Desymmetrization of Cyclohexanes by Site- and Stereoselective C–H Functionalization

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Abstract: C–H bonds have long been considered as generally unreactive, but new methods are being continually developed to transform these bonds that are otherwise inert to traditional chemical reagents.[1-9] The challenge, however, is to achieve such transformations in a highly selective manner, especially if the C–H bonds are unactivated[10] or not adjacent to a directing group.[11-13] Having catalyst-controlled site-selectivity, whereby the natural tendencies of the substrates[14] can be overwhelmed simply by choosing an appropriate catalyst, is a very attractive concept. Therefore, substantial effort has been made in catalyst-controlled C–H functionalization.[6, 15-17] In particular, methylene C–H bond functionalization has attracted wide scientific interest, and while several new methods have targeted these bonds in cyclic alkanes, the levels of selectivity were relatively poor.[18-20] Here, we illustrate a new level of sophistication in catalyst-controlled C–H functionalization, in which unactivated cyclohexane derivatives can be desymmetrized in a highly site- and stereoselective manner through donor/acceptor carbene insertion.

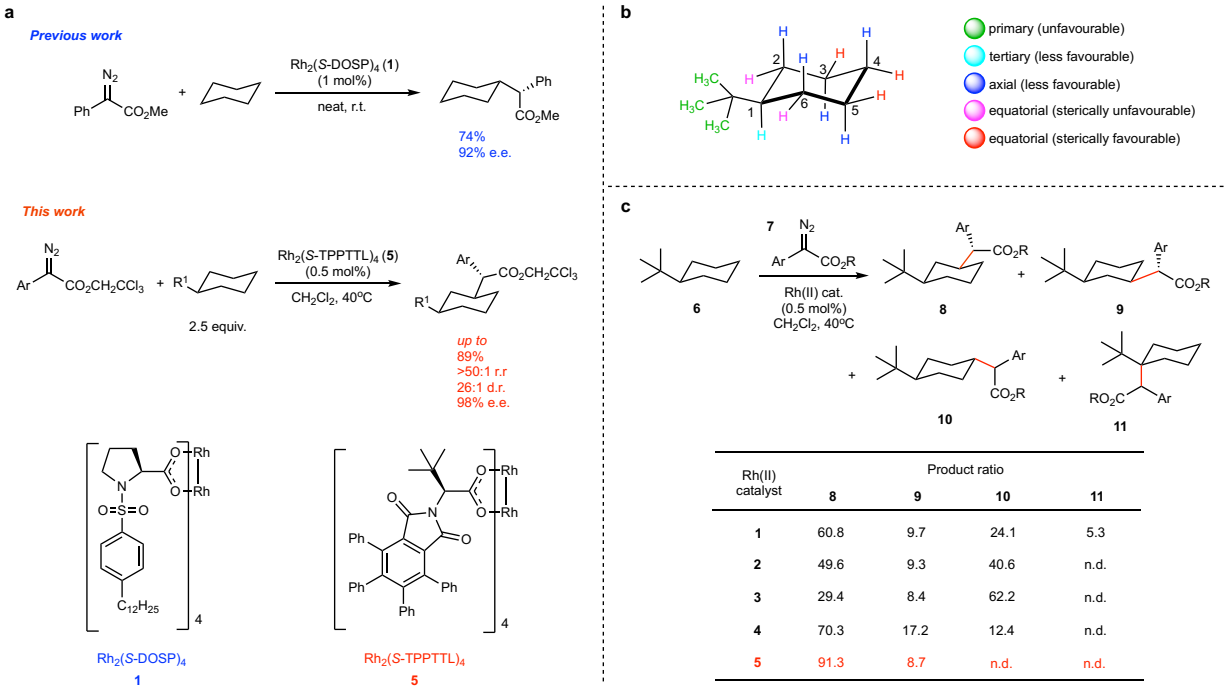
Selective reactions on certain cyclohexanes or polycyclic systems with appropriately positioned deactivating functionalities have been achieved.[18-22] However, in simple, electronically neutral cyclohexanes, good control of site- and stereoselectivity remains an unsolved challenge. Representative strategies in this area include carbene-induced C–H insertion,[23] C–H oxidation,[18] and radical-induced C–H functionalizations,[20-21, 24] although they have achieved limited levels of selectivity. Therefore, the principal

challenge of achieving these C–H functionalization processes in a highly site- and stereoselective fashion has not been satisfactorily addressed.

