Catalyst-Controlled Site-Selective and Stereoselective Functionalization of Non-Activated Tertiary C–H Bonds

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The standard logic for the synthesis of complex organic compounds relies on controlling the reactions of the functional groups. In recent years, it has become recognized that a new logic for synthesis is possible by carrying out reactions on the previously considered "unreactive" C–H bonds instead of the functional groups.[1-3] One of the major challenges is to control the site-selectivity because most organic compounds have many similar C–H bonds. The most well-developed procedures so far rely on the use of substrate control, in which, the substrate has an inherently more reactive C–H bond than any of the other C–H bonds,[4] or contains a directing group[5-6] and/or the reaction is conducted intramolecularly[7] so that a specific C–H bond is favored. A more versatile but more challenging approach would be to use catalysts to control which site in the substrate is functionalized. Nature has demonstrated the power of such an approach with the C–H oxidation site-selectivity exhibited by p-450 enzymes, in which the enzyme scaffold causes a specific C–H bond to be functionalized by placing it close to the iron-oxo heme complex.[8] Several studies have been directing towards emulating the enzymatic site-selectivity with designed transition metal catalysts but achieving exceptionally high levels of site-selectivity is challenging.[9-11] We have recently demonstrated that a dirhodium catalyst is effective at the site-selective functionalization of the most accessible non-activated secondary C–H bonds by means of rhodium carbene-induced C–H insertion.[12] In the continuation of our studies to develop a tool-box of catalysts to achieve site-selectivity at different positions within the substrate, we now describe a dirhodium catalyst that is capable of exquisite site-selectivity at non-activated tertiary C–H bonds.

In previous studies, we have demonstrated that many substrates are capable of site-selective and stereoselective C–H functionalization under dirhodium tetracarboxylate-catalyzed reactions of donor/acceptor metal carbenes.[13-14] These carbenes are sufficiently reactive to insert into C–H bonds but have attenuated reactivity compared to

the more traditional carbenes lacking a donor group,[15-16] leading to better opportunities to achieve highly selective intermolecular C–H functionalization. In general, the tertiary C–H bond would be electronically favored with these carbenes, but this is counter-balanced by steric effects. Recently, we demonstrated that a new class of dirhodium catalysts with triphenylcyclopropanecarboxylate (TPCP] ligands are sterically demanding and can cause the reaction to favor more sterically accessible C–H bonds.[17-18] The highlight of this was the demonstration that Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$ is capable of site-selective C–H functionalization at the non-activated C2 position (the most accessible secondary C–H bond) of *n*-alkanes or terminally-substituted *n*-alkyl compounds (Figure 1).[12] In order to further advance the concept of catalyst-controlled C–H functionalization, we have now explored the possibility of identifying a less sterically demanding catalyst that would be capable of achieving high site- and enantioselectivity at tertiary C–H bonds. We had attempted such reactions previously,[19] but the results for both the site-selectivity and enantioselectivity were relatively poor. Here, we demonstrate that by using a modified carbene reagent and Rh_2(*S*-TCPTAD)$_4$[20-21] as catalyst, we can achieve exceptional site-selectivity at the most accessible tertiary C–H bonds for a range of substrates.

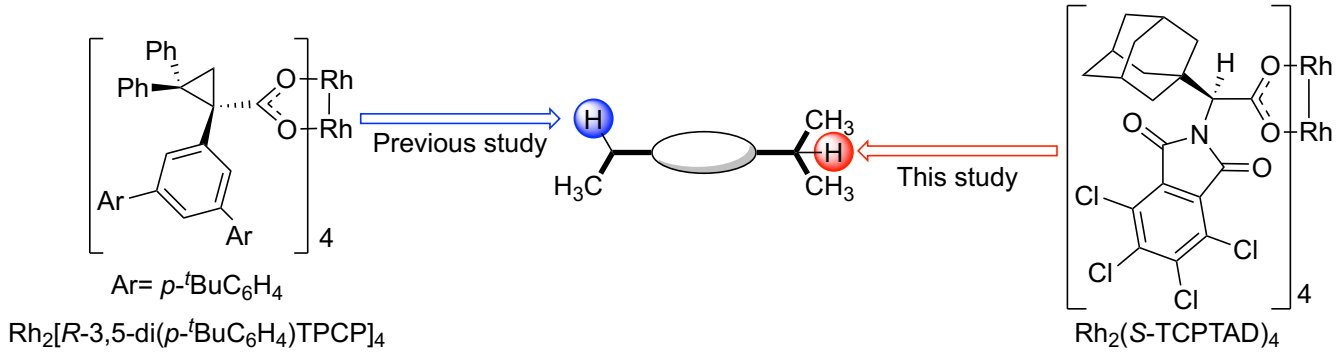
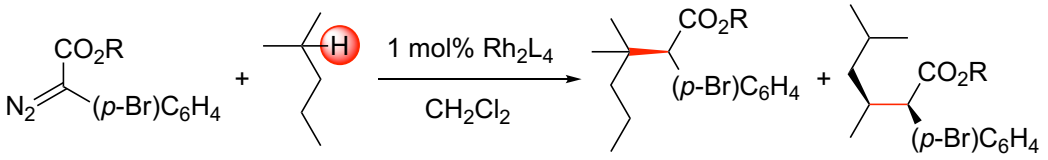


