ACCOUNTS
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The Combined C−H Functionalization/Cope Rearrangement: Discovery and Applications in Organic Synthesis

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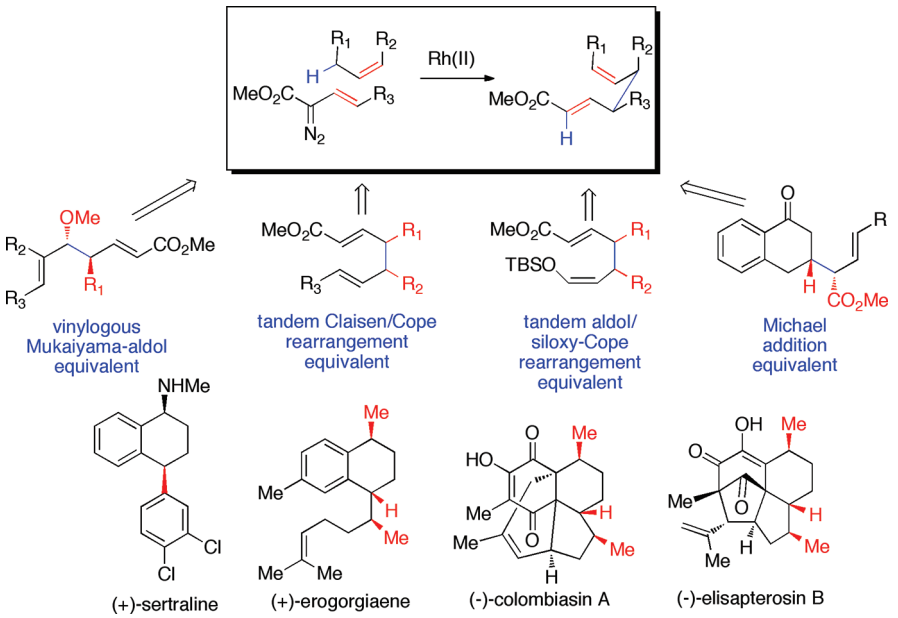
CONSPECTUS



The development of methods for the stereoselective functionalization of sp^3 C−H bonds is a challenging undertaking. This Account describes the scope of the combined C−H functionalization/Cope rearrangement (CHCR), a reaction that occurs between rhodium-stabilized vinylcarbenoids and substrates containing allylic C−H bonds. Computational studies have shown that the CHCR reaction is initiated by a hydride transfer to the carbenoid from an allyl site on the substrate, which is then rapidly followed by C−C bond formation between the developing rhodium-bound allyl anion and the allyl cation. In principle, the reaction can proceed through four distinct orientations of the vinylcarbenoid and the approaching substrate. The early examples of the CHCR reaction were all highly diastereoselective, consistent with a reaction proceeding via a chair transition state with the vinylcarbenoid adopting an *s-cis* conformation. Recent computational studies have revealed that other transition state orientations are energetically accessible, and these results have guided the development of highly stereoselective CHCR reactions that proceed through a boat transition state with the vinylcarbenoid in an *s-cis* configuration.

The CHCR reaction has broad applications in organic synthesis. In some new protocols, the CHCR reaction acts as a surrogate to some of the classic synthetic strategies in organic chemistry. The CHCR reaction has served as a synthetic equivalent of the Michael reaction, the vinylogous Mukaiyama aldol reaction, the tandem Claisen rearrangement/Cope rearrangement, and the tandem aldol reaction/siloxy-Cope rearrangement. In all of these cases, the products are generated with very high diastereocontrol. With a chiral dirhodium tetracarboxylate catalyst such as Rh_2(*S*-DOSP)$_4$ or Rh_2(*S*-PTAD)$_4$, researchers can achieve very high levels of asymmetric induction. Applications of the CHCR reaction include the effective enantiodifferentiation of racemic dihydronaphthalenes and the total synthesis of several natural products: (−)-colombiasin A, (−)-elisapterosin B, and (+)-erogorgiaene. By combining the CHCR reaction into a further cascade sequence, we and other researchers have achieved the asymmetric synthesis of 4-substituted indoles, a new class of monoamine reuptake inhibitors.

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I. Introduction

New methods for C–H functionalization offer new strategies for synthesis, either by means of late stage functionalization or by enabling new disconnection strategies to complex targets.[1,2] The majority of transition-metal-catalyzed C–H functionalization methods rely on an "activation" step, in which the metal inserts into a C–H bond. An alternative strategy for C–H functionalization is the insertion of a metal carbenoid into a C–H bond. This Account describes our development of the combined C–H functionalization/Cope rearrangement (CHCR), a reaction occurring between vinylcarbenoids and substrates containing allylic C–H bonds (eq 1). The reaction represents one of the most stereoselective methods developed to date for intermolecular C–H functionalization. The first section of this Account describes the key stages in the journey that led to the discovery of the CHCR reaction. This is followed by a description of the synthetic potential, and the current mechanistic understanding of the CHCR reaction will then be given.

II. Background on Donor/Acceptor Carbenoids

We have had a long-standing interest in the chemistry of rhodium-stabilized vinylcarbenoids.[2k,3] During our group's early studies on the tandem cyclopropanation/Cope rearrangement between vinylcarbenoids and dienes, we recognized that carbenoids flanked with both an acceptor group (such as an ester) and a donor group (such as a vinyl or aryl) were much more selective than the classic carbenoids, which contained only acceptor groups (such as the carbenoid derived from ethyl diazoacetate) (Scheme 1).[4] We also developed a series of chiral dirhodium tetracarboxylate catalysts, most notably Rh_2(*S*-DOSP)$_4$[5] and Rh_2(*S*-PTAD)$_4$[6] (Scheme 2), which give high asymmetric induction in a variety of reactions of donor/acceptor carbenoids.[7]

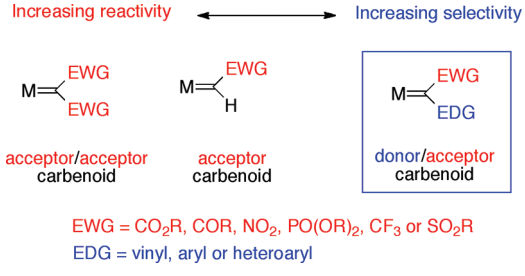
The attenuated reactivity of donor/acceptor carbenoids makes them capable of undergoing a range of stereoselective intermolecular transformations.[2k] For example, intermolecular cyclopropanations with donor/acceptor carbenoids are generally highly diastereoselective whereas cyclopropanation with ethyl diazoacetate is only highly diastereoselective with specialized catalysts.[1m,8] The high synthetic impact of donor/acceptor carbenoids was underscored by our discovery in 1997 that highly enantioselective intermolecular C–H functionalization reactions can be achieved with aryldiazoacetates and vinyldiazoacetates, precursors to donor/acceptor carbenoids.[9] Prior to this discovery, intermolecular C–H insertions were not considered to be synthetically useful.[10] This reaction has been developed into a general C–H functionalization process and many examples are known, displaying high levels of site selectivity, diastereoselectivity, and enantioselectivity.[1b,11] In recent years, many new synthetic methods using donor/acceptor carbenoids have been reported.[2b,12]

III. Discovery of the CHCR Reaction

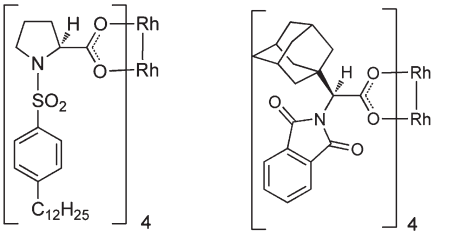
By the late 1990s, our major research focus was on the C–H functionalization chemistry of aryldiazoacetates.[11c,13] We discovered the CHCR reaction during this period, but the breakthrough was made while studying a totally different project.[14] We had published many papers on the racemic synthesis of seven-membered carbocycles by the tandem cyclopropanation/Cope rearrangement and had, by then, developed Rh_2(*S*-DOSP)$_4$ as an effective chiral catalyst. Therefore, three students were asked to run a quick study on the Rh_2(*S*-DOSP)$_4$-catalyzed reactions between vinyldiazoacetates and some standard dienes, with the optimistic goal of completing the project within a few weeks (Scheme 3).[14] This was expected to be a straightforward project and, indeed, the study was completed in a short period. However, one diene gave an unexpected result.

