equatorial positions. The axial allylic C−H would be in sufficient proximity to participate in the hetero-ene reaction. Thus, the ensuing hydroxyl group would be generated on the opposite face to the phenyl group in the cyclohexane **8** as observed.

The stereochemical rationale of the carbonyl ene reaction for substrates wherein the product cyclohexane contains four stereogenic centers is further analyzed in Scheme 7. The ketoester **11** can be rendered into two possible chairlike transition states (**TS-III**), which can interconvert by a chair flip. In the top transition state, all of the more encumbered substituents (carbomethoxy, R^1, and R^2) occupy equatorial positions of the chair. The ketone and methyl groups occupy pseudoaxial positions allowing for efficient orbital overlap for the sigmatropic rearrangement to occur. In the chair flipped transition state, the bulkier substituents (carbomethoxy, R^1, and

Scheme 7. Stereochemical Rationale for the Ene Cyclization of Ketoester 11



R^2) are all in less favorable axial positions. Again, the ketone and methyl group involved in the ene reaction are in the requisite axial positions for the rearrangement to occur, which would also bear the consequence of 1,3-diaxial interactions with the R^1 group. Thus, the top chairlike transition state is solely operative in the conversion of the generic ketoester **11** to the cyclohexane **13**, which is consistent with the observed stereochemistry for all substrates.

In conclusion, we have developed a novel convergent strategy for the direct synthesis of highly elaborate cyclohexanes by a domino reaction involving vinyldiazoacetates and chiral allyl alcohols. By employing only 0.1 mol % of a chiral rhodium catalyst, cyclohexanes bearing four stereogenic centers are formed with excellent levels of diastereo- and enantioselectivity (>97:3 dr, 99% ee) and in good yields. In addition, the use of cyclic allyl alcohols, including monoterpenoid-derived substrates, enables the synthesis of elaborate fused bicyclic products.

■ 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

*E-mail: hmdavie@emory.edu.

Notes

The authors declare no competing financial interest.

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