Dirhodium Tetracarboxylates: Privileged Catalysts for Selective Intermolecular C–H Functionalization

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Abstract: C–H Functionalization has become widely recognized as an exciting new strategy for the synthesis of complex molecular targets. Instead of relying on functional groups as the controlling elements of how molecules are assembled, it offers a totally different logic for organic synthesis. For this type of strategy to be successful, reagents and catalysts need to be developed that generate intermediates that are sufficiently reactive to functionalize C–H bonds but still capable of distinguishing between the different C–H bonds and other functional groups present in a molecule. The most well-established approaches have tended to use substrates that have inherently a favored site for C–H functionalization or rely on intramolecular reactions to control where the reaction will occur. A challenging but potentially more versatile approach would be to use catalysts to control the site-selectivity without requiring the influence of any directing group. One example that is capable of achieving such transformations is the C–H insertion chemistry of transient metal carbenes. Dirhodium tetracarboxylates have been shown to be especially effective catalysts for these reactions. This review will highlight the development of these dirhodium catalysts and illustrate their effectiveness to control both site-selective and stereoselective C–H functionalization of a wide variety of substrates.

Introduction:

Numerous strategies have been developed to achieve site-selective C–H functionalization and this area of research continues to be a very active field of study.[1-12]

Some have a long history such as the venerable Hofmann–Löffler-Freytag reaction, which achieves site-selective radical-induced hydrogen abstraction to occur by means of intramolecular reactions.[13-20] Numerous modern radical-induced C–H functionalization reactions have been developed, including radical processes, but the site selectivity in these reactions is usually controlled by the inherent reactivity profile of the substrate (Fig. 1a).[4,21-33] Enzymatic C–H oxidations are capable of exquisite site selectivity and bio-inspired approaches to replicate such selectivity for a broad array of substrates is of considerable interest.[34] The use of a directing group to coordinate to a metal catalyst, which thus, places the metal in close proximity to a specific C–H bond has become a very popular method for C–H functionalization and has been broadly applied for the synthesis of pharmaceutical and other complex targets (Fig. 1b).[35-44] This approach can also be applied to enantioselective C–H functionalization by using relatively weak directing groups and chiral ligands on the catalyst (Fig. 1c).[45-47]

Considerable interest has also been shown in developing catalyst-controlled C–H functionalization methodologies, which avoid having defined directing groups within the substrate or prior coordination of the catalyst to the substrate (Fig. 1d).[48-56] The most extensively studied reactions have been C–H oxidation,[57] C–H borylation,[58] C–H amination,[59] and C–H alkylation by metal carbenes.[29] This review will describe recent progress in site-selective intermolecular sp^3 C–H functionalization using rhodium carbene intermediates.[52-54,560-65] Dirhodium tetracarboxylates are the optimum catalysts for these reactions, and this review will describe the evolution of these catalysts to the current stage in which catalyst-controlled intermolecular functionalization of unreactive primary, secondary or tertiary C–H bonds can be achieved by simply choosing the appropriate catalyst.[9,66-70]

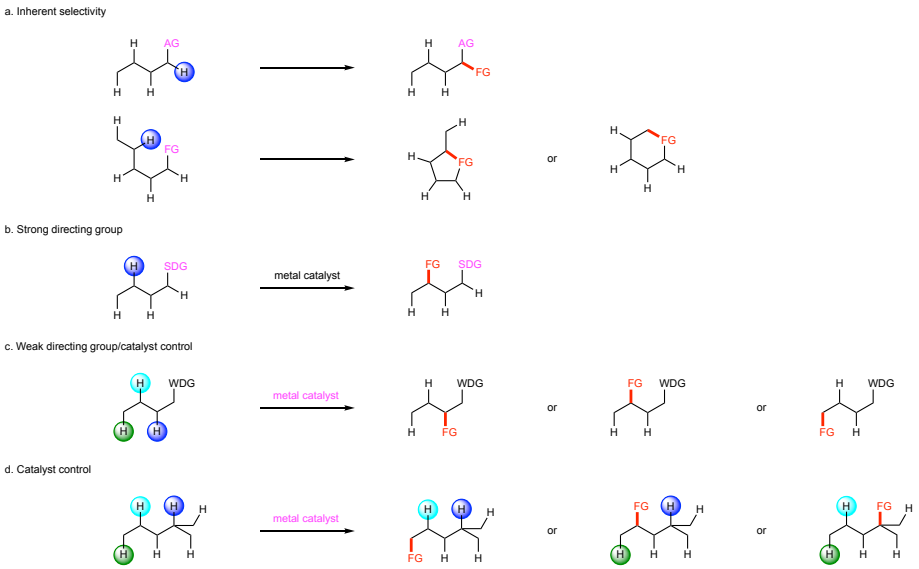

Figure 1: **Introduction to the most significant strategies for site selective C–H functionalization**. **a**: radical type reaction in which an activating group (AG) in the substrate causes a specific C–H bond to be most reactive and the introduction of a functional group (FG) at that specific position. **b**: Strong directing group (SDG) that coordinates to the metal catalyst and places it in close proximity to a specific C–H bond. **c**: Weak directing group (WDG) that coordinated to the metal catalyst but the selectivity can be varied depending on the nature of the ligands around the catalyst. **d**: Catalyst controlled C–H functionalization without prior coordination to the catalyst, in which site selectivity is dependent on which catalyst is used.

Background on Rhodium Carbene-Induced C–H Functionalization

The first example of the metal carbene-induced intermolecular C–H functionalization was the copper oxide-catalyzed reaction of cyclohexane (**1**) with ethyl diazoacetate (**2**) to form the functionalized product **3**, reported by Scott in 1974 (Fig. 2a).[71] This reaction is proposed to proceed via a copper carbene intermediate **4**, and the carbene inserts into the C–H bond. A few years later, Teyssié demonstrated that dirhodium tetracarboxylates were far superior as catalysts compared to copper for intermolecular

C–H functionalization of alkanes with ethyl diazoacetate (Fig. 2b).[72] The yields were generally high for both cyclic and acyclic alkanes but the reaction generated mixtures of products with substrates containing different C–H bonds, as illustrated in the reaction with pentane (**5**), which generated all three possible products **6-8**. The rhodium catalyst **9** is highly electrophilic and the electron-withdrawing ester group further reinforces this characteristic. Consequently, the metal carbene is sufficiently reactive to insert into C–H bonds but lacks the selectivity to distinguish effectively between different C–H bonds. Since this period, efforts have been made to design catalysts to improve on the site selectivity with ethyl diazoacetate. Silver complexes with bulky ligands such as **10**, developed by Pérez[73] and rhodium complexes developed by Callott[74-76]have been shown to direct the C–H functionalization towards less crowded C–H bonds, but still, the selectivity is relatively modest.[77] Iridium carbenes have modulated reactivity compared to their silver- and rhodium-carbene counterparts, and enantioselective C–H functionalization has been reported by Katsuki using the chiral iridium catalyst **11** but the range of substrates applicable to these reactions have been limited to cycloalkanes and cyclic ethers.[27] An example is the functionalization of tetrahydrofuran **12** with ethyl diazopropionate **13** to form **14** in 90% enantiomeric excess (e.e.) (Fig. 2c).