Although 1,3-cyclohexadiene (**1**) is a good diene for cycloaddition chemistry, its reaction with the styryldiazoacetate **2** did not proceed as planned (Scheme 4).[13a] The major

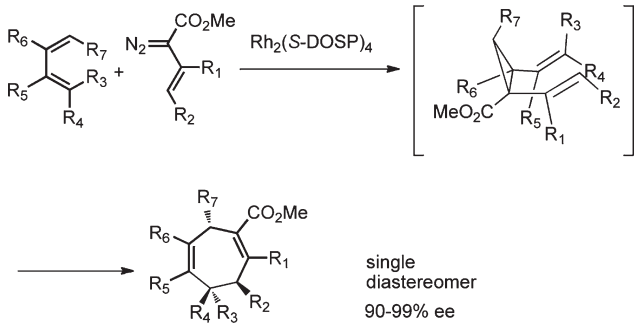
SCHEME 1. Classification of Metal Carbenoids



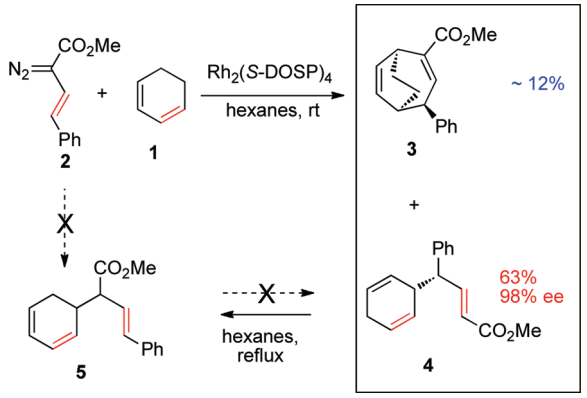
SCHEME 2. Chiral Dirhodium Catalysts for Donor/Acceptor Carbenoids



SCHEME 3. Enantioselective Tandem Cyclopropanation/Cope Rearrangement



SCHEME 4. Discovery of the CHCR Reaction

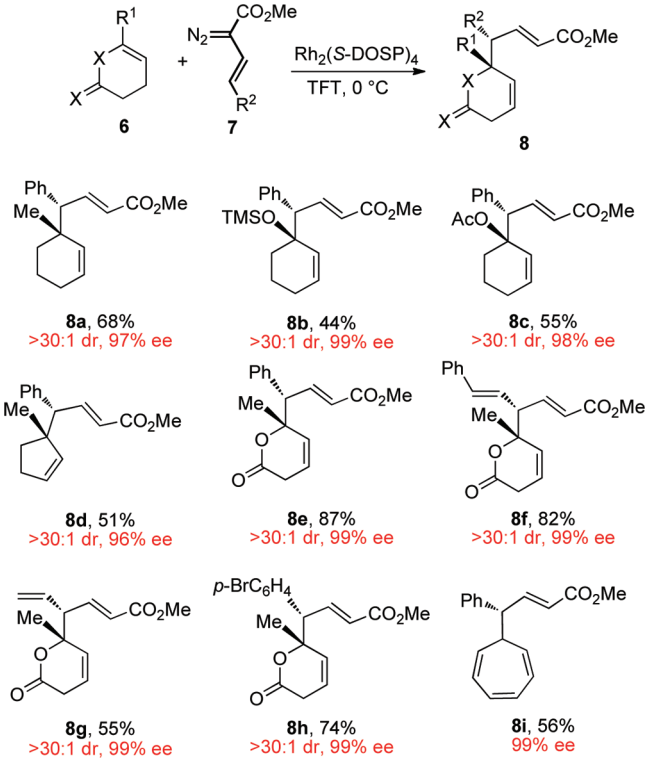


product was the C–H functionalization product **4**, instead of the expected [4 + 3] cycloadduct **3**. Remarkably, **4** was formed with very high asymmetric induction (98% ee). Unlike the product of a normal C–H insertion (**5**), the double bonds of the cyclohexadiene in **4** were no longer in conjugation and the new C–C bond had been formed at the vinylogous position to the carbenoid site. Initially, we considered that the reaction was a C–H insertion to form **5** followed by a Cope rearrangement to form **4**, but control experiments revealed this could not be the case because **5** was more stable than **4**. Indeed on heating in hexanes under reflux, the isolated product **4** rearranged cleanly to **5**. Therefore, we coined the term "combined C–H functionalization/Cope rearrangement" (CHCR) because the reaction appeared to be initiated by some form of C–H functionalization which was interrupted by the Cope rearrangement. The remainder of this Account highlights the scope and our current mechanistic understanding of this unusual transformation.

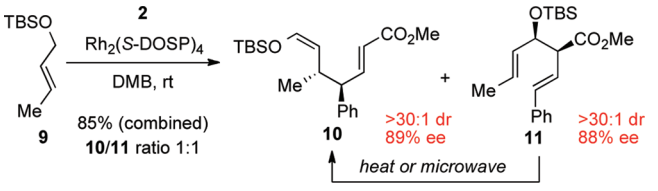
IV. Substrate Scope of the CHCR Reaction

Cyclic Olefins. After the discovery of the CHCR reaction with 1,3-cyclohexadiene, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction

CHART 1. CHCR with Cyclic Alkenes



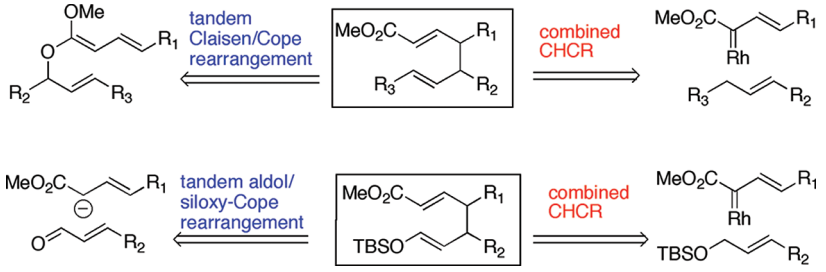
SCHEME 5. Reactions of Allyl Silyl Ethers



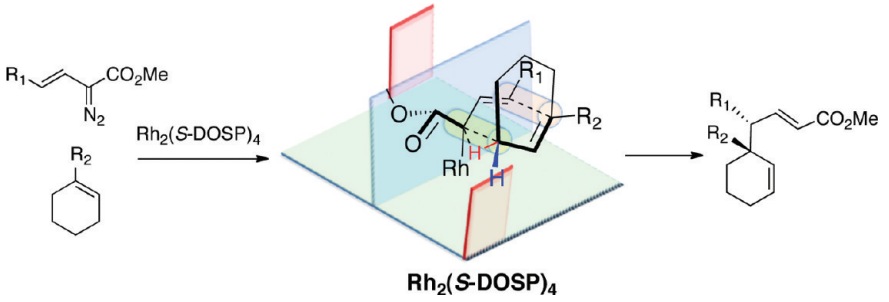
was applied to some representative cyclic olefins **6** and vinyldiazoacetates **7** (Chart 1).[15] In the cases where two new stereogenic centers were generated, the products **8a**–**h** were formed with very high levels of diastereoselectivity (>30: 1 dr) and enantioselectivity (≥96% ee). The isolated yields of the CHCR products **8** in some instances were moderate, because direct C–H insertion was a competing process. Cycloheptatriene was found to be an effective substrate and the resulting CHCR product **8i** was formed in 56% yield and 99% ee.

