C–H Functionalization

DOI: 10.1002/anie.201103568

Computationally Guided Stereocontrol of the Combined C–H Functionalization/Cope Rearrangement**

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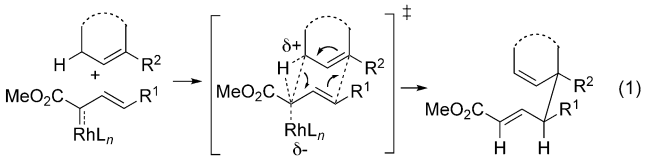
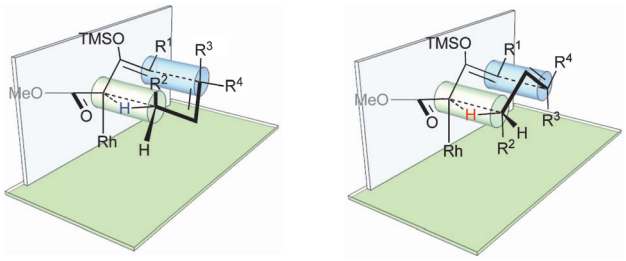
Developing practical methods for C–H functionalization has attracted considerable attention from the synthetic community.[1] One of the major challenges in this field is to achieve transformations that are not only site selective, but also stereoselective.[2] One highly stereoselective intermolecular C–H functionalization method is the combined C–H functionalization/Cope rearrangement (CHCR) between allylic C–H bonds and vinylcarbenoid compounds.[3] This transformation can generate two new stereocenters. When chiral dirhodium catalysts such as $[Rh_2\{(S)\text{-dosp}\}_4]$[4] (see Scheme 2) are used, the products are formed essentially as single diastereomers and in the majority of cases with >97% *ee*. This method has been developed into a powerful protocol for the synthesis of natural products and pharmaceutical targets.[3] In all of the studies reported to date, the stereochemistry is consistent with a reaction occurring on the *s-cis* conformation of the vinylcarbenoid and proceeding through a chair transition state, as illustrated in [Eq. (1)].



(1)

Recently, we completed a detailed computational study of the CHCR reaction.[5] The reaction was shown to be an asynchronous process, involving an initial hydride transfer event followed by carbon–carbon bond formation. Even though all the previously reported examples of CHCR reactions are highly diastereoselective, the calculations showed that different product outcomes are possible, depending on whether the *s-cis* or *s-trans* configurations of the vinylcarbenoid species[6] are involved and whether the reaction proceeds through a chair or a boat transition state. Furthermore, the calculations on a model system showed that the transition states for other products were energetically accessible. In particular, the *s-cis* chair transition state was only 2 kcal mol^{-1} more stable than the *s-cis* boat transition state. Inspired by the computational studies, the current study is directed towards switching the diastereoselectivity of the CHCR reaction by forcing the reaction to proceed through the *s-cis* boat transition state **B** instead of the *s-cis* chair transition state **A** (Figure 1).

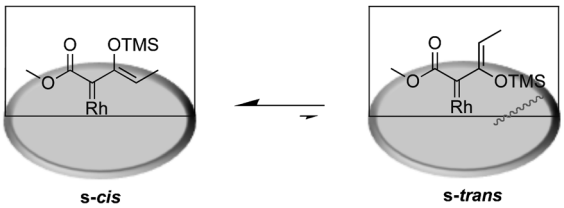


s-*cis*/*chair* approach **A** s-*cis*/*boat* approach **B**

Figure 1. The chair and boat transition states for the CHCR reaction. TMS = trimethylsilyl.

To limit the number of potential transition states available for the CHCR reaction, the study described herein was conducted with β-siloxyvinyldiazoacetates. The carbenoid derived from (*E*)-vinyldiazoacetates has little preference for the *s-trans* over the *s-cis* configuration,[5] whereas the internal substituent in the vinylcarbenoid derived from the β-siloxyvinyldiazoacetate strongly prefers the *s-cis* configuration.[5] In the *s-trans* configuration, the siloxy group would point towards the "wall" of the catalyst (Scheme 1).

Previous studies have shown that $[Rh_2\{(S)\text{-ptad}\}_4]$ (Scheme 2) is the optimum chiral catalyst for asymmetric reactions with siloxyvinyldiazoacetate **1**.[7] To test a baseline substrate, the $[Rh_2\{(S)\text{-ptad}\}_4]$-catalyzed reaction of diazoacetate **1** with the siloxycyclohexene **2a** was examined [Eq. (2); TFT = trifluorotoluene, TBDPS = *tert*-butyldiphenylsilyl]. Characterizable material was obtained by hydrolysis



Scheme 1. The *s-cis* and *s-trans* configurations of the rhodium carbenoid derived from **1**.