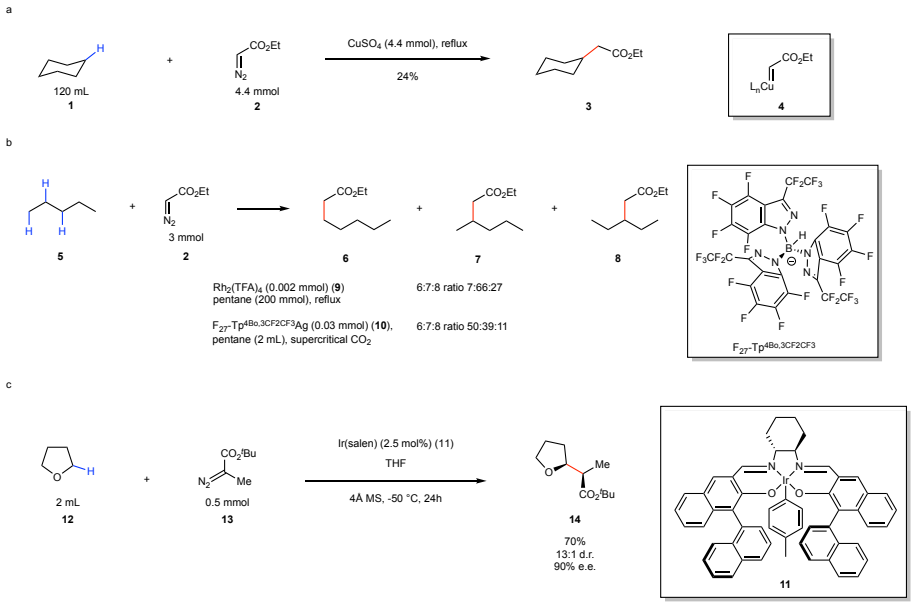

Figure 2: **Background to carbene-induced intermolecular C–H insertion with diazoacetates. a**: Seminal studies with copper catalysis. **b**: Enhanced reactivity with dirhodium tetracarboxylates as catalysts and enhanced site-selectivity with bulky silver catalysts. **c**: Enhanced enantioselectivity with an iridium catalyst.

In order to overcome the site-selectivity challenges of the carbene-induced C–H functionalization reaction, early studies in the 1980's focused on the intramolecular version, as illustrated in the rhodium acetate-catalyzed reaction of the diazoacetoacetate **15** to form the bicycle **16** (Fig. 3a).[78] Cyclization to form five-membered rings is generally preferred, although with certain substrates four- or six-membered ring products are the preferred.[70,79-82]The utility of the process was further enhanced with the development in the 1990's of enantioselective variants with the highly effective chiral dirhodium tetracarboxylates, such as Rh_2(*S*-PTTL)$_4$ and dicarboxamides catalysts, such as Rh_2(4*S*-MACIM)$_4$, developed by Hashimoto[83] and Doyle[84], respectively (Fig. 3b). Representative examples of the use of these catalysts, is the cyclization of the diazoacetoacetate **17** to form the bicycle **18**, which after

deacylation, generated **19** in 53% e.e.**,** and the desymmetrization of the diazoacetate **20** to from **21** in 97% e.e.. The synthetic potential of these intramolecular reactions is broad and the reaction has been applied to the synthesis of a variety of complex targets as illustrated in the conversion of **22** to **23** as a key step in the synthesis of (+)-isolauricerisinol **24** (Fig. 3c).[85] The intramolecular C–H functionalization is now well established and has been extensively reviewed[70] and will not be discussed further here.

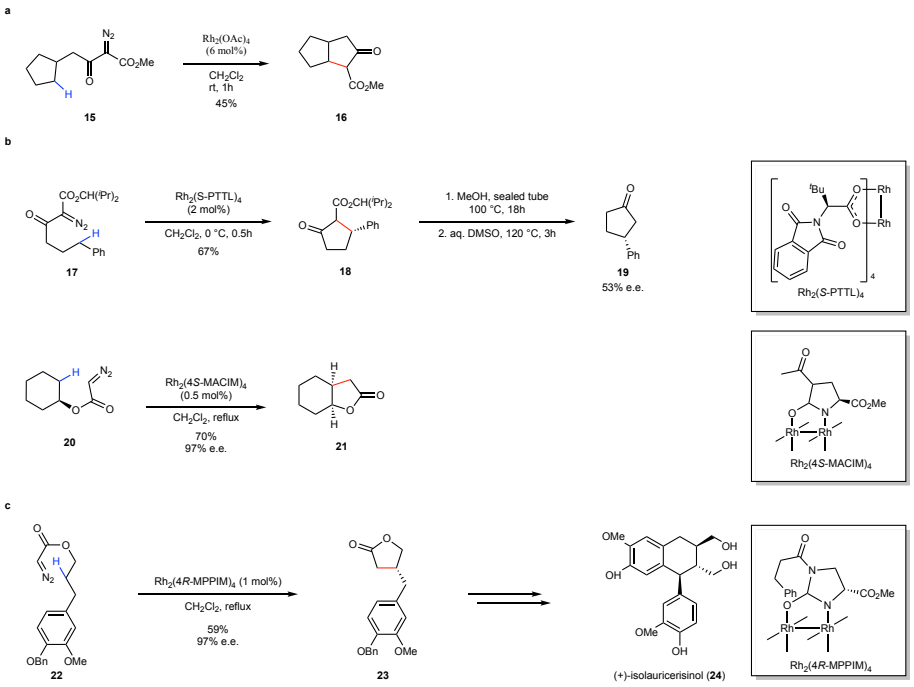

Figure 3. **Overview of intramolecular C–H insertion reactions. a**: Early example using an achiral catalyst. **b**: Enantioselective C–H functionalization examples using chiral dirhodium catalysts. **c**: Example of a key carbene C–H functionalization step in the total synthesis of (+)-isolauricerisinol.

Development of Donor/Acceptor Carbenes for C–H Functionalization

The carbene generated from ethyl diazoacetate has been characterized as an "acceptor carbene" (Fig. 4a), and these carbenes are generally too reactive for exceptional control of site selectivity in intermolecular reactions.[86] Copper and rhodium carbenes have limited back-bonding from the metal and thus are highly electrophilic. Addition of further electron-withdrawing groups to the carbene increases the electrophilic character of the carbene, which explains why the established acceptor and acceptor/acceptor carbenes have had most success in intramolecular reactions. In order to achieve selectivity in intermolecular reactions, less reactive and more selective types of carbenes would be needed. The Davies group developed a new class of metal carbenes in the 1980's, the so called "donor/acceptor" carbenes, which contain both an acceptor group, such as an ester, and a donor group, such as aryl or vinyl (Figure 4).[87,88] During extensive early studies on cyclopropanation reactions, his group discovered that these carbenes are much more selective than the conventional carbenes lacking a donor group. Furthermore, these carbenes will undergo highly enantioselective cyclopropanation when the reactions are catalyzed by the rhodium prolinate catalysts $Rh_2(DOSP)_4$, as illustrated in the cyclopropanation of styrene **25** with the styryldiazoacetate **26** to form **27** in 98% e. e.[89] The *n*-dodecyl group was incorporated into the catalyst to make it soluble in hydrocarbon solvents, even at low temperature, which are the optimized conditions for high asymmetric induction. In 1997, highly enantioselective C–H functionalization of cycloalkanes catalyzed by $Rh_2(DOSP)_4$ was reported, as illustrated in the reaction of cyclohexane **2** with methyl aryldiazoacetate **28** to form **29** in 95% e. e..[22] These studies represented the first examples of highly enantioselective intermolecular C–H functionalization by rhodium carbene intermediates. Recently, there have been some interesting C–H functionalization studies going beyond donor/acceptor carbenes to donor/donor carbenes. So far, the reported examples have been limited to intramolecular versions,[90-93] presumably because the carbenes are no longer sufficiently reactive to undergo effective intermolecular C–H functionalization reactions.