Acyclic Olefins. Achieving a selective CHCR reaction over the direct C–H insertion reaction is a challenge for the CHCR methodology, especially as the direct C–H insertion product is generally the thermodynamic product.[15] In order to circumvent this problem, acyclic systems were examined in which the direct C–H insertion product would no longer be the thermodynamic product. This was accomplished by

SCHEME 6. Retrosynthesis Using C–H Functionalization



SCHEME 7. Initial Stereochemical Model for the CHCR Reaction



using allyl silyl ethers as substrates, because the direct C–H insertion product would be susceptible to a favorable siloxy-Cope rearrangement (Scheme 5).[16] The reaction of styryldiazoacetate **2** with the allyl silyl ether **9** afforded a 1:1 mixture of the CHCR product **10** and direct C–H insertion product **11**. Both products were generated with high diastereoselectivity (>30:1 dr) and similar enantioselectivity (88–89% ee). In this case, the CHCR product **10** was more stable than the direct C–H insertion product **11**, and on heating **11** underwent a siloxy-Cope rearrangement to **10**.

C–H Functionalization methodologies offer a new way to look at some of the classic retrosynthetic disconnections used in organic synthesis. For example, the CHCR reaction of vinylcarbenoids with allylic C–H bonds could be considered as strategically equivalent to the tandem Claisen rearrangement/Cope rearrangement (Scheme 6). Alternatively, the products derived from the combined C–H functionalization/siloxy Cope rearrangement could be classically generated from a tandem aldol reaction/siloxy Cope rearrangement.[17]

V. Initial Stereochemical Model for the CHCR Reaction

The early examples of the Rh_2(*S*-DOSP)$_4$-catalyzed CHCR reactions were found to be highly diastereoselective (>30:1 dr) and enantioselective (89–99% ee). The relative configurations of the products are consistent with a mechanism starting with a C–H functionalization event, which is interrupted by a Cope rearrangement, proceeding though a chairlike transition state (Scheme 7).[19] Rh_2(*S*-DOSP)$_4$ is considered to adopt a D_2-symmetric arrangement and can be simply viewed as containing a blocking group in front of the ester group and a second blocking group at the back of the vinyl moiety.[7,18] Due to the symmetry, the same effect would occur if the carbenoid bound to the other face of the dirhodium complex. The chair transition state organizes the substrate and the carbenoid in a defined orientation, which is likely to contribute to the profound chiral influence of the catalyst.

VI. CHCR Reaction Followed by a Reverse Cope Rearrangement

One of the major challenges we faced in the development of the CHCR reaction was expanding the substrate scope. In the early studies, we found that planar substrates, such as 1,3-cyclohexadiene and cycloheptatriene, cleanly underwent the CHCR reaction with minimal competing direct C–H insertion.[15] On the basis of these observations, the Rh_2(*S*-DOSP)$_4$-catalyzed reactions of styryldiazoacetates **2** with dihydronaphthalenes and related systems (**12**) were examined (Chart 2).[19] Surprisingly, these reactions gave the products of an apparent direct C–H insertion (**13**) as single diastereomers (>30:1 dr) with exceptionally high enantioselectivities (95–99% ee).

The highly diastereoselective nature of these products is not consistent with a direct C–H insertion because related direct C–H insertion reactions between aryldiazoacetates and various cycloalkenes displayed only moderate levels of diastereoselectivity.[9] Instead, we considered that the reaction involves the CHCR pathway to form **14** followed by an extremely favorable reverse Cope rearrangement to form **15**, proceeding through a chair transition state (Scheme 8).[20] The driving force for the Cope rearrangement is believed to be the highly sterically crowded nature of **14** having adjacent quaternary and tertiary stereocenters. Indeed, in systems that were less crowded, the CHCR products could be isolated and then rearranged to the formal direct C–H insertion product upon heating.[19]

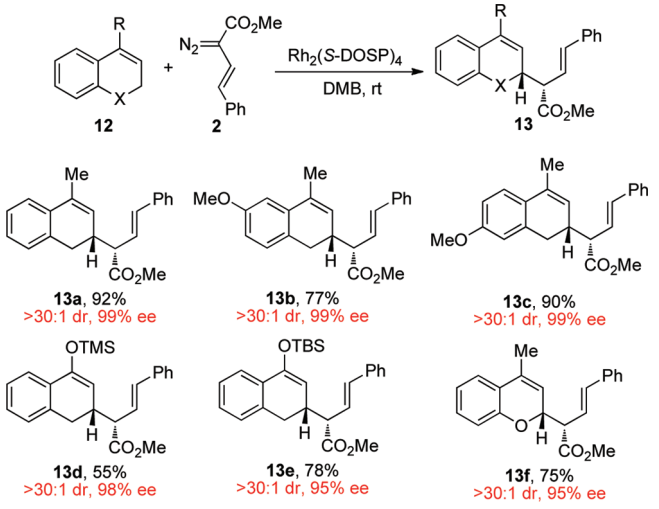
C–H Functionalization has the potential to access compounds that would be difficult to make using conventional synthetic methodology. The CHCR reaction of siloxy dihydronaphthalenes illustrated this point because treating the product **13e** with HF yielded ketone **16** in 84% yield (Scheme 9).[19] A classic approach for the synthesis of **16**, containing a 1,5-dicarbonyl relationship, would be by means of a Michael addition, except in this case it would be impossible because the requisite enone **17** would be the keto tautomer of 1-naphthol.

In certain systems, it is possible to functionalize two adjacent C–H bonds in a highly diastereoselective and enantioselective fashion. During the process of optimizing the CHCR reaction of dihydronaphthalenes **18**, we discovered that the double C–H insertion products **20** were formed when an excess of the styryldiazoacetates **19** were used.[21] Products with four new stereogenic centers were generated in >30:1 dr and 99% ee (Chart 3). Higher yields of products were obtained (86–92%) when a methoxy group was introduced at the 6-position of the dihydronaphthalene, which facilitated the benzylic C–H insertion.