Our group has reported the design and development of a series of chiral dirhodium catalysts (**1**-**5**) with different steric environments (Fig. 1a and Extended Data Fig. 1). These catalysts are effective at catalyzing C–H functionalization reactions of acyclic alkanes via donor/acceptor carbene insertion.[6, 10, 15, 25] We have also described the functionalization of cyclohexane using Rh_2(*S*-DOSP)$_4$ (**1**) (Fig. 1a).[10] As the next challenge for our Rh(II)-catalyzed C–H functionalization program and with the recent development of 2,2,2-trichloroethyl aryldiazoacetates as a more robust source of donor/acceptor carbenes,[26] we became intrigued with the possibility of achieving site selective C–H functionalization of more elaborate substrates, such as substituted cyclohexanes. In this paper, we describe the development and evaluation of a new dirhodium catalyst, Rh_2(*S*-TPPTTL)$_4$ (**5**), leading to a site-selective carbene insertion process with high asymmetric induction. In particular, a higher level of sophistication in stereocontrol is achieved, as the reaction generates three stereocenters in one step from an achiral substrate. For monosubstituted cyclohexanes, the catalyst is not only able to differentiate between C-3 and C-4, but also between C-3 and C-5, leading to desymmetrization of the substrate and generation of the products with high diastereoselectivity and enantioselectivity (Fig. 1).

We first examined *tert*-butylcyclohexane as our model substrate. With the bulky *tert*-butyl group preferentially in equatorial position, there exist 11 different C–H bonds, excluding primary ones, that are electronically favored toward C–H functionalization (Fig. 1b). The C-1 axial position may be accessible for a structurally flexible catalyst but still largely unfavored due to steric reasons. In addition, C–H bonds at C-2 and C-6 positions are likely to be too crowded for functionalization due to steric bulk of the rhodium carbene. For similar considerations, equatorial C–H bonds are more favored than their axial counterparts. Therefore, it is reasonable to expect that three sites would be most favorable: the equatorial C–H bonds at C-3, C-4, and C-5 (marked in red, Fig. 1b).