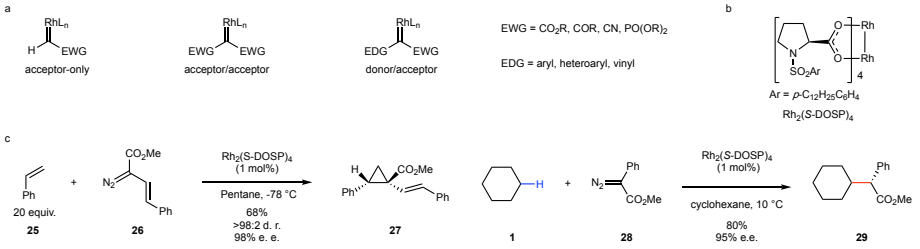

Figure 4. **Early development of the donor/acceptor carbenes. a**: Introduction to the three major types of reactive carbene intermediates. **b**: $Rh_2(DOSP)_4$ – a highly effective chiral catalyst for the reactions of donor/acceptor carbenes. **c**: Early examples of $Rh_2(DOSP)_4$-catalyzed asymmetric cyclopropanation and C–H functionalization with donor/acceptor carbenes.

The $Rh_2(DOSP)_4$/aryldiazoacetate combination was effective for enantioselective intermolecular C–H insertion of a wide variety of substrates.[66,68] Even though relatively moderate site selectivity was found with alkanes, the reactions with substrates containing electronically activated sites were very site-selective. The most favored groups for C–H functionalization are summarized in Fig. 5a. C–H Functionalization next to groups that can stabilize positive charge build up in the transition state for the C–H functionalization are favored. Thus benzylic, allylic and C–H bonds adjacent to nitrogen or oxygen are electronically favored. C–H Functionalization generally occurs at secondary C–H bonds because even though tertiary C–H bonds are electronically favored the rhodium carbene is sterically demanding. If the two groups adjacent to the secondary site are distinctly different in size, the reaction can be highly diastereoselective. Non-crowded tertiary sites such as adamantane can be readily functionalized as well as primary C–H bonds that are electronically activated. However, in general if there is competition between electronically activated primary and secondary sites, functionalization of the secondary site is preferred unless there is extreme steric crowding. The mechanism of the C–H functionalization has been studied computationally and was proposed to be a concerted asynchronous process as shown in Fig 5b.[94] The reaction begins more as a hydride transfer event before finally the carbene inserts into the C–H bond. Based on this computational analysis, a model was

developed that is predictive of both the relative and absolute configurations of the C–H functionalization products. The substrate is considered to approach the carbene with the large group pointing away from the catalyst, and the medium group resides on the side of the donor group rather than the acceptor group, because the acceptor group lies orthogonal to the carbene and would point towards the approaching substrate.

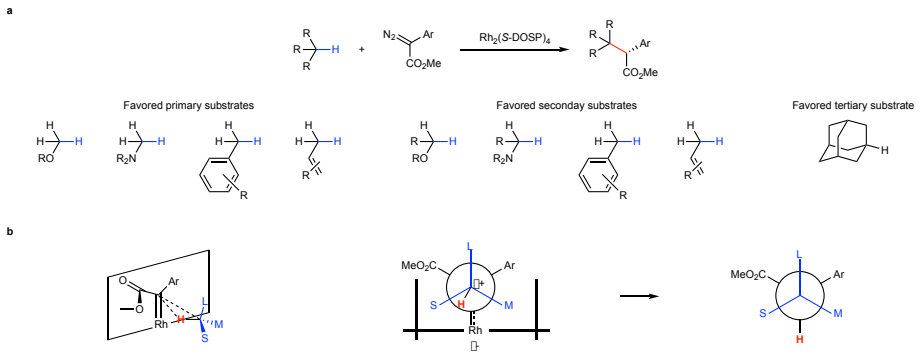

Figure 5. **Overview of $Rh_2(DOSP)_4$-catalyzed intermolecular C–H functionalization**. **a**: Favored sites for C–H Functionalization. **b**: Predictive model for the relative and absolute configuration for $Rh_2(DOSP)_4$-catalyzed C–H functionalization. The large (L) group points away from the catalyst, the medium (M) group is on the side of the aryl group, which is in the same plane as the rhodium-carbene, and the small (S) group is on the side on the esters group which is orthogonal to the rhodium carbene-aryl plane and points towards the approaching substrate.

The general scope of the $Rh_2(DOSP)_4$-catalyzed intermolecular C–H functionalization has been reviewed elsewhere[66,68] and only the highlights will be discussed here. The C–H functionalization can be considered as equivalent to some of the classic strategic reactions of organic synthesis.[66] Particularly effective substrates are those with electronically activated methylene sites in which the two methylene substituents are distinctly different in size because the reactions with these substrates are highly diastereoselective and enantioselective as illustrated in Fig. 6. The reaction with various siloxy derivatives generated protected beta-hydroxy esters, as illustrated for the reaction with tetraethoxysilane **30** to form **31**. The reaction is a C–H functionalization equivalent

to an aldol reaction as illustrated in the retrosynthetic scheme from the acetaldehyde **32** and the enolate **33**.[23,22] Reaction with *N*-Boc-pyrrolidine **34** generated the beta-amino ester **35**, containing the functionality typically generated by a Mannich reaction derived from the imine **36** and the enolate **33**.[95] Various other examples of surrogates of classic reactions have been reported, such as the Claisen rearrangement[96], Michael addition[97] and the Claisen condensation[98].

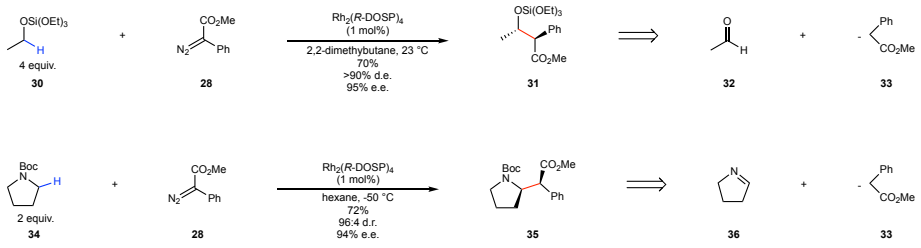

Figure 6. **C–H Functionalization as a strategic equivalent of classic strategic reactions of organic synthesis**. C–H functionalization adjacent to oxygen is a surrogate equivalent of an aldol reaction. C–H functionalization adjacent to nitrogen is equivalent to a Mannich reaction

A related C–H functionalization process of great synthetic utility is the reaction of vinyldiazoacetates **37** with allylic substrates **38**, the so-called *combined C–H functionalization/Cope rearrangement*. The product **40** of this reaction is not the normal C–H functionalization product but one in which it appears as if the C–H functionalization product has undergone a Cope rearrangement (Fig. 7a). However, this is not the case because the C–H functionalization product is the thermodynamic product. Computational studies revealed that the reaction begins with a hydride transfer event to generate a complex **39**, consisting essentially of an allyl cation and a rhodium-bound allyl anion, which then immediately forms a C-C bond at the distal position before any bond rotation can occur.[99] The synthetic transformation has been reviewed[100] and so, only two representative examples will be discussed here.[101-103] In most cases, the products are formed with exceptionally high levels of asymmetric induction and diastereocontrol. Typically, the high diastereocontrol is caused by the reaction proceeding through a chair-like transition state as illustrated for **39**, but in certain cases,

steric interference with the face of the catalyst forces the reaction to proceed through a boat transition state. The C–H functionalization process offers some interesting synthetic possibilities. For example, the reaction of the vinyldiazoacetate **41** with the alkene **42** generates **43** with two new stereogenic centers (Fig 7b).[102] The transformation can be considered as a surrogate of the vinylogous Mukaiyama aldol surrogate, equivalent to the Lewis acid catalyzed reaction of the aldehyde **44** with the diene **45**. The process is applicable as a powerful strategic reaction in total synthesis as illustrated in the synthesis of colombiasin A (**46**, Fig 7c).[104] The reaction of the racemic dihydronaphthalene **47** with the vinyldiazoacetate **48** generates the C–H functionalization product **49** with control of stereochemistry at three stereogenic centers. This key step is enantiodivergent as only one enantiomer of the dihydronaphthalene **47** undergoes the desired C–H functionalization to form **49** whereas the other enantiomer undergoes a cyclopropanation reaction. Previous efforts at the total synthesis of colombiasin A had struggled to control these stereogenic centers but with **49** in hand, the completion of the total synthesis was readily achieved in six additional steps.