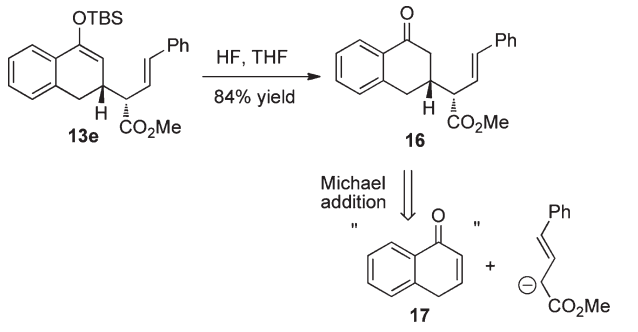
VII. CHCR Reactions Followed by Aromatization

The rhodium carbenoid intermediates in these reactions are reactive enough to initiate elaborate cascade sequences.[22] We envisioned that the inclusion of an appropriately positioned leaving group could cause the CHCR reaction to

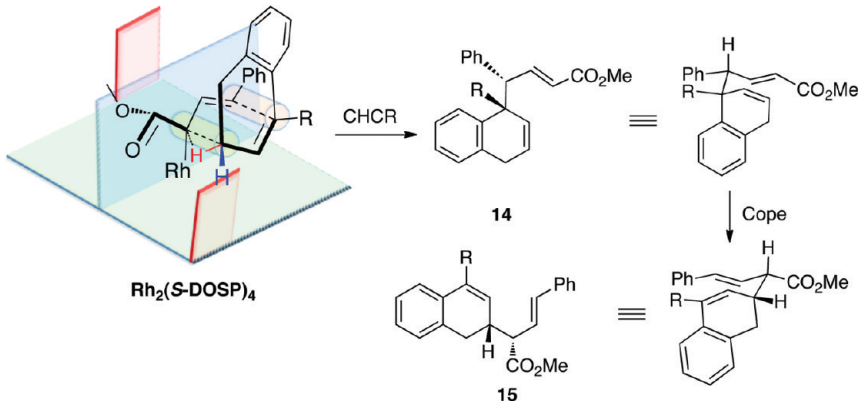
CHART 2. Formal Direct C–H Insertion of Dihydronaphthalenes and Related Systems



SCHEME 9. C–H Functionalization as a Michael Addition Surrogate



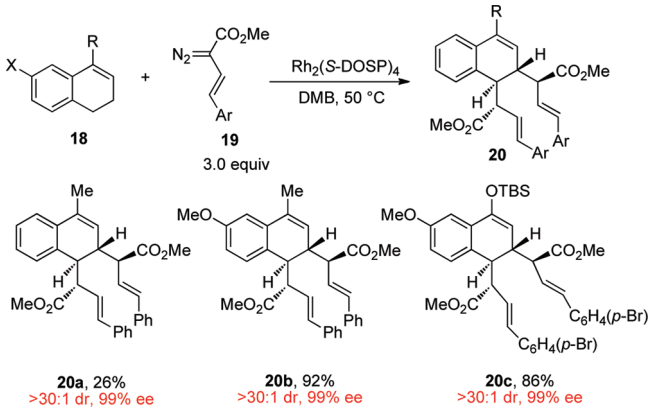
SCHEME 8. Reaction Mechanism for the Formal Direct C–H Insertion



be followed by elimination to generate a new aromatic ring. The reactions of 4-acetoxy-1,2-dihydronaphthalene **21** with a variety of vinyldiazoacetates **22** illustrates this general concept (Chart 4).[23] A series of 2-(1-naphthyl)-2-arylbutenoates **23** were readily formed with high enantioselectivity by a CHCR reaction followed by elimination of acetic acid.

A more elaborate application of this strategy has been demonstrated in the enantioselective synthesis of 4-substituted indoles from 4-acetoxy-6,7-dihydroindole precursor **24** (Chart 5).[24] These examples are particularly interesting since the 4-position of indoles is difficult to functionalize selectively by traditional processes.[25] The reaction was found to be amenable to a range of aryl, heteroaryl, or alkyl-substituted (*E*)-vinyldiazoacetates. An excellent illustration of the method is the formation of trisindole derivative **26i** in 82% yield and 97% ee. These indole derivatives were further converted into 4-indoyl arylalkylamines, which showed selective monoamine reuptake inhibitory activity.[26]

CHART 3. Double C–H Functionalization of Dihydronaphthalenes



VIII. Enantiodifferentiation and Application to the Syntheses of Complex Targets

The CHCR reaction has been demonstrated to be a powerful protocol for the synthesis of complex natural products and pharmaceutical targets. The first illustrated use of the CHCR reaction was the formal synthesis of antidepressant (+)-sertraline (Scheme 10).[13a] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of vinyldiazoacetate **27** with 1,3-cyclohexadiene **(1)** generated 1,4-cyclohexadiene **28** in 59% yield with 99% ee. Compound **28** was subsequently converted to the 4-aryltetralone **29** in a four-step sequence, providing a formal synthesis of (+)-sertraline (**30**).

Dihydronaphthalene derivatives are excellent substrates for the CHCR reaction.[19] When the reaction was conducted on racemic dihydronaphthalene **31** with styryldiazoacetate **2** in the presence of Rh_2(*S*-DOSP)$_4$, a very efficient enantiodifferentiation was observed. While the (*R*)-enantiomer of the substrate selectively underwent a matched CHCR reaction, the (*S*)-enantiomer underwent a matched cyclopropanation (Scheme 11).[27] The CHCR product **32**, containing three stereogenic centers was generated with excellent stereocontrol at all three stereogenic centers. A similar