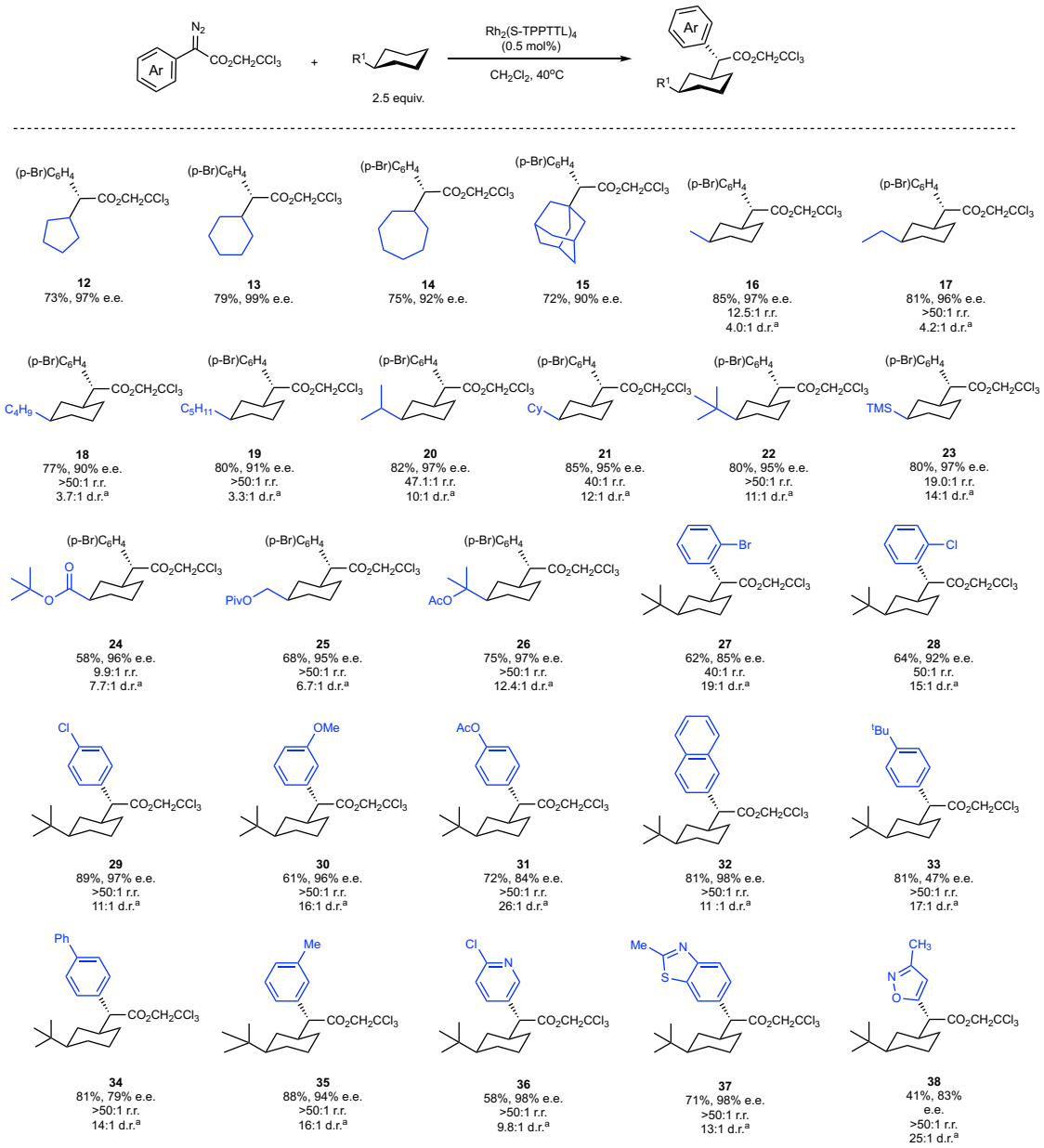
Initial exploratory studies of the reaction were conducted using 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**7**) as the carbene source. When the relatively uncrowded catalyst, Rh_2(*S*-DOSP)$_4$ (**1**) was used, the reaction gave primarily a mixture of three methylene insertion products **8**-**10** with a small but noticeable quantity of C-1 methine insertion product **11**. Catalysts **2**-**4** were sufficiently sterically hindered to block methine insertion, but still gave a mixture of products **8-10** (entries 2-4, Fig. 1c). During the course of these studies we evaluated a range of other established catalysts (see Supplementary Information section 3 for complete optimization study), as well as the new catalyst, Rh_2(*S*-TPPTTL)$_4$, which was readily prepared on multi-gram scale in two steps. Rh_2(*S*-TPPTTL)$_4$ has not been reported previously, even though it is structurally related to Rh_2(*S*-TCPTAD)$_4$[6] and other phthalimido-based catalysts developed by Hashimoto.[27-30] We were pleased to discover that, in contrast to all the previous catalysts we had studied, Rh_2(*S*-TPPTTL)$_4$ gave a very clean reaction (entry 5, Fig. 1c), favoring predominately a single methylene C–H functionalization product (**8**) with high site selectivity (>50:1 r.r.) and asymmetric induction (95% e.e.) (see Supplementary Information section 7 for X-ray structure of **8**). Notably, the product derived from C-4 insertion (**10**) was not seen in the reaction catalyzed by Rh_2(*S*-TPPTTL)$_4$. The products **8** and **9** are diastereomers and are formed through a desymmetrization event, and therefore, this catalyst effectively distinguishes between C-3 and C-4, and between the enantiotopic equatorial hydrogens at C-3 and C-5, which have not been reported previously for any C–H functionalization of alkyl cyclohexanes.