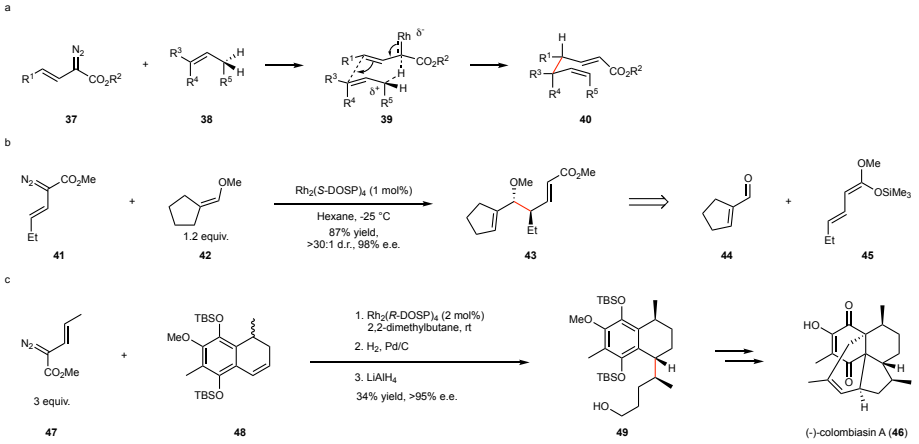

Figure 7. **Combined C–H functionalization/Cope rearrangement. a:** General scheme of the transformation. Due to the ordered transition state, the reactions are generally highly enantioselective and diastereoselective. **b:** Representative example illustrating the highly stereoselective nature of these transformations. **c:** Application to the total synthesis of colombiasin A. Even though the dihydronaphthalene **47** is racemic, the resulting C–H functionalization product **49** is generated with high

asymmetric induction because only one of the two enantiomers of **47** undergoes the reaction under the Rh_2(*R*-DOSP)$_4$-catalyzed conditions.

Catalyst-Controlled C–H functionalization with Donor/Acceptor Carbenes

One of the grand challenges in the field of C–H functionalization is to be able to use catalyst control to overcome the inherent reactivity profile of a substrate. Rh_2(DOSP)$_4$ was a good start as it is an effective catalyst for many carbene-induced C–H functionalization reactions. Certain types of substrates with the right balance of steric and electronic influences work well with Rh_2(DOSP)$_4$. In order to move from substrate control to the era of catalyst control, new classes of chiral catalysts were required with varied steric demand. Che demonstrated that bulky rhodium-porphyrin catalysts tended to favor C–H functionalization of alkanes preferentially at less crowded sites.[105] However, the major breakthrough in this area has been the use of bulky chiral dirhodium catalysts.

A critical design element for dirhodium tetracarboxylate catalysts has been to exploit the symmetry of the dirhodium tetracarboxylate core. A freely rotating achiral dirhodium tetracarboxylate with four identical ligands is D_{4h} symmetric. Several years ago, we proposed that if the ligand contained a very large substituent, then that substituent would not be able to align in the periphery of the catalyst and would need to exist on either the top (α) or bottom (β) face of the catalyst. Depending on the specific orientations of the chiral ligands, the catalysts could adopt higher symmetry than the ligands themselves (Fig. 8a).[106] Originally, we proposed, the complexes could be C_4, D_2 or C_2 symmetric (**50**-**52**). More recently, complexes adopting an alternative C_2 symmetric orientation **53** has been identified, in which all the bulky groups are on the same face of the catalysts, but two are orientated differently from the other two.

The three major classes of chiral dirhodium catalysts for intermolecular C–H functionalization with donor/acceptor carbenes are shown in Figs 8b-d. The original

chiral catalyst $Rh_2(DOSP)_4$ was proposed to behave as if it was D_2 symmetric (Fig 8b). However, the D_2 model for $Rh_2(DOSP)_4$ has not been confirmed experimentally. Since then two other classes of chiral catalysts have been developed and they dramatically influence the site-selectivity of the C–H functionalization. One class is related to the phthalimido amino acid catalysts originally developed by Hashimoto (Fig. 8c).[107, 108] $Rh_2(TCPTAD)_4$ (**54**)[109] and $Rh_2(TPPTTL)_4$ (**55**)[65] both adopt a slightly distorted C_4 symmetric structure. Previously, related catalysts have been considered as adopting a C_2-symmetric chiral crown, rather than as a pseudo-C_4 symmetric structure.[110-113] However, we propose that considering the catalyst as essentially adopting a pseudo-C_4 symmetric structure is more appropriate because these ligands adopt an induced fit when the carbene binds and the resulting rhodium complex is not altered by the initial carbene orientation to the dirhodium. An intriguing feature of $Rh_2(TPPTTL)_4$ is the orientation of the 16 phenyl groups, which adopt a preferred twist of each ring leading to an additional induced chiral influence due to a C_4-propeller-like structure of the phenyl groups.

The second class of chiral dirhodium catalysts is based on triphenylcyclopropane carboxylate (TPCP) ligands (Fig. 8d), and they are sterically much more crowded that the other two classes of catalysts. They are readily synthesized by a 3 or 4-step synthesis: Rh-DOSP catalyzed cyclopropanation of 1,1-diarylethylene, followed by ester hydrolysis and ligand exchange.[52,60] Furthermore, a library of catalysts with differing steric environment can be generated by means of a subsequent multifold Suzuki coupling reaction on the preformed catalyst.[52,114]

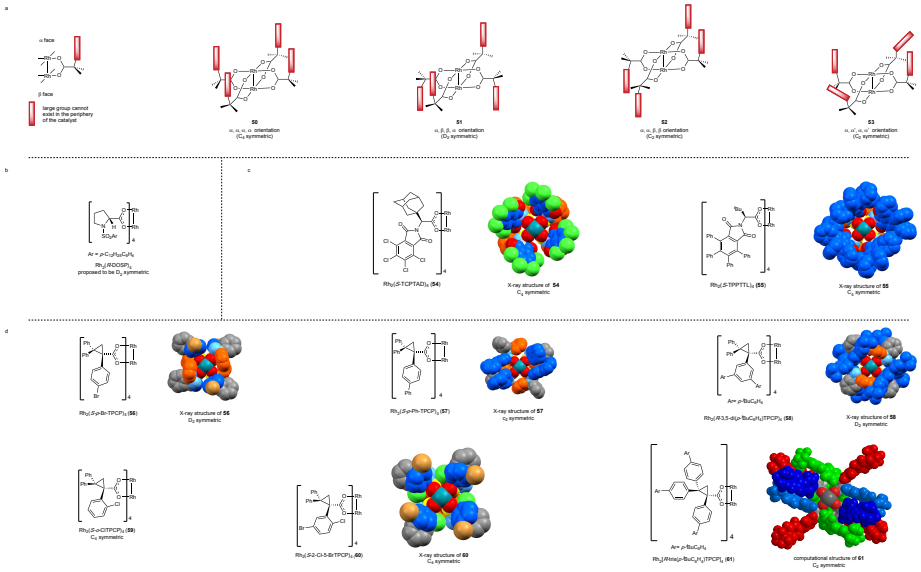

Figure 8. **Chiral dirhodium catalysts for intermolecular C–H functionalization. a:** Design models for chiral catalysts, illustrating that if the ligands contain a large group (marked in red) that cannot exist in the periphery of the catalyst, then the resulting complex can have higher symmetry that the ligands themselves. **b:** The original catalyst, $Rh_2(DOSP)_4$, has been proposed to be D_2 symmetric but this has not been verified experimentally. **c:** The phthalimido-derived catalyst $Rh_2(TCPTAD)_4$ (**54**) and $Rh_2(TPPTTL)_4$ (**55**) adopt a C_4 symmetric structure and not especially sterically demanding, capable of effective C–H functionalization of tertiary and secondary C–H bonds. **d:** The TPCP catalysts **56**-**61** are sterically demanding and depending on the substitution pattern can adopt different orientations, leading to complexes that are D_2, C_4 or C_2 symmetric.