CHART 4. Synthesis of 2-(1-Naphthyl)-2-arylbutenoates

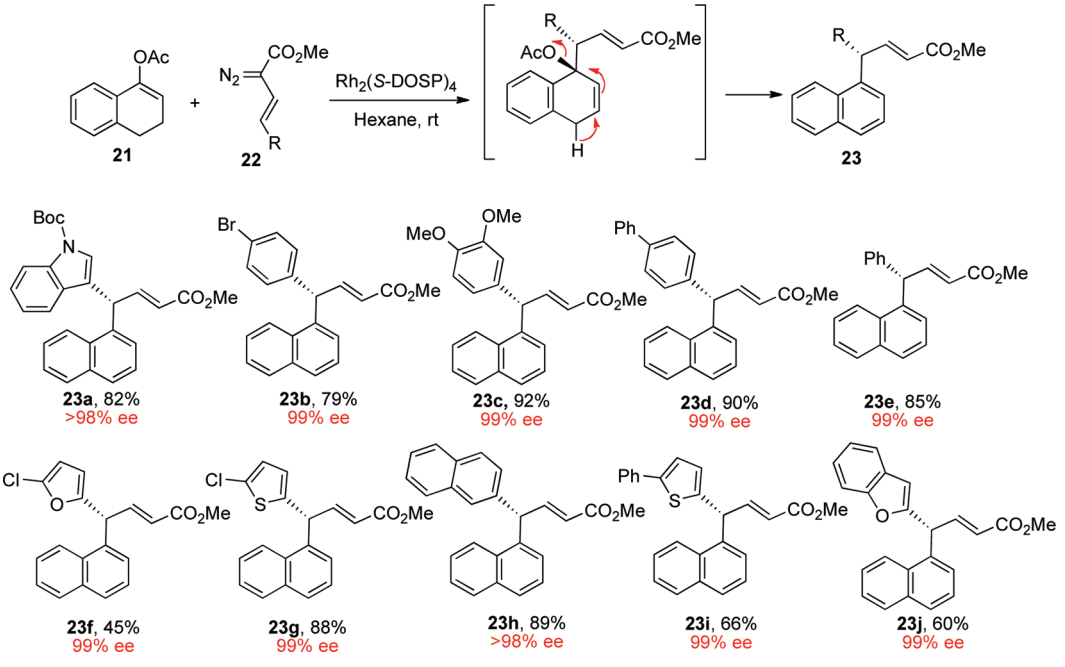
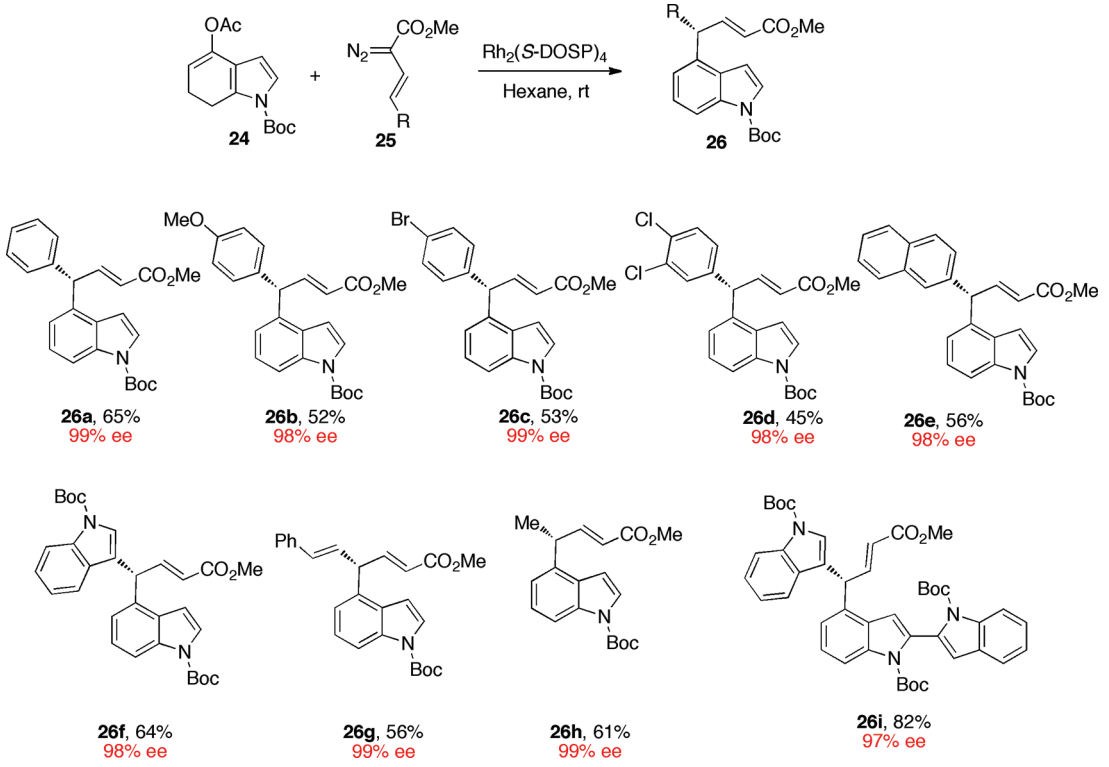
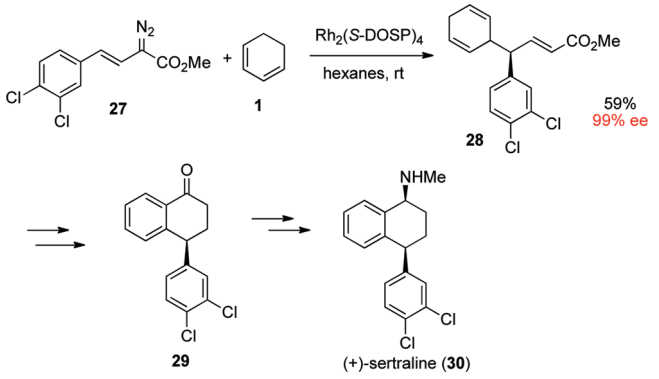


CHART 5. Synthesis of 4-Substituted Indoles



SCHEME 10. Formal Synthesis of (+)-Sertraline

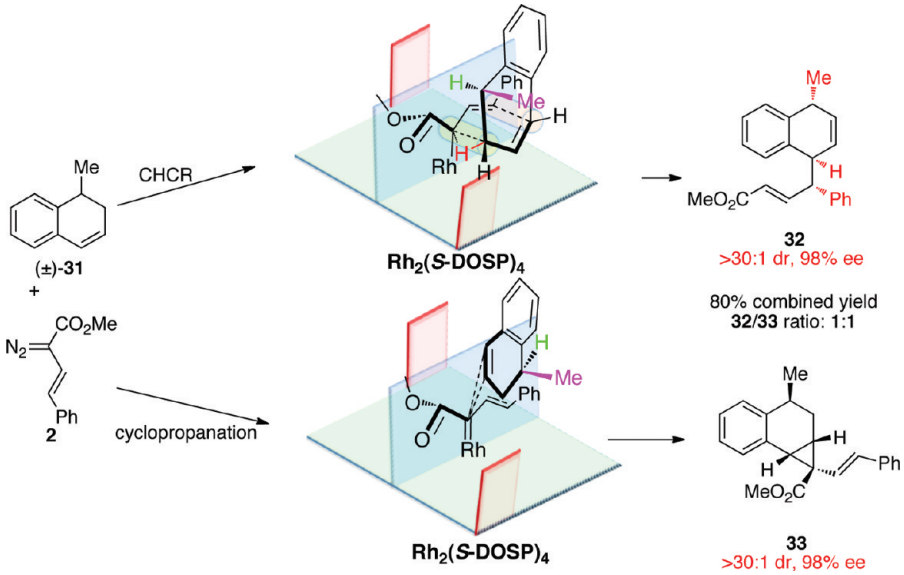


amount of the cyclopropane **33** was also isolated with excellent enantioselectivity. The stereochemical result is consistent with the transition state models that had been previously proposed for the CHCR and cyclopropenation reactions.[19,28]

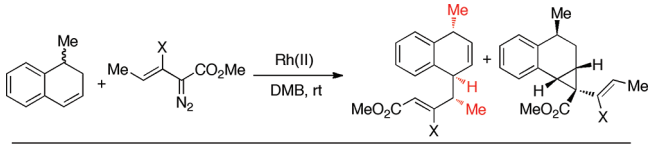
Further studies demonstrated that the effectiveness of the enantiodifferentiating step depended on the combination of catalyst and substrate.[29] A favorable enantiodifferentiation required the rates of the cyclopropanation and C–H functionalization pathways to be approximately equal, such that a stereogenic center in the substrate could determine which reaction would occur. The selectivity between the two processes varied depending on the catalyst and diazo compound, as illustrated in Scheme 12. 2-Diazo-3-pentenoate **34** favored cyclopropanation over C–H functionalization compared to the siloxyvinyldiazoacetate **35**, whereas Rh_2(*S*-DOSP)$_4$ favored C–H functionalization over cyclopropanation compared to Rh_2(*S*-PTAD)$_4$. Thus, 2-diazo-3-pentenoate **34**/Rh_2(*S*-DOSP)$_4$ and siloxyvinyldiazoacetate **35**/Rh_2(*S*-PTAD)$_4$ were the best combinations for effective enantiodifferentiation reactions.