Figure 1 **Catalyst-controlled site-selective C–H functionalization**. Previous study revealed that Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$ is capable of site-selective C–H functionalization at the most sterically accessible secondary site. This study showed that a less sterically encumbered dirhodium catalyst, Rh_2(*S*-TCPTAD)$_4$, results in site-selective C–H functionalization at the most sterically accessible tertiary site.

The reaction of methyl aryldiazoacetate (**1a**) with 2-methylpentane (Figure 2) was used as the reference reaction to evaluate catalysts for tertiary C–H bond selectivity. 2-Methylpentane has eight distinct C–H bonds (three diastereotopic sites) but the most reactive sites with our standard catalysts are the tertiary C-H bond and the most accessible methylene site. As previously reported in related systems, the venerable catalyst Rh_2(*R*-DOSP)$_4$, preferentially reacts at the tertiary C-H bond (85:15 ratio favoring **2a** over **3a**) but the enantioselectivity is low (43% e.e.). As expected the bulky Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$,[12] preferentially reacts at methylene site over the tertiary site (65:35 r.r.) but the overall yield was low (23%), presumably because the methylene sites are sterically compromised as they are too close to the isopropyl group. The two phthalimido–derived catalysts, Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-PTAD)$_4$, prefer the tertiary C-H bond (74:26 ratio) but again with low enantioselectivity

(34% e.e.). Considerable improvement was obtained with tetrachloro derivatives of Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-PTTL)$_4$; both Rh_2(*S*-TCPTTL)$_4$ and Rh_2(*S*-TCPTAD)$_4$ performed well with Rh_2(*S*-TCPTAD)$_4$ giving the slightly better ratio (87:13) and enantioselectivity (79% e.e.). A slight improvement in the site-selectivity was obtained on using trihaloethyl esters instead of methyl esters,[12] with the trifluoroethyl derivative **1d** giving the highest site-selectivity and yield. In order to further improve the selectivity, the effect of reaction temperature was examined. The regioselectivity and enantioselectivity of the reaction improved when the reaction was conducted at lower temperatures, and the reaction conducted at -40 °C generated **2d** with 96:4 r.r. and 86% e.e. However, the yield decreased at lower temperature, presumably because it became harder to achieve a clean reaction with the non-activated C–H bonds. Therefore, CH_2Cl_2 under reflux was used as the standard conditions to explore the scope of the reaction and lower temperature optimization studies were conducted when needed.



1a-d 3 *equiv.* **2a-d** **3a-d**

Catalyst	**1**	R	condition [a]	yield (%) [b]	r.r. (**2**:**3**)	e.e. (**2**, %)
Rh_2(*R*-DOSP)$_4$	**1a**	CH_3	39 °C	83	85:15	-43
Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$	**1a**	CH_3	39 °C	23	35:65	-10
Rh_2(*S*-PTAD)$_4$	**1a**	CH_4	39 °C	50	74:26	-34
Rh_2(*S*-PTTL)$_4$	**1a**	CH_3	39 °C	80	74:26	-33
Rh_2(*S*-TCPTTL)$_4$	**1a**	CH_3	39 °C	86	86:14	77
Rh_2(*S*-TCPTAD)$_4$	**1a**	CH_3	39 °C	89	87:13	79
Rh_2(*S*-TCPTAD)$_4$	**1b**	CH_2CCl_3	39 °C	84 (74) [c]	89:11	84
Rh_2(*S*-TCPTAD)$_4$	**1c**	CH_2CBr_3	39 °C	88 (77)	87:13	77
Rh_2(*S*-TCPTAD)$_4$	**1d**	CH_2CF_3	39 °C	92 (83)	90:10	77
Rh_2(*S*-TCPTAD)$_4$	**1d**	CH_2CF_3	24 °C	85 (77)	91:9	80
Rh_2(*S*-TCPTAD)$_4$	**1d**	CH_2CF_3	0 °C	85 (79)	93:7	82
Rh_2(*S*-TCPTAD)$_4$	**1d**	CH_2CF_3	-10 °C	82 (78)	95:5	84
Rh_2(*S*-TCPTAD)$_4$	**1d**	CH_2CF_3	-40 °C	80 (77)	96:4	86
Rh_2(*S*-TCPTAD)$_4$	**1d**	CH_2CF_3	-78 °C	65 (65)	96:4	80