The first two catalysts developed were Rh_2(*p*-BrTPCP)$_4$ (**56**) and Rh_2(*p*-PhTPCP)$_4$ (**57**) and these catalysts were prepared directly by a ligand exchange reaction with dirhodium tetraacetate.[60] X-ray crystallographic studies reveal that Rh_2(*p*-BrTPCP)$_4$ (**56**) adopts a D_2 symmetric structure in the solid state whereas in (*p*-PhTPCP)$_4$ (**57**), the biphenyl groups are on the same face but they are involved in π-stacking with each other, which breaks the C_4 symmetry and leads to a C_2 symmetric structure.[54] More recently, the 3,5-diaryl-TPCP catalyst **58**, formed by an 8-fold Suzuki coupling,[52] the

ortho-chloro-TPCP catalysts Rh_2(*o*-ClTPCP)$_4$ (**59**) and Rh_2(2-Cl-5-BrTPCP)$_4$ (**60**),[54,65] and the fully-*para*-substituted TPCP catalyst **61**, formed by 12-fold Suzuki coupling,[114] have been developed and they all display their own distinctive selectivity characteristics for C–H functionalization. These catalysts adopt different shapes and these greatly influence their site selectivity characteristics. The 3,5-diaryl TPCP catalyst **58** adopts an up-down-up down arrangement of the large 3,5-diaryphenyl groups leading to a D_2 symmetric structure, similar to Rh_2(*p*-BrTPCP)$_4$.[52] The *ortho*-chloro-phenyl group in Rh_2(*o*-ClTPCP)$_4$ (**59**) and Rh_2(2-Cl-5-BrTPCP)$_4$ (**60**) also cannot align in the periphery of the catalyst but in this case they adopt an up-up-up-up arrangement leading to a C_4 symmetric structure.[54,65] A distinctive feature of **59** and **60** is the induced axial chirality observed between the cyclopropane and the *ortho*-chloro-phenyl group, and consequently, adoption of the C_4-symmetric structure ensures that the *ortho*-chlorine groups are far away from each other. The 2-chloro-5-bromo catalyst **60** gives significantly higher asymmetric induction than the other *ortho*-chloro-TPCP catalysts because the bromine atoms are better positioned to help distinguish between the two faces of the rhodium-bound carbene. In the case of the fully-*para*-substituted TPCP catalyst **61** computational studies reveal that the biphenyl groups at the geminal carbon to the acid are all on the same face but are involved in π-stacking, analogous to Rh_2(*p*-PhTPCP)$_4$ (**57**), leading to a C_2 symmetric structure.[54]

The distinction between the Rh_2(TPCP)$_4$ catalysts and the more established catalyst Rh_2(DOSP)$_4$ has been demonstrated in reactions at electronically activated benzylic sites (Fig. 9).[61] The Rh_2(DOSP)$_4$ catalyzed reaction of aryldiazoacetate **63** with *p*-ethyltoluene (**62**) preferentially occurs at the secondary benzylic site to form **64** (Fig. 9a). In contrast, the Rh_2(p-PhTPCP)$_4$-catalyzed reaction of **62** with **63** preferentially occurs at the primary benzylic site to form **65**. The site selectivity and enantioselectivity could be further improved by using the trichloroethyl ester of the aryldiazoacetate as illustrated in the formation of **66** (Fig. 9b). A similar switch in site selectivity was observed in competition studies between tertiary and primary benzylic sites as illustrated in the formation of **67**. Rh_2(p-PhTPCP)$_4$ gave similar enhanced site selectivity for primary C–H bonds at other activated sites such as allylic and α to oxygen as shown

for **68**-**70**.[61-63] These studies revealed that the $Rh_2(TPCP)_4$ catalysts are much more sterically demanding than the original catalyst $Rh_2(DOSP)_4$ and that this steric requirement can be used to control site selectivity.

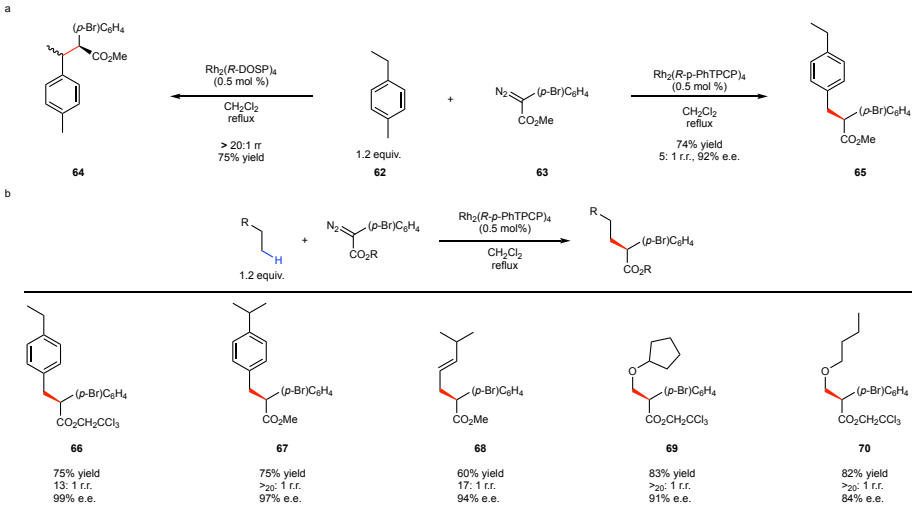

Figure 9. **Catalyst-controlled site selective functionalization at activated C–H bonds. a:** $Rh_2(DOSP)_4$ prefers C–H functionalization at secondary benzylic site whereas Rh_2(p-PhTPCP)$_4$ favors the primary benzylic site. **b:** representative examples of primary C–H functionalization at benzylic and allylic sites and adjacent to oxygen.