Rh(II) catalyst	Product ratio 8	9	10	11
1	60.8	9.7	24.1	5.3
2	49.6	9.3	40.6	n.d.
3	29.4	8.4	62.2	n.d.
4	70.3	17.2	12.4	n.d.
5	91.3	8.7	n.d.	n.d.

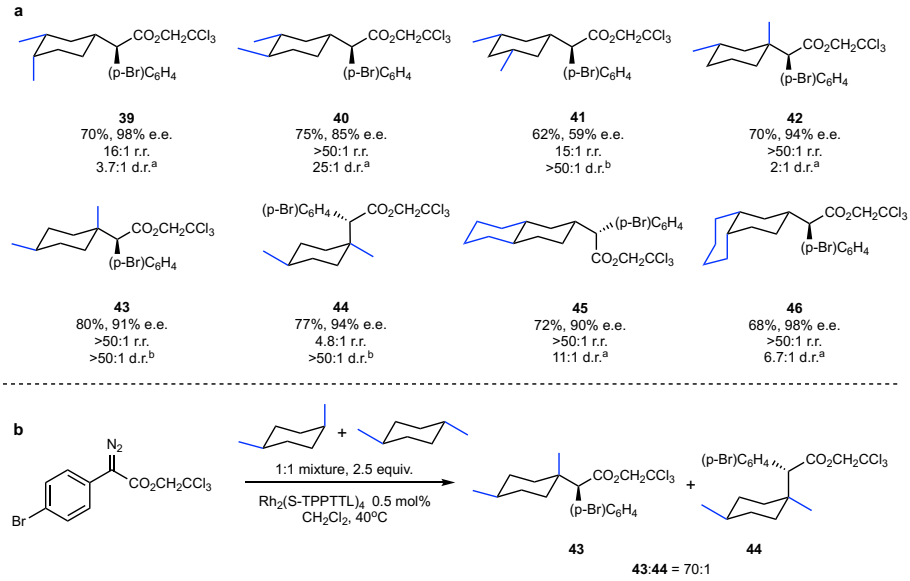
Having established that Rh_2(*S*-TPPTTL)$_4$ is the optimal catalyst, we then sought to explore the reaction with other cycloalkanes (Fig. 2). Simple cycloalkanes were readily functionalized to produce **12**-**15** in good yield (73-79% yield) and high enantioselectivity (90-99% e.e.). With these benchmark data, we then explored a series of alkyl cyclohexanes to study the influence of the size of the substituent. All substrates underwent functionalization at the desired C-3 position to form **16**-**22** with very high site selectivity, although in a few cases regioisomers were observed in minute amounts in the crude reaction mixture. Excellent levels of enantioselectivity (≥90% e.e.) were achieved for these substrates, indicating that Rh_2(*S*-TPPTTL)$_4$ routinely gives high asymmetric induction at the carbene site. Particularly notable compounds are **18** and **19**, because regioisomers derived from possible reactions at the alkyl chains were formed only in trace amounts (>50:1 r.r.), even though these C–H bonds are very accessible. The levels of diastereoselectivity were about 4:1 d.r. when the substituent was methyl or primary (**16**-**19**), but steadily improved when it was secondary or tertiary (**20**-**22**, 10-12:1 d.r.). These results indicate that the desymmetrization is more pronounced as the size of the alkyl substituent increases. Replacing the *tert*-butyl group in the model substrates with trimethylsilyl (TMS) group led to minimal change of reaction outcome (**23**). Furthermore, cyclohexanes bearing various ester groups also underwent

clean functionalization to generate products **24**-**26** with good regio- and stereocontrol. In addition, the reaction was compatible with a variety of aryldiazoacetates, including some that contain heteroaryl donor groups (**27**-**38**). However, the level of asymmetric induction is somewhat sensitive to the steric bulk of the *para* substituent of the aryl group, as **33** and **34** were generated with high diastereoselectivity but lower enantioselectivity (47% and 79% e.e. respectively).