The enantiodifferentiation of dihydronaphthalenes has been applied to the total synthesis of several natural products belonging to a family of marine diterpenes isolated from *Pseudopterogorgia elisabetha*.[30] Members of this class of natural products have three characteristic stereogenic centers, which have proven to be challenging to introduce in a stereoselective manner.[31] The CHCR reaction solved this stereochemical problem in one step, as illustrated in the concise synthesis of (+)-erogorgiaene (**38**) (Scheme 13).[27] The Rh_2(*R*-DOSP)$_4$-catalyzed reaction of vinyldiazoacetate **34** with racemic dihydronaphthalene **36** generated a 1:1 inseparable mixture of the desired CHCR product (single diastereomer in 90% ee) and the corresponding cyclopropane. When the mixture was subjected to hydrogenation and reduction, the alcohol **37** was formed in 31% overall yield (62% from *S*-**36**). The completion of the total synthesis

SCHEME 11. Enantiodifferentiation of Racemic Dihydronaphthalene

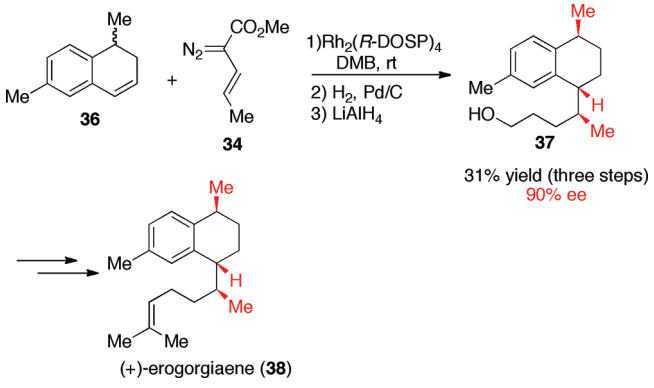


SCHEME 12. Controlling Factors for Enantiodifferentiation



entry	X	Rh(II)	ratio	ee(%)		combined yield (%)
1	H, **34**	Rh_2(*S*-DOSP)$_4$	1:1	91	74	72
2	H, **34**	Rh_2(*S*-PTAD)$_4$	1:7	-40	-34	42
3	OTBS, **35**	Rh_2(*S*-DOSP)$_4$	3:1	86	53	58
4	OTBS, **35**	Rh_2(*S*-PTAD)$_4$	1:1	88	96	90

SCHEME 13. Total Synthesis of (+)-Erogorgiaene



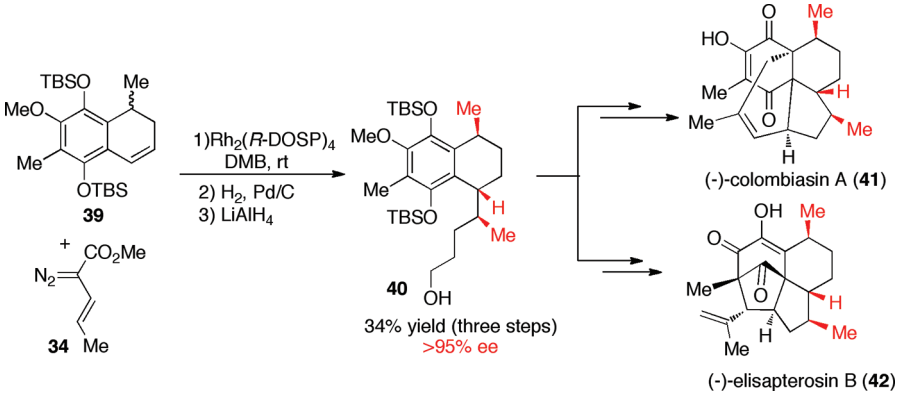
was readily achieved by oxidation of the alcohol, followed by a Wittig reaction. Although not discussed in the original publication, we measured the success of our methodology in terms of a "time economical" synthesis. The total synthesis of **38**, which included the five-step synthesis of the starting dihydronaphthalene **36**, the key CHCR reaction, and the final steps to complete the synthesis of **38**, was accomplished over a period of just 10 days!

This enantiodifferentiation reaction has also been applied to more complex systems[32] as illustrated in the total syntheses of (–)-colombiasin A (**41**) and (–)-elisapterosin B (**42**) (Scheme 14). The key step was the CHCR reaction of the dihydronaphthalene **39**. Subsequent reductions generated intermediate **40**, which was ideally suited for the completion of the synthesis of **41** and **42**.

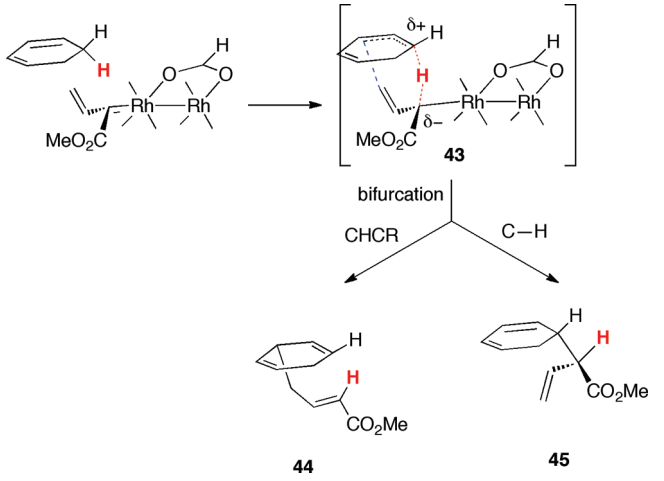
IX. Further Refinement of the Mechanistic Model for the CHCR Reactions

In the early development of the CHCR reaction, we proposed the reaction was a concerted asynchronous process. We speculated that it was initiated by a C–H insertion event at an allylic position, but before the C–H insertion was completed, a Cope rearrangement occurred to form the observed product.[19] The stereochemistry of the transformation suggested the Cope rearrangement occurred through a chairlike transition state. A detailed computational analysis was recently conducted to interrogate this initial mechanistic hypothesis.[33] This study revealed that the initiation of the C–H functionalization appeared to be a hydride transfer event, leading to a charged transition state **43**, which could then bifurcate to the CHCR product **44** or the direct C–H insertion product **45** (Scheme 15). This would explain why, with several substrates, both types of products could be formed and the enantioselectivity for the formation of the two products was often very similar, if not identical.[16,33]

SCHEME 14. Total Synthesis of (-)-Colombiasin A (41) and (−)-Elisapterosin B (42)

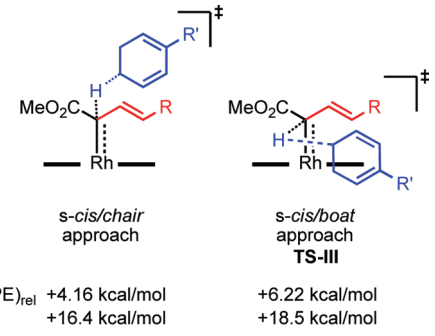


SCHEME 15. Refined Mechanistic Model for the CHCR Reaction



One of the most revealing aspects of the computational study was the demonstration that a chairlike transition state was not as energetically favorable as anticipated, suggesting that it could be feasible to access other transition states.[33] In principle, four possible transition states are available for the CHCR reaction. The rhodium-bound vinylcarbenoid could react in an *s-cis* or *s-trans* orientation, and the CHCR reaction could proceed through a chairlike or boatlike transition state. The calculations for a simple model system revealed that all four are energetically accessible. For the sake of the discussion herein, we will focus on the two possible orientations for the vinylcarbenoids in the *s-cis* configuration (Scheme 16). Even though all the earlier experimental results generated products derived from a chairlike transition state, the calculation on a model system of the CHCR reaction with cyclohexadiene revealed that the boat transition state was only 2 kcal/mol less stable than the chair transition state.