Site-Selective and Enantioselective C-H Functionalization of Unactivated C–H Bonds

With the advent of the new classes of catalysts, procedures have been developed to go beyond selective functionalization of electronically activated C–H bonds. Catalysts have been developed for site selective reactions to occur at either primary, secondary or tertiary C–H bonds that are unactivated.[52,53,114] The optimum catalyst for tertiary C–H functionalization is $Rh_2(TCPTAD)_4$.[53] The tertiary sites are the most electronically activated and $Rh_2(TCPTAD)_4$ is sufficiently small to be able to sterically access tertiary

C–H bonds as long as they are in the periphery of the structure (Fig. 10). The reaction can be applied not only to relative simple substrates as illustrated in the formation of **71**-**75** (Fig 10a), but also, to complex structures, containing a large number of different C–H bonds (Fig. 10b). Examples to illustrate the level of possible site selectivity are the reactions with cholesteryl acetate (**77**) and vitamin E (**79**). These substrates have multiple tertiary C–H bonds and electronically activated sites such as allylic and benzylic. Yet the C–H functionalization occurs cleanly at the most accessible tertiary site to form **78** and **80**, respectively. Detailed computational studies on the catalyst and the rhodium-carbene complex have been reported to explain the site-selectivity preference.[53] The catalyst adopts a relatively shallow bowl shape as can be seen in the X-ray structure of **54** (Fig. 8b). The tertiary C–H bonds are electronically preferred, and when the carbene is bound to the catalyst, the most accessible C–H tertiary bond is able to approach the carbene but other tertiary and even electronically activated C–H bonds in the center of the substrate are unable to do so. The carbene bound complex causes distortion of the pseudo-C_4 symmetric orientation of the ligands, due to π-stacking between the ligands and the carbene, and this is considered to be a key factor for the relatively high asymmetric induction generated in these reactions.

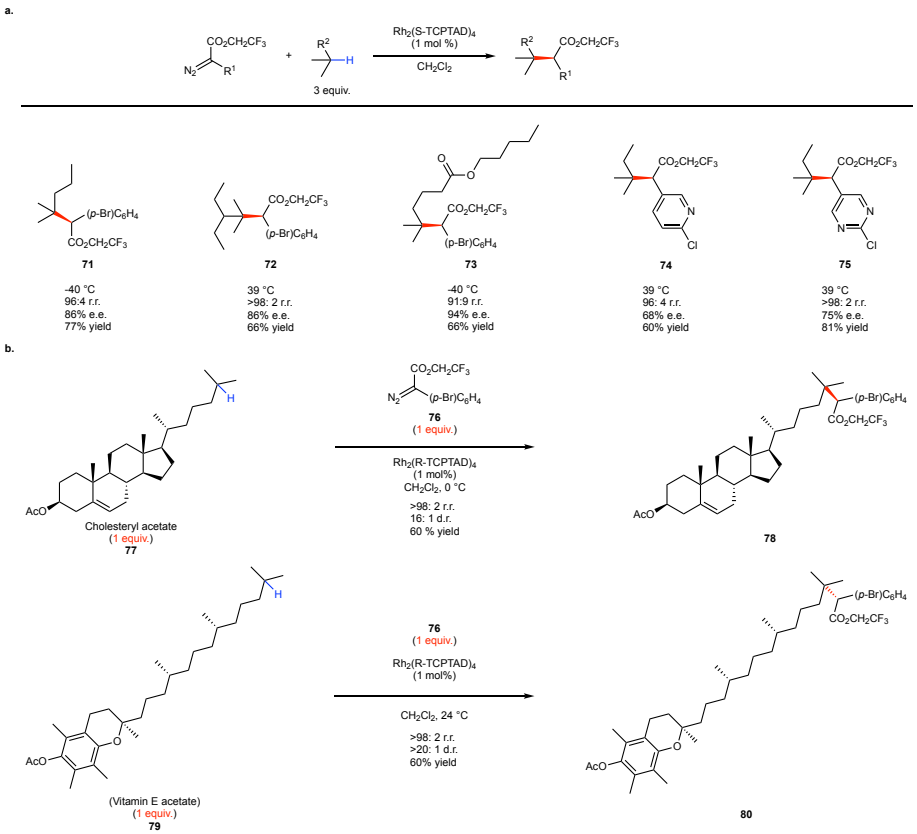

Figure 10. **Rh_2(TCPTAD)$_4$ catalyzed functionalization of tertiary C–H bonds. a:** representative simple substrates. **b:** application to the C–H functionalization of complex substrates, containing multiple C–H bonds.

The 3,5-diaryl-TPCP catalyst **58** was found to be a very effective for selective functionalization of unactivated secondary C–H bonds.[52] An impressive example of the selectivity possible with this catalyst is the reaction with pentane (Fig. 11). Even though pentane has two relatively similar methylene sites the reactions occurs cleanly at C-2 to form **81** with high levels of regioselectivity (the competing site is C1), diastereoselectivity and enantioselectivity. The reaction was applied to a variety of

substrates, as illustrated for the formation of **82-88**, and in all cases the reaction preferentially occurred at the most sterically accessible methylene site. Furthermore, these studies showed that the reaction at unactivated C–H bonds could be carried out in the presence of some functional groups such as esters, halides and silanes. The catalyst **58** adopts a D_2 symmetric structure (Fig. 8d) and thus, the bound carbene is also in a bowl-shaped cavity. In this case, however, the bowl is steeper than in the case of Rh_2(TCPTAD)$_4$, and consequently, it is difficult for any tertiary C–H bond or even secondary C–H bonds unless one of the substituents is methyl to approach the carbene bound to the catalyst.

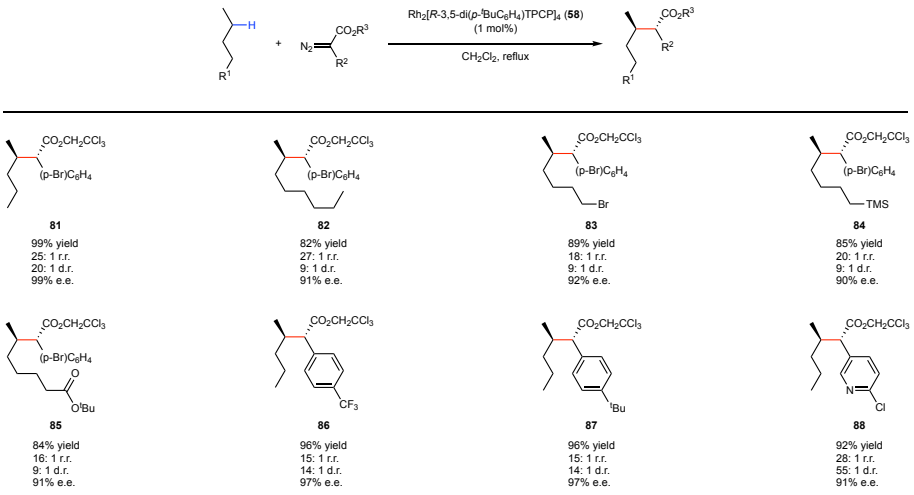

Figure 11. **C–H functionalization of the most sterically accessible secondary C–H bond.**

More recently, the *ortho*-chloro-TPCP catalysts, **59** and **60**, have been shown to be even more selective than 3,5-diaryl-TPCP catalyst **58** for unactivated secondary C–H bonds.[54] A good demonstration of the subtleties of steric control is the reaction with alkylbenzene derivatives (Fig. 12).[65] The two preferred sites for reaction are the electronically activated benzylic site and the most sterically accessible unactivated C–H bonds. In the Rh_2(TCPTAD)$_4$-catalyzed reaction, a strong preference for the benzylic site is observed. However, in the case of the reaction catalyzed by the *ortho*-chloro-

427 TPCP catalysts, the reaction preferentially occurs at the most accessible methylene site
428 (Fig. 12). Of the *ortho*-chloro-TPCP catalysts, Rh_2(2-Cl-5-BrTPCP)$_4$ (**60**) is the best for
429 high asymmetric induction, and its reactions can proceed with good regiocontrol,
430 diastereocontrol and enantiocontrol. The reaction was applied to a range of alkylarenes
431 and alkyl heteroarenes as illustrated in the representative examples to form **89**-**93** (Fig.
432 12a). In each case, the Rh_2(2-Cl-5-BrTPCP)$_4$ (**61**)-catalyzed reaction preferentially
433 occurred at the C2 site. The synthetic possibilities of this transformation have been
434 illustrated through the synthesis of the macrocyclic core of the cylindrocyclophanes
435 class of natural products (Fig. 12b). The scheme consists of two carbene-induced C–H
436 functionalization reactions, the first of which is an intermolecular to form **96** and the
437 second is intramolecular to form the macrocycle **98**, and between them they control the
438 stereochemistry at four new stereogenic centers.
439