The selectivity of C–H functionalization by rhodium carbene is generally considered to be governed by a combination of steric and electronic influences of the substrate and

the catalyst of choice.[10, 15, 25] Attempting to further evaluate these selectivity principles and to test the catalyst in more complex systems, we also subjected disubstituted alkyl cyclohexanes to the C–H functionalization reaction (Fig. 3). *cis*-1,2-Dimethylcyclohexane and *trans*-1,3-dimethylcyclohexane are interesting substrates because they exist as a 1:1 mixture of enantiomeric chair forms. Both substrates were capable of effective C–H functionalization, generating the products **39** and **42** with moderate to high level of asymmetric induction (98% and 59% e.e.). However, the diastereoselectivity in the formation of **39** and **42** is quite low (2.2-3.7:1 d.r.), indicating that the reaction was occurring with both enantiomeric chair forms for the substrates. *trans*-1,2-Dimethylcyclohexane is chiral and was reacted as the racemate mixture. Even so, the reaction was very effective, generating **40** with excellent site- and stereoselectivity. In addition, *trans*- and cis-1,4-dimethylcyclohexane are interesting substrates because they allow an evaluation of the difference in reactivity between an axial and an equatorial C–H bond. Reaction with *cis*-1,4-dimethylcyclohexane resulted in C–H functionalization into a tertiary C–H site to form **43**. *trans*-1,4-Dimethylcyclohexane would be expected to exist primarily in the chair form with the two methyl groups in equatorial positions, yet this substrate is also capable of C–H functionalization to form **44**. However, the regioselectivity is lower (4.3:1 r.r.), presumably due to unfavored axial insertion and competition at other methylene sites. A substrate competition experiment using an equal mixture of both 1,4-dimethylcyclohexane isomers indicated that an equatorial C–H bond reacted approximately 140 times faster than an axial C–H bond (see Supplementary Information section 3 for experimental details). The equatorial preference observed here is much higher than what has been seen in other C–H functionalization reactions.[23, 24] Finally, the study was extended to *cis*- and *trans*-decalin and they also gave clean transformations, forming **45** and **46** with excellent regio- and stereocontrol. The structure of **45** was confirmed by X-ray crystallography (see Supplementary Information section 7).