Figure 2 **Catalyst optimization for site-selective functionalization of tertiary C–H bonds**. The regioisomeric ratios (r.r.) were determined by ^{1}H NMR spectra of the crude reaction mixtures and the enantiomeric excess (e.e.) were determined by chiral HPLC. The optimum system for high tertiary site-selectivity, enantioselectivity and yield is Rh_2(*S*-TCPTAD)$_4$ as catalyst and the trifluoroethyl derivative **1d** as the carbene precursor**.** [a] The boiling point of CH_2Cl_2 is 39 °C. [b] Combined yield of **2** and **3**. [c] Isolated yield of **2** shown in the parenthesis. See Supporting Information for the structure of the catalysts and complete experimental details.

Having developed the optimum conditions for tertiary C–H functionalization, the scope of the reaction was then examined with various substrates using the trifluoroethyl derivative **1d** as the carbene source (Figure 3). Highly selective C–H functionalization of the tertiary sites could be achieved in good yields (66-93% yield) and enantioselectivity (77-86% e.e.) with a range of alkane substrates (Figure 3, **4**-**10**). The system is sensitive to the steric environment around the tertiary site because when the tertiary site becomes crowded another more accessible tertiary or secondary site is prefered (Figure 3, **7** and **8**). The reaction could be conducted with substrates containing other functionalities such as bromo and ester functional group (Figure 3, **11**-**13**). The reactions have been primarily carried out with the *p*-bromophenyl derivative **1d** as the carbene precursor, and the products would be readily diversified either by ester modification or metal-catalyzed cross coupling.[12] The reaction can be extended to carbene precursors containing other aryl functionalities and heterocycles (Figure 3, **14**-**17**). Most notable are the examples with the pyridyl and pyrimidyl heterocycles (**14** and **15**), which illustrate that substrates with relatively nucleophilic sites are still effective. As illustrated in the reactions of **5**, **6** and **13**, the site-selectivity and enantioselectvity (87-94% ee) can be improved if the reactions are conducted at lower temperatures, but under these conditions the yields tend to be somewhat decreased (see supporting information for detail).