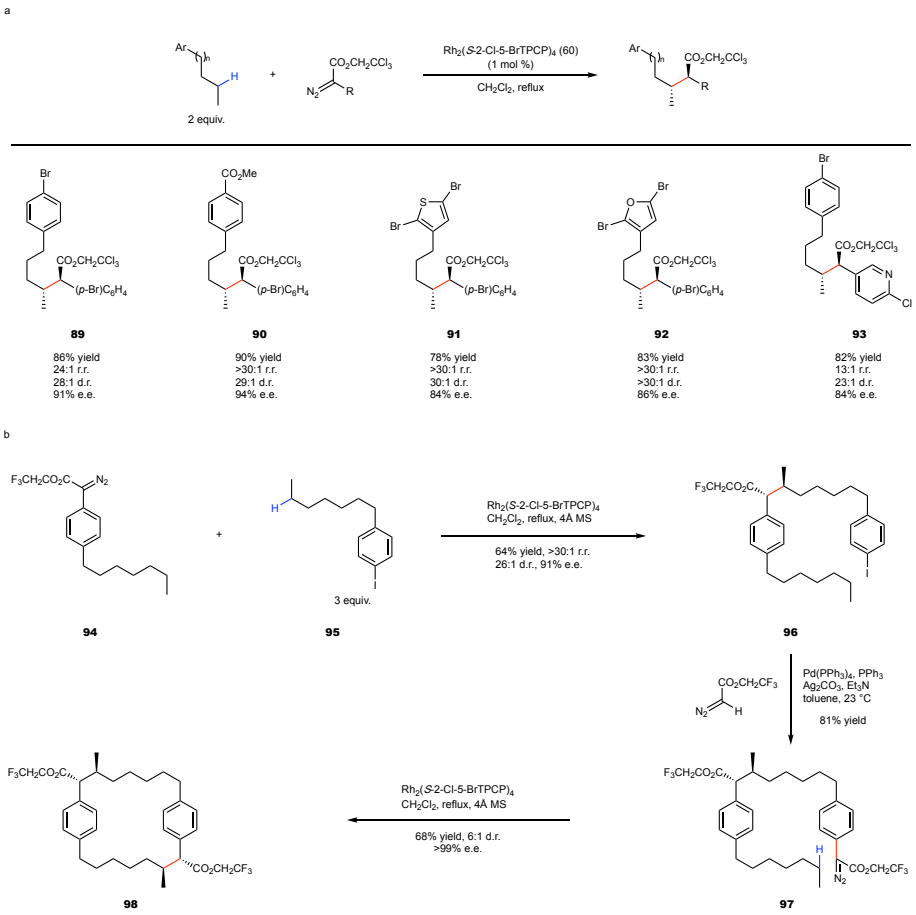

Figure 12. **Selective functionalization of unactivated C–H bonds in the presence of benzylic C–H bonds. a:** illustrative examples of functional group compatibility. **b:** demonstration of application to the synthesis of the macrocyclic core of the cylindrocyclophane natural products

The fully-*p*-substituted TPCP catalyst (**61**) is an even more bulky catalyst and is capable of blocking C–H functionalization at both tertiary and secondary sites. It leads to the preferential functionalization of primary C–H bonds, as illustrated in the simple substrates shown in Fig. 13a, generating the products **99**-**103** with exceptionally high

asymmetric induction.[114] Some illustrative examples of the potential of this chemistry are illustrated in the reaction with the chiral substrates **104** and **105** (Fig 13b). These substrates contain functional groups and even electronically activated C–H bonds, but the chemistry occurs cleanly at the most accessible primary C–H bonds. This catalyst gives very high asymmetric induction, and either diastereomeric series (**106** and **107** or **108** and **109**) can be generated, depending on which enantiomer of the catalyst **61** is used. The reaction can be extended to the steroid **110** and this substrate illustrates the subtleties of the catalyst control. The Rh-TCPTAD (**54**) reaction occurs at the most accessible tertiary C–H bond to form **111**. In contrast, the fully-p-substituted TPCP (**61**)-catalyzed reaction occurs at the most accessible primary C–H bond to from **112**.

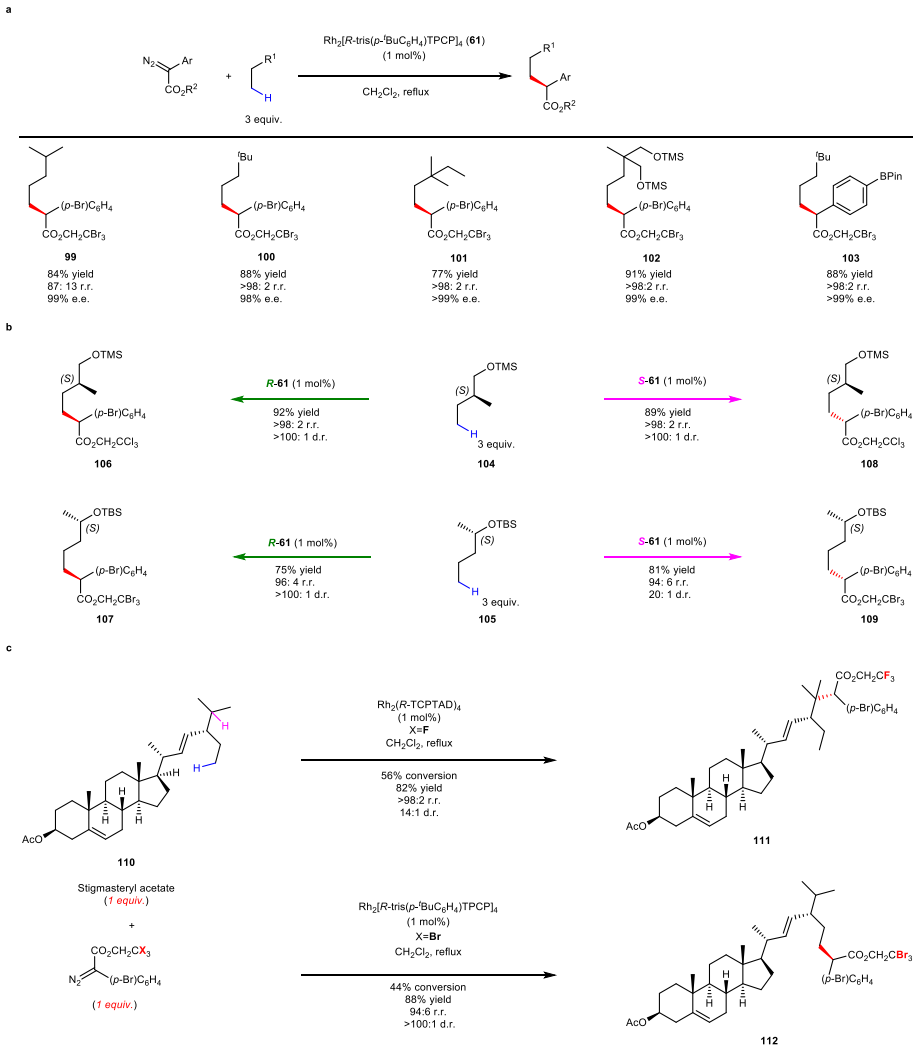

Figure 13. **Selective functionalization of unactivated primary C–H bonds. a:** reactions of relatively simple substrates. **b:** reactions of chiral substrates to form either diastereomeric series of the products. **b**: illustrative examples of functional group compatibility. **c:** catalyst-controlled site selective functionalization of a steroid.