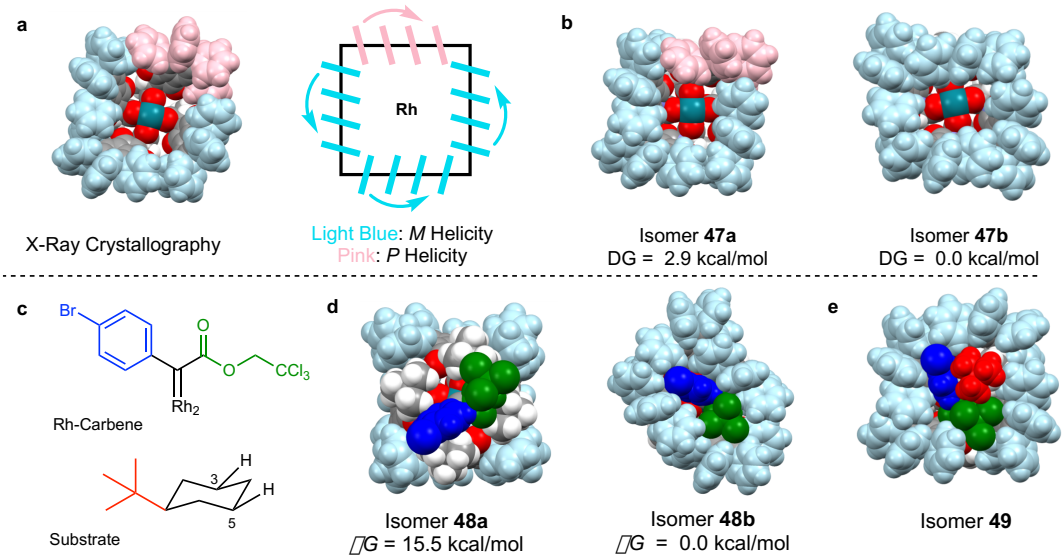


In order to understand what features of Rh_2(*S*-TPPTTL)$_4$ make it such an exceptional catalyst for the desymmetrization of cyclohexanes, the structure of the catalyst was interrogated by X-ray crystallography and by DFT calculations (see Supplementary Information section 6 and 7 for details). The X-ray data indicate that the catalyst comprises a dirhodium core and four phthalimido groups with the four *S*-TPPTTL ligands that adopt a "chiral crown" shape,[29] slightly distorted from a perfect C_4 symmetric structure (Fig. 4), and is similar to other phthalimido dirhodium catalysts.[6, 29] The flanking phthalimido groups are projected upward in relation to the dirhodium core, embedding an approximate C_4 symmetry on the macrocycle. A unique structural feature of Rh_2(*S*-TPPTTL)$_4$ is the orientation of the 16 phenyl groups bound to the phthalimido ligands. The X-ray crystallographic structure of Rh_2(*S*-TPPTTL)$_4$ shows that twelve of the phenyl groups are tilted to the right and four are tilted in the opposite direction. Further computational studies indicate that structure **47b** with all the phenyl groups tilted to the right (*M* configuration) is lower in energy by 2.9 kcal/mol than structure **47a**. Closer inspection of the structure reveals that the *tert*-butyl group of one ligand influences the tilt direction of the phenyl rings on the adjacent ligand. Indeed, attempts at calculating the energy of the complex with all the phenyl groups tilted to the left were not successful because the structure reverted back to the *M* configuration (see Supplementary Information section 6 for details). Thus, the point chirality of the ligands induces a pseudo C_4 propeller chirality in the complex by causing the sixteen phenyl

groups to tilt preferentially in one direction over the other. We propose that the orientations of these phenyl groups play a critical role in the observed selectivities.

Even though the ligands generate a deep pocket around the rhodium, computational studies indicate that binding of the carbene to this face (structure **48b**) is strongly preferred by 15.5 kcal/mol in energy as compared to structure **48a**, presumably because of the steric influence of the four *tert*-butyl groups. In structure **48b**, all phenyl groups are tilted in the same direction, and its other isomers, including the one with two oppositely tilted ligands, are higher in energy (see Supplementary Information section 6 for details). Interestingly, comparison between the free catalyst (**47b**) and carbene-bound catalyst (**48b**) structures reveals that the overall shape of the ligand framework has changed to accommodate the carbene, indicative of an induced fit model.

The next stage of the computational study was to understand how *tert*-butylcyclohexane approaches the rhodium carbene. We therefore calculated several isomers of the Rh-(carbene)(substrate) complexes.[30] These studies reveal that attack at the C-4 position of the cyclohexane was very unfavorable because the *tert*-butyl group would be pointing toward the "wall" of the catalyst, generated by the 16 phenyl groups. The most favorable structure of the Rh-(carbene)(substrate) complex is **49**, where the *tert*-butyl group is pointing away from the "wall" of the pocket, toward the opening of the binding face. This places one of the enantiotopic equatorial C-3 hydrogens close to the carbene, leading to the correct prediction of the observed asymmetric induction during desymmetrization. Examination of structure **49** shows that the shape of the catalyst has adjusted once again to accommodate the substrate. Overall, these calculations show that Rh_2(*S*-TPPTTL)$_4$ has a high degree of flexibility to adjust its shape when the carbene and substrate approach the catalytically active rhodium center, which may explain why the reaction can be extended to disubstituted cyclohexanes and decalins.



In conclusion, this study serves to demonstrate that catalyst-controlled C–H functionalization of substituted cyclohexanes in a site- and stereoselective manner is a viable process. This study also further underscores the subtle controlling influences in the C–H functionalization reactions of donor/acceptor carbenes in the presence of appropriately designed dirhodium catalysts.

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Fig. 1 Background on C–H functionalization of unactivated alkanes and relationship to current work. a, functionalization of cyclohexanes with donor/acceptor carbenes. We have previously described the asymmetric C–H functionalization of cyclohexane using catalyst **1**. In this work we show that the new catalyst **5** is capable of functionalizing the C-3 equatorial C–H bond of substituted cyclohexanes, leading to a stereoselective desymmetrization process. Ar = aryl or heteroaryl. **b**, illustration of the structure and challenge of functionalization of *tert*-butyl cyclohexane. **c**, optimization using the model substrate indicates that **5** can catalyze the functionalization of *tert*-butyl cyclohexane in a highly regioselective manner. See Supplementary Information Section 4 for experimental details and relevant spectra. Ar = (*p*-Br)C_6H_4, R = $CO_2CH_2CCl_3$.