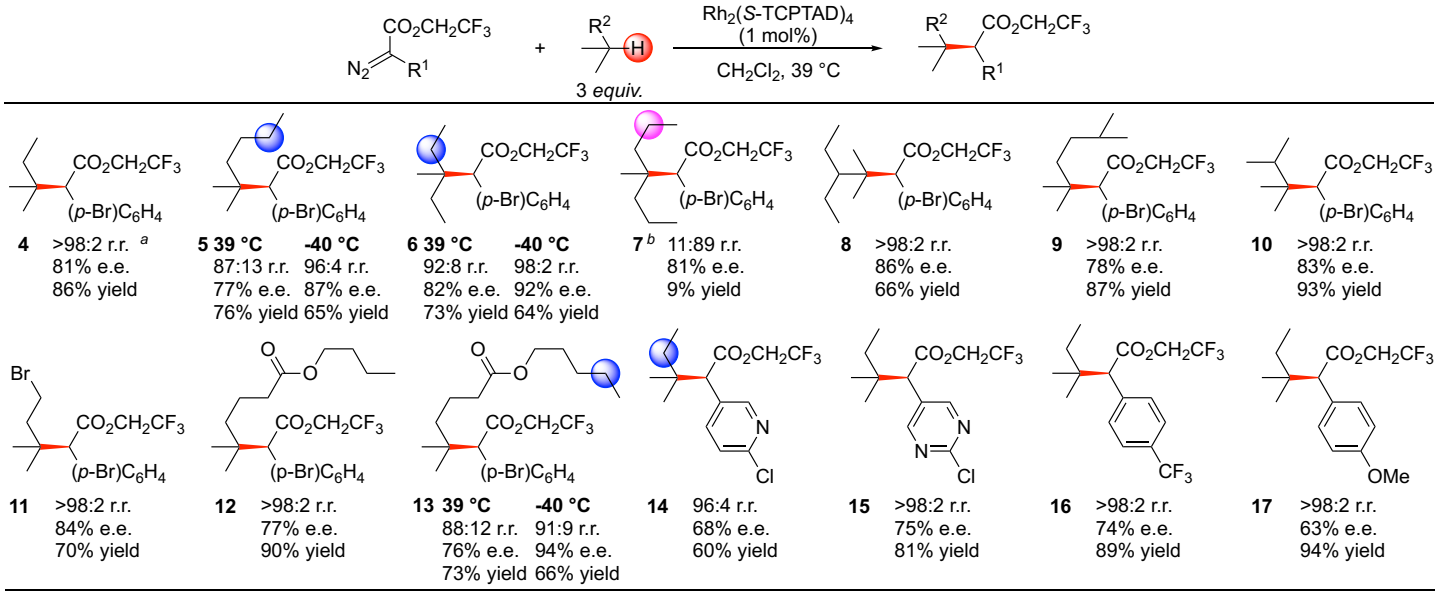
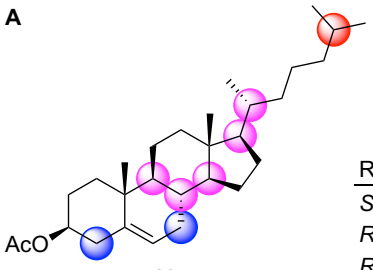


Figure 3 **Substrate scope of the Rh_2(*S*-TCPTAD)$_4$-catalyzed C–H functionalization**. Compounds **4-10** illustrate the effect of modifications to the alkane structure. Compounds **11-13** illustrate the effect of bromo and ester functionality. For compound **5**, **6**, **13** and **14**, certain amount of the C–H functionalization occurred at the most accessible secondary position (marked in blue) of the substrates was also observed. Compound **14-17** illustrate that aryl groups with either electron withdrawing or donating substituents and heteroaryl functionalities are compatible. [a] >98:2 r.r.: no signal of the other regioisomer was observed in the ^{1}H NMR spectra. [b] For 4-methylheptane, the most accessible secondary C–H bond (marked in pink) functionalization product was the major product (79% yield). See Supporting Information for complete experimental details.

A major test for site-selective C–H functionalization is the determination if control can be achieved in elaborate substrates. Therefore, the reactions of some representative natural products were examined (Figure 4). The C–H functionalization of steroids has been of great historical significance because many seminal studies involving radical chemistry have been reported using appropriate directing groups to achieve site-selectivity.[22-23] Therefore, we examined the reaction with the acetyl derivative of cholesterol as a substrate (Figure 4A). As the natural products are valuable substrates, these reactions were conducted with a 1:1 ratio of the substrate to diazo (**1d**). Cholesteryl acetate (**18**) is a challenging substrate because it has forty-eight different C–H bonds including six tertiary C–H bonds (marked in pink and red) and four allylic C–H bonds (marked in blue). Even so, the reaction proceeded cleanly and gave a high yield of the C–H functionalization product **19** derived from reaction at the most accessible tertiary C–H bond marked in red at the end of the steroid side chain. A particularly intriguing feature of this transformation is the total lack of reactivity at the steroid nucleus, especially the electronically activated allylic positions. The stereochemistry of the reaction is under catalyst control as Rh_2(*R*-TCPTAD)$_4$ and Rh_2(*S*-TCPTAD)$_4$ favored opposite diastereomers by a diastereomeric ratio (d.r.) of 11:1. When the reaction was conducted at lower temperatures, the diastereoselectivity could be improved (16:1 d.r.), but the yield was lower (60 %).