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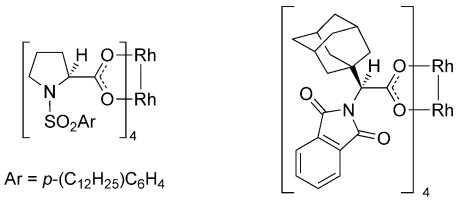
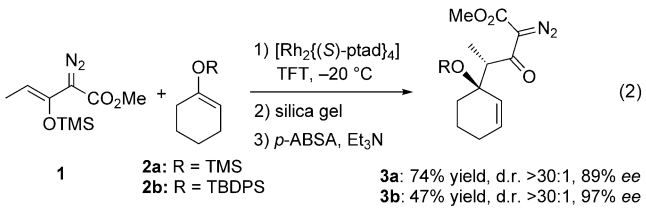
[**] This material is based on work supported by the National Science Foundation under the Center for Chemical Innovation in Stereoselective C–H Functionalization (CHE-0943980) and by the National Institutes of Health (GM080337).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103568.



Scheme 2. Structures of $[Rh_2\{(S)\text{-dosp}\}_4]$ and $[Rh_2\{(S)\text{-ptad}\}_4]$.

of the silyl enol ether of the crude product followed by conversion of the β-keto ester into the β-keto-α-diazoacetate **3a** in 74% yield for the three-step sequence.[8] The β-keto-α-diazoacetate **3a** was formed as a single diastereomer with 89% *ee*. The reaction with the bulky siloxycyclohexene **2b** selectively afforded the diazoacetate **3b** with even higher enantioselectivity (97% *ee*). The relative and absolute configuration of product **3b** was determined unambiguously by X-ray crystallography.[9]



The observed stereochemistry is consistent with the previously published examples of the CHCR reaction and would occur in a reaction proceeding through a chair transition state.[3e] An examination of the two possible transition states reveals that in the boat transition state **C** the remainder of the cyclohexyl ring would point towards the "wall" of the catalyst, and therefore, it would be reasonable to propose that this arrangement would be unfavorable (Figure 2).

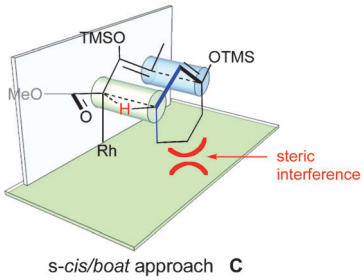
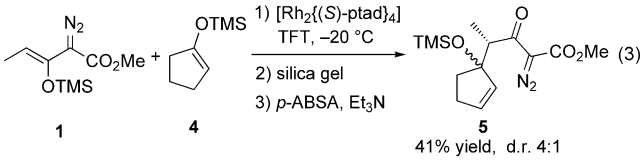


Figure 2. The s-*cis*/boat transition state model for the reaction of **1** with **2**.

We envisioned that a possible way to limit the steric influence of the ring would be to use a smaller ring size. Indeed, when the reaction was repeated with the siloxycyclopentene **4**, two diastereomers of the CHCR product **5** were produced in a 4:1 ratio [Eq. (3)]. This is the first example of a CHCR reaction generating a mixture of diastereomeric products.



Further evaluation of the proposed transition states **D** and **E** related to the formation of **5** suggested that the cyclopentyl ring could be incorporated into the boat transition state **E** (Figure 3). Furthermore, it became evident that a 2-substituent on the cyclopentenyl ring would cause the chair transition state **D** to be destabilized. If this proved to be the case, then the opposite diastereomeric series of products would become accessible.

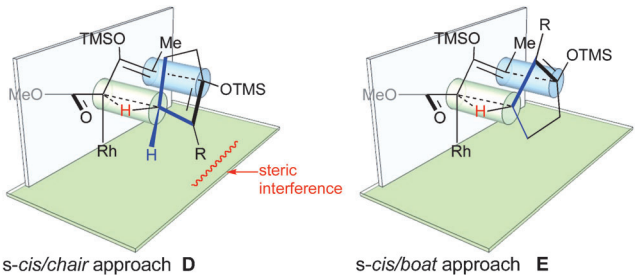
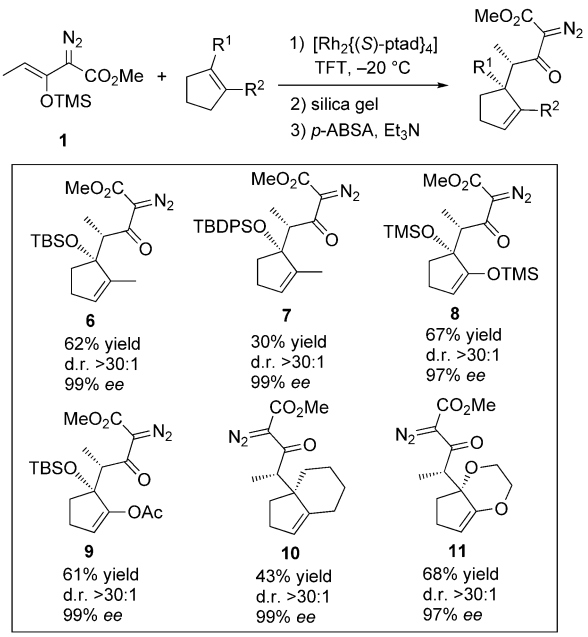


Figure 3. Transition state models for reaction of **1** with cyclopentenes.