Fig. 2 Scope of the reaction with respect to substrates and aryldiazoacetates. Simple cycloalkanes were readily functionalized with good yield and high enantioselectivity. For substituted cyclohexane substrates, high site selectivity is routinely observed, resulting in C-3 insertion via a desymmetrization event, although diastereoselectivity is lower when the size of the substituent is small. The scope of aryldiazoacetates was broad, but sterically bulky *para*-substituents can lower enantioselectivity, as illustrated in compounds **33** and **34**. Heteroaryl donor groups were also compatible with this chemistry, as indicated by **36**-**38**. a: No ring diastereomers were observed. Abbreviations: r.r., regioisomeric ratio; d.r., diastereomeric ratio; e.e., enantiomeric excess.

Fig. 3 Functionalization of disubstituted cyclohexanes. a, C–H functionalization of disubstituted cyclohexanes is more challenging, and the selectivity is governed by catalyst influence and subtle electronic preference of certain C–H bonds. Products were generally formed with high site- and stereoselectivity, although in a few cases d.r. is lower due to reaction with both enantiomeric chair forms. a: No ring diastereomers were observed. b: Due to symmetry, there are no side chain diastereomers. **b**, A substrate competition study indicated that the equatorial C–H bond reacted 140 times faster than its axial counterpart, illustrating the general steric influence of the rhodium carbene complex.

Fig. 4 Rationalization of observed selectivities. a, top view of the crystal structure and the illustrative view of the helicity of the phenyl groups; **b**, two calculated and energetically most stable isomers (**47a** and **47b**) of the catalyst. Isomer **47a** was optimized based on X-ray data; **c**, illustration of color-coding of atoms in carbene and *tert*-butyl cyclohexane in the calculated structures: donor group of carbene (blue), acceptor group of carbene (green), *tert*-butyl group of the substrate (red); **d**, calculated Rh-carbene complexes. Energetically, carbene binding to the top face (**48b**) is strongly favored over binding to the bottom face (**48a**); **e**, calculated lowest energy Rh-(carbene)(substrate) complex **49.** The atoms are color-coded according to default setting of Mercury: rhodium (blue), oxygen (red), hydrogen (white), carbon (grey). The highlighted atoms are marked according to the direction the phenyl group rotated: the phenyl groups in *M* helicity are marked light blue, and the ones in *P* helicity are marked pink.

Supplementary Information is available in the online version of the paper.

Data Availability: Crystallographic data for the structures reported in this Letter have been deposited at the Cambridge Crystallographic Data Centre, under deposition number CCDC 1855619, 1855620 and 1855295. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. Complete experimental procedures and compound characterization data are available in the Supplementary Information, or from the corresponding author upon request.

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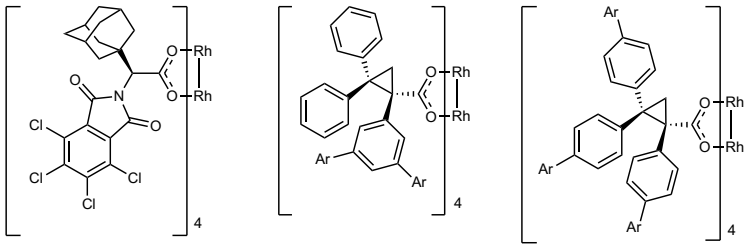
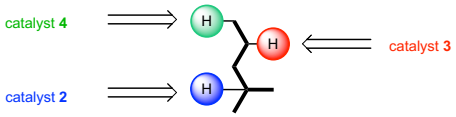
The authors have no competing financial interests.





Extended Data Fig. 1 Structures of previously established catalysts. We have previously shown that through catalyst-directed C–H functionalization, we were able to selectively functionalize the most accessible primary, secondary and tertiary C–H bonds within a linear alkane substrate by using catalyst **2**, **3**, or **4**.