SCHEME 16. Comparison of the *s-cis*/Chair and *s-cis*/Boat Transition States



$\Delta(E+ZPE)_{rel}$	+4.16 kcal/mol	+6.22 kcal/mol
ΔG_{rel}	+16.4 kcal/mol	+18.5 kcal/mol

X. Computationally Guided Stereocontrol of the CHCR Reaction

Ideally, molecular calculations help rationalize a particular transformation and lead to insights on how to further enhance it. In this case, the calculations suggested that it should be possible to change the stereochemical outcome by favoring the *s-cis*/boat transition state over the *s-cis*/chair transition state by using appropriate substrates (Figure 1). Attack at an allylic C–H bond with a cis substituent (R_4), such as cyclic substrates, would be expected to be unfavorable in the *s-cis*/boat orientation. Conversely, internal substituents (R_2) would be expected to disfavor the *s-cis*/chair orientation.

Substrate control of the diastereoselectivity of the CHCR reaction was demonstrated in the reactions of cyclic vinyl ethers.[34] To minimize the number of potential transition states available in these reactions, the siloxyvinyldiazoacetate **46** was chosen as the carbenoid source because the presence of an internal substituent in the vinylcarbenoid would favor the *s-cis* configuration.[33] The Rh_2(*S*-PTAD)$_4$-catalyzed reaction of siloxyvinyldiazoacetate **46** with cyclohexene **47**, followed by hydrolysis and a diazo transfer reaction afforded the diazo compound **48** as a single

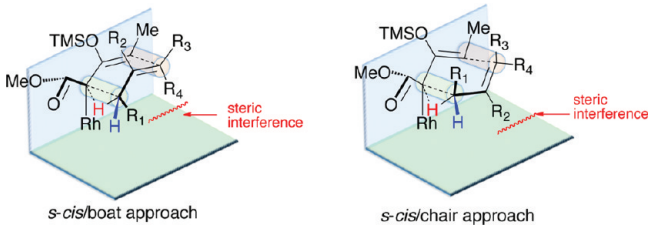
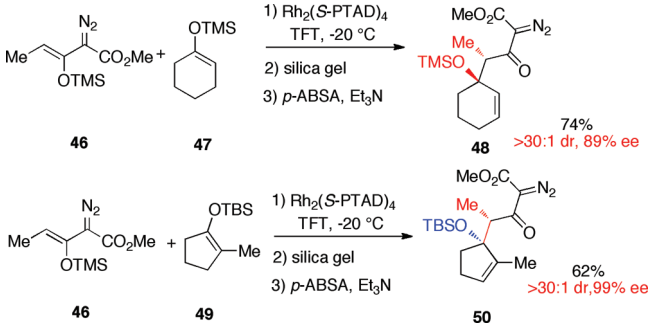


FIGURE 1. Steric effects in the *s-cis*/boat and *s-cis*/chair transition states.

SCHEME 17. Substrate Effect on Diastereocontrol



diastereomer (Scheme 17). A similar reaction of **46** with the cyclopentene **49** generated the CHCR product **50** as a single diastereomer, but in this case it was in the opposite diastereomeric series.

The change in the configuration of **48** and **50** is consistent with **48** forming via a chairlike transition state and **50** forming via a boatlike transition state (Figure 2).[34] In the *s-cis*/boat approach with cyclohexene **47**, the remainder of the cyclohexyl ring would be pointing toward the "wall" of the catalyst, and this approach would be expected to be unfavorable. We proposed that in the cyclopentene **49** the five-membered ring could be accommodated in the *s-cis*/boat approach, but the R group would point toward the catalyst in the *s-cis*/chair transition state. When R = methyl, this would sterically interfere with the *s-cis*/chair transition state. Evidence to support this hypothesis was obtained in the reaction of the cyclopentene derivative with R = H, which resulted in the formation of a mixture of diastereomers.[34]

The CHCR reaction was found to be effective with a series of 2-substituted-1-siloxycyclopentenes **51** (Chart 6).[34] In each case, a single diastereomer of CHCR product **52** with very high enantioselectivity was generated. The stereochemical outcome was consistent with reactions proceeding through s-*cis*/boat transition states.

The reaction was extended to the more elaborate substrate **53**, which showed that desymmetrization was

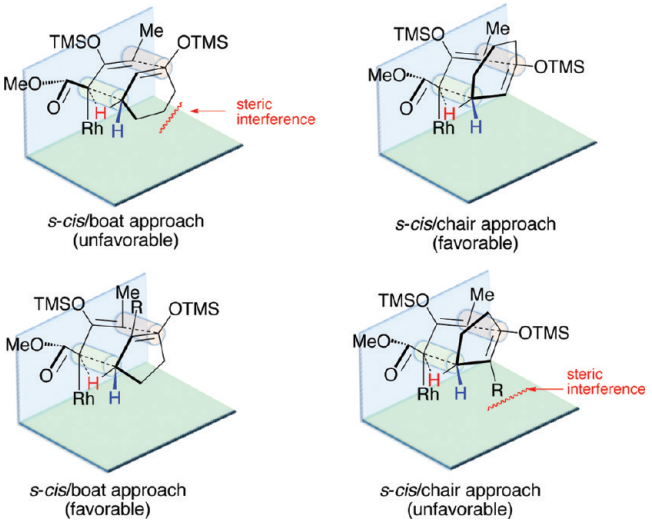
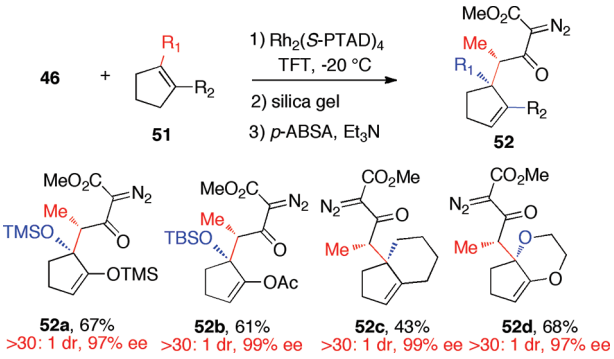
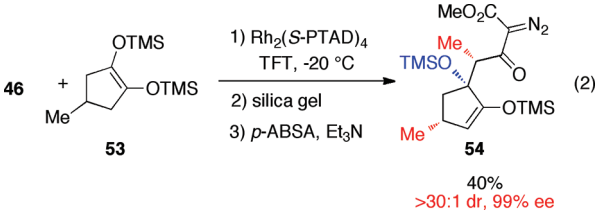


FIGURE 2. Transition state analysis of the CHCR reactions of **48** and **50**.