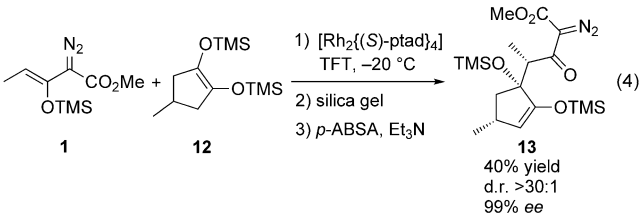
The $[Rh_2\{(S)\text{-ptad}\}_4]$-catalyzed decomposition of siloxydiazoacetate **1** in the presence of 1,2-disubstituted cyclopentenyl derivatives afforded the β-keto-α-diazoacetates **6**–**11** (Scheme 3). In all cases, a single CHCR product was produced with excellent diastereoselectivity (d.r. > 30:1) and enantioselectivity (> 97% *ee*). In the case of the unsymmetrical cyclopentene substrates, the resulting products, **6**, **7**, and **9**, are derived from site-selective C–H functionalization initiated at the methylene group allylic to the siloxy group. The relative and absolute configuration of **7** was unambiguously assigned by X-ray crystallography. The configurations of products **9** and **10** were also unambiguously confirmed by X-ray crystallographic analysis of products derived from them (see the Supporting Information). In each case, the relative configuration was consistent with a reaction proceeding through a boat transition state, and is opposite to the products **3a** and **3b** derived from the cyclohexene derivatives **2a** and **2b**. The structures of **6**, **8**, and **11** were tentatively assigned by assuming they are formed through a similar boat transition state.

Normally, the CHCR reaction is influenced by the presence of other stereogenic centers in the substrate and high levels of enantiomeric differentiation have been reported.[3a–d] Consequently, we explored if a desymmetrization would be feasible in a CHCR reaction. The reaction with cyclopentene **12** successfully generated product **13** as a single diastereomer with extremely high enantioselectivity [Eq. (4)]. This represents the first example of desymmetrization in the



Scheme 3. The CHCR reactions with cyclopentenyl derivatives. TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

CHCR reaction. The relative configuration of **13** inside the ring was assigned by NOE studies and was consistent with the outcome predicted by a boat transition state model (see the Supporting Information), while the stereochemistry in the chain was tentatively assigned assuming a boat transition state.



In conclusion, the synthetic utility of the CHCR reaction has been greatly expanded by the design of substrates that will react through a boat transition state instead of a chair transition state. This has led to the formation of the reversed diastereomeric series of products in a highly stereoselective manner. This study demonstrates the value of computational studies, not only to rationalize a new synthetic process, but also to identify opportunities to develop new reactions. The results showcase the synthetic potential of using carbenoid chemistry to achieve highly enantioselective C–H functionalization reactions.

Experimental Section

Typical procedure for the C–H functionalization: A solution of (*Z*)-methyl 2-diazo-3-((trimethylsilyl)oxy)pent-3-enoate (**1**) (365 mg, 1.6 mmol, 1.6 equiv) in dried trifluorotoluene (6 mL) was added by syringe pump over 3 h at –20 °C to an oven-dried 25 mL flask containing $\{Rh_2\{(S)\text{-ptad}\}_4\}$ (16.5 mg, 0.01 equiv) and substrate (1.0 mmol, 1.0 equiv) in dried trifluorotoluene (6 mL) under argon. The solution was warmed to room temperature over 2 h. The mixture was concentrated under reduced pressure and then stirred with 5 g silica gel in hexanes (15 mL) for 30 mins. The mixture was filtrated and washed with several portions of Et_2O. The organic solution was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (5–30% diethyl ether in pentane) to provide a colorless oil, which was dissolved in 5 mL dried CH_3CN containing *p*-ABSA (240 mg, 1.0 mmol, 1.0 equiv) and Et_3N (0.30 mL, 2.0 mmol, 2.0 equiv). The mixture was stirred for an additional 3 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5–30% diethyl ether in pentane) to provide β-keto diazoacetates.

Received: May 24, 2011
Published online: August 30, 2011

Keywords: carbenoids · C–H functionalization · Cope rearrangement · diastereoselectivity · rhodium

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[8] *p*-ABSA: *p*-Acetamidobenzenesulfonylazide (CAS 2158–14–7).

[9] CCDC 815184 (*ent*-**3b** from $[Rh_2\{(R)\text{-ptad})_4]$-catalyzed reaction), 815183 (**7**), 815179 (**9a** derived from **9**), and 815180 (**10b** derived from **10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