Field Code Changed

The expanded tool-box of catalysts enables even more challenging C–H functionalization reactions to be envisioned. A notoriously challenging site-selectivity problem has been the C–H functionalization of alkyl-substituted cyclohexanes.[115-118] Even though it appears deceptively simple, the alkyl-substituted cyclohexane **113** actually has eleven different C–H bonds within the ring, ten of which would be secondary (Fig. 14a). Although, rich mixtures of products were formed with most of the dirhodium catalysts examined, Rh_2(*S*-TPPTTL)$_4$ (**55**) gave an exceptionally clean reaction.[64] The reaction with *tert*-butyl cyclohexane resulted in an effective desymmetrization to form cleanly the C-3 equatorial substituted product **116** with high regioselectivity, diastereoselectivity and enantioselectivity (Fig 14b). The reaction was applied to a variety of cyclohexane derivatives and some representative example of the types of products formed (**117**-**119**) are shown in Fig. 14c. Rh_2(*S*-TPPTTL)$_4$ (**55**) is not an exceptionally bulky catalyst at the carbene site but the sixteen phenyl groups on the ligands generate a well-defined wall at the periphery of the catalyst, which has a dramatic effect in how substrates can approach. As can be seen in Fig. 8b, the chiral pocket for Rh_2(*S*-TPPTTL)$_4$ (**55**) has a relatively deep bowl shape, and if the substrate is relatively big it needs to be pointing out of the bowl. This can be seen in the transition state model for *tert*-butylcyclohexane reaction (Fig. 14d) where the large *tert*-butyl group is pointing out of the catalyst. If attack had occurred at C4 of the cyclohexane, the *tert*-butyl group would be pointing into the wall of the catalyst, generating a very unfavorable steric clash.

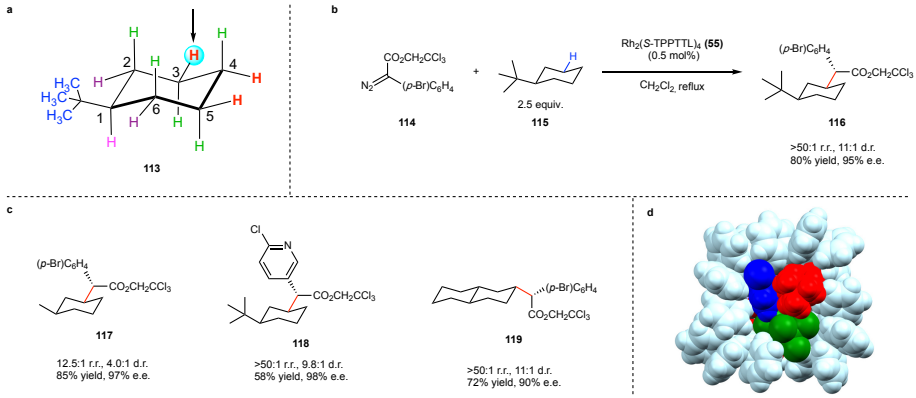

Figure 14. **Desymmetrization of alkyl-substituted cycloalkanes. a:** challenges associated with the reaction of alkylcycloalkanes. The system contains ten different secondary C–H bonds. **b:** C–H functionalization of *tert*-butylcyclohexane proceeds with exceptional site-selectivity and stereoselectivity. **c:** other representative examples, illustrating that heteroaryl derivatives and more elaborate cyclohexane derivatives can be used. **d:** computationally calculated transition state for the reaction of *tert*-butylcyclohexane at C3 with the rhodium bound carbene. The sixteen phenyl groups forming the wall of the catalyst are colored light blue. The trichloroethyl group of the carbene is green and the aryl group of the carbene is dark blue. The *tert*-butyl group of the cyclohexane is marked in red and is projecting out of the pocket. If attack had occurred at C4 of the cyclohexane, then, the *tert*-butyl group would have a steric clash with the wall of the catalyst.

The carbene C–H functionalization has been combined with other C–H functionalization strategies to rapidly generate synthetic complexity as illustrated in Fig. 15. A carbene C–H functionalization between **120** and **121** to form **122**, followed by a palladium catalyzed C–H oxidation on **123** offers a flexible entry to the dihydrobenzofuran **124** (Fig. 15a),[119] An intermolecular carbene C–H functionalization on the oxabicycle **125** generate **126** followed by an intramolecular C–H activation/Heck reaction generated the indoxamycin core **127** (Fig. 15b).[120]

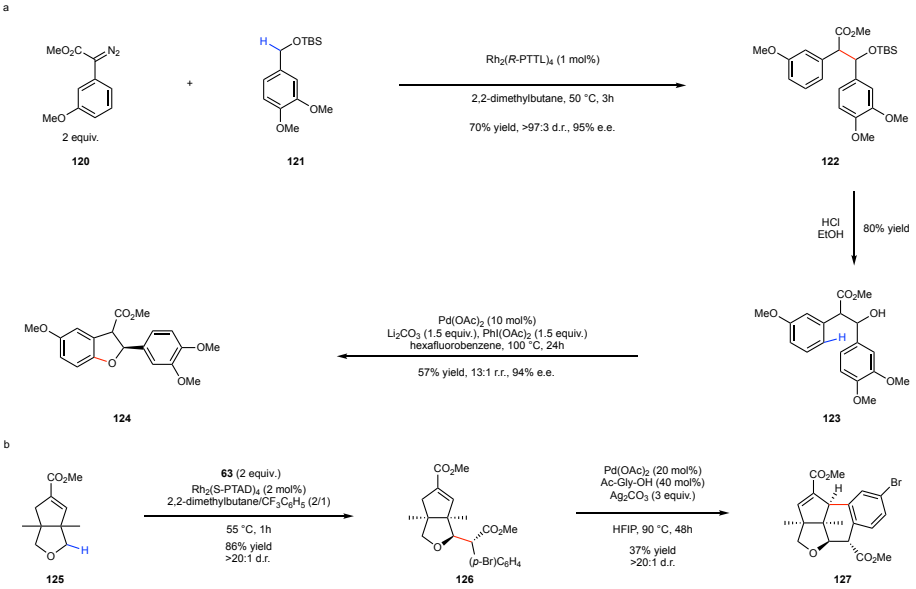

Figure 15. **Streamlined synthesis by sequential C–H functionalization reactions. a:** intermolecular carbene-induced intermolecular benzylic C–H functionalization followed by two palladium catalyzed C–H functionalizations. **b:** intermolecular carbene-induced intermolecular C–H functionalization followed by a palladium-catalyzed C–H activation/Heck reaction.

In conclusion, the rhodium-catalyzed reactions with donor/acceptor carbenes show that it is indeed possible to achieve site selective C–H functionalization at unactivated C–H bonds without resorting to the use of directing groups on the substrate. Indeed, a series of catalysts have been designed with different steric demands such that the site selectivity can be tailored by using the appropriate catalysts. The next challenge in this system is to incorporate electronic and coordinating influences into the catalyst design to achieve even more subtle control of site selectivity. Also, as the catalysts involve an expensive metal, conditions need to be developed so that the reactions can be conducted at extremely low catalyst loading, and ideally would be recyclable. The high levels of carbene-induced site-selectivities can currently only be achieved with donor/acceptor carbenes and dirhodium tetracarboxylate catalysts, a rather specialized

reagent/catalyst combination. This work, however, should inspire further attempts to discover other reactive systems capable of similar levels of site selectivity.

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H.M.L.D. is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued March 10, 2015). K. L. has no competing financial interests.

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