CHART 6. CHCR Reactions of Cyclopentene Derivatives

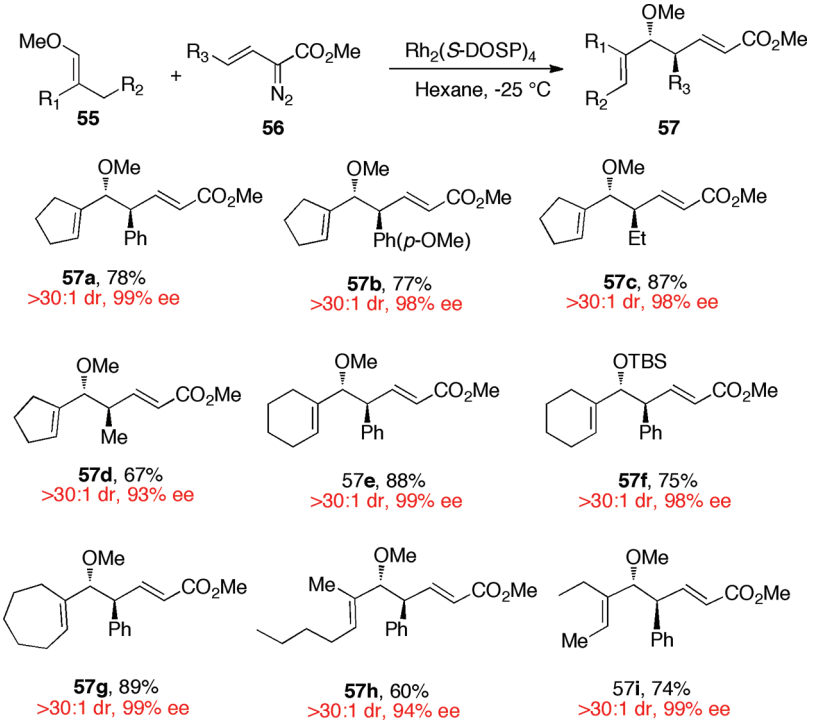


possible in the CHCR reaction.[34] The reaction of **46** with cyclopentene **53** successfully generated **54** as a single diastereomer with high asymmetric induction (eq 2).

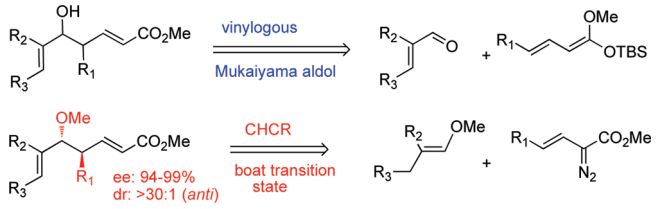


Acyclic trisubstituted vinyl ethers **55** were found to be excellent substrates for CHCR reactions proceeding *via* a boat transition state (Chart 7).[35] In this case, the reactions could be applied to a series of vinyldiazoacetates **56**. Single diastereomers of the CHCR products **57** were produced in good yields and with excellent enantioselectivity, in the majority of cases >98% ee.

CHART 7. CHCR Reactions of Acyclic Vinyl Ethers



SCHEME 18. C–H Functionalization as a Surrogate to the Vinylogous Mukaiyama Aldol Reaction



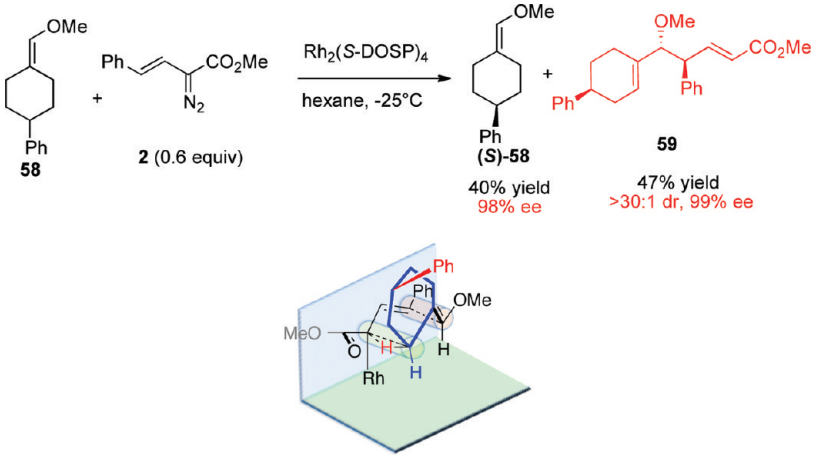
The CHCR reactions between vinyl ethers and vinylcarbenoids can be considered as a surrogate of the traditional vinylogous Mukaiyama aldol condensation (Scheme 18).[36] The CHCR reactions generated the typical *anti*-products of the vinylogous Mukaiyama aldol in a highly stereoselective fashion.

Donor/acceptor carbenoids have been shown to be capable of kinetic resolution, desymmetrization, and enantiodifferentiation.[12,27,34,37] When the CHCR reaction was extended to racemic vinyl ether **58**, an efficient kinetic resolution was achieved (Scheme 19).[35] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **58** with **2** generated the CHCR product **59** as a single diastereomer in good isolated yield with 99% ee (94% yield based on one enantiomer of ether **58**). The unreacted vinyl ether **58** was recovered in 40% isolated yield with 98% ee. This kinetic resolution approach provided a convenient way of making cyclic vinyl ethers with axial chirality, which would be challenging to make by conventional methods.[38] This result is in agreement with the CHCR reaction proceeding through a boat transition state, in which the phenyl group is pointing away from the carbenoid.

XI. Summary and Outlook

The combined CHCR reaction has been demonstrated to be an effective synthetic method. Two new stereogenic centers are generated with excellent diastereo- and enantiocontrol. More complex cascade reactions can be initiated by the CHCR reaction, adding further versatility to the methodology. The earlier examples were consistent with the CHCR reaction proceeding through an *s-cis*/chair transition state, but an enhanced mechanistic understanding of the methodology revealed what would be required to change the diasteroselectivity by forcing the reaction to proceed through a *s-cis*/boat transition state. This convergent C–C bond forming process can be considered as a surrogate to some of the classic strategies of organic synthesis. The synthetic potential of this methodology has been demonstrated by application of the CHCR reaction in the streamlined total synthesis of natural products and pharmaceutical targets. The future directions for this work are to

SCHEME 19. Kinetic Resolution of 58



broaden the potential coupling partners and to demonstrate a wider range of applications to the synthesis of complex targets.

We wish to thank the current and past members of the Davies group who have contributed to our studies of donor/acceptor carbenoids, especially those who contributed to developing the CHCR reaction. Financial support for much of the research described in this Account was obtained from the National Science Foundation and the National Institutes of Health (GM080337), and more recently from the National Science Foundation under the Center of Chemical Innovation in Stereoselective C–H Functionalization (CHE-0943980).

BIOGRAPHICAL INFORMATION

Huw M. L. Davies was born in Aberystwyth, Wales, U.K. He began his independent academic career at Wake Forest University. In 1995 he moved to the University at Buffalo, SUNY, where he held the positions of UB Distinguished Professor and Larkin Professor of Organic Chemistry. In 2008, he joined the faculty at Emory University as the Asa Griggs Candler Professor of Chemistry. A major current research theme in his group is catalytic asymmetric C–H functionalization.

Yajing Lian was born in Xiamen, Fujian, P. R. China. He received his B.S. in chemistry from Xiamen University. After obtaining his M.S. from the College of William and Mary under the direction of Dr. Robert Hinkle, he joined Huw Davies' group at the University at Buffalo, SUNY in 2006 and obtained his Ph.D. from Emory University in 2011. He is currently working as a postdoctoral associate with Dr. Jonathan Ellman at Yale University.

FOOTNOTES

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The authors declare no competing financial interest.

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