The site-selectivity was also examined in the case of vitamin E acetate (**20**) (Figure 4B). This is also a challenging substrate for C–H functionalization because it contains fifty-two C–H bonds, eleven benzylic C–H bonds (marked in blue) and three tertiary C–H bonds (marked in pink and red). Once again, the reaction was selective for the most accessible tertiary C–H bond (marked in red). Rh_2(*R*-TCPTAD)$_4$ generated the product **21** in 84% yield, whereas Rh_2(*S*-TCPTAD)$_4$ generated the opposite diastereomer in 64% yield. Both reaction produced the same d.r. as 11:1, indicating that the formation of the new stereogenic center during the reaction is under catalyst control. When the reaction was conducted at room temperature (24 °C), the diastereoselectivity was improved to >20:1 d.r.. Phytyl pivalate (**22**) is also a challenging substrate because it has three tertiary C–H bonds (marked in pink and red) and seven allylic C–H bonds (marked in blue). Allylic C–H bonds would be expected to be electronically activated and in this case, are not sterically constrained within a ring system. Even so, the reaction was still selective for the most accessible tertiary C–H bond to form **23** over the allylic position to form **24**. Under refluxing conditions the ratio of the products was about 3:1 but when the reaction was conducted at room temperature it improved to 89:11, albeit with somewhat decreased yield.

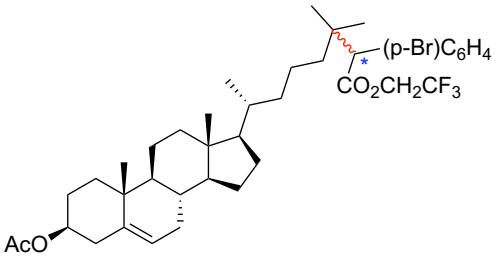
A



18
Cholesteryl acetate
(1 *equiv.*)

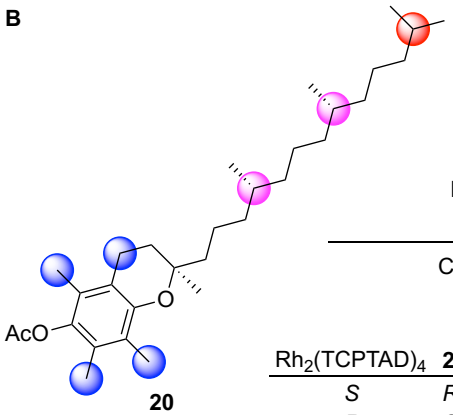
1d
(1 *equiv.*)
$Rh_2(TCPTAD)_4$
CH_2Cl_2, condition

$Rh_2(TCPTAD)_4$	**18**	condition	r.r.	d.r.	yield (%)
S, 1 mol%	*R*	39 °C	>98:2	11:1	78
R, 1 mol%	*S*	39 °C	>98:2	11:1	86
R, 0.1 mol%	*S*	39 °C	>98:2	9:1	83
R, 1 mol%	*S*	24 °C	>98:2	13:1	80
R, 1 mol%	*S*	0 °C	>98:2	16:1	60



19

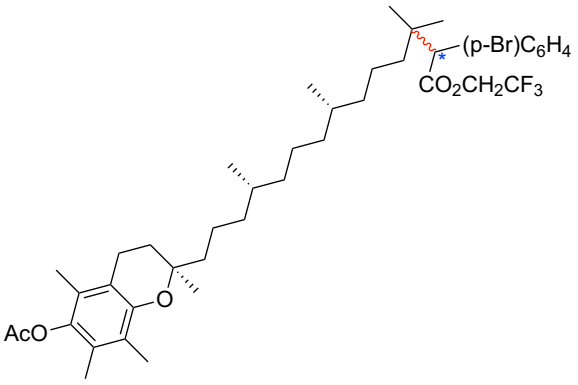
B



20
(Vitamin E acetate)
(1 *equiv.*)

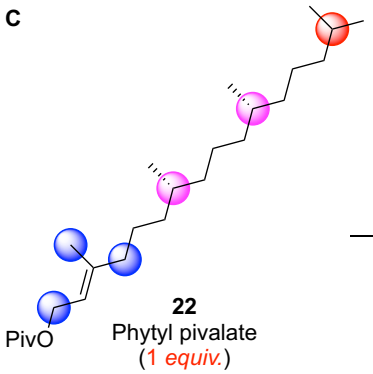
1d
(1 *equiv.*)
$Rh_2(TCPTAD)_4$
(1 mol%)
CH_2Cl_2, condition

$Rh_2(TCPTAD)_4$	**20**	condition	r.r.	d.r.	yield (%)
S	*R*	39 °C	>98:2	11:1	64
R	*S*	39 °C	>98:2	11:1	82
S	*R*	24 °C	>98:2	>20:1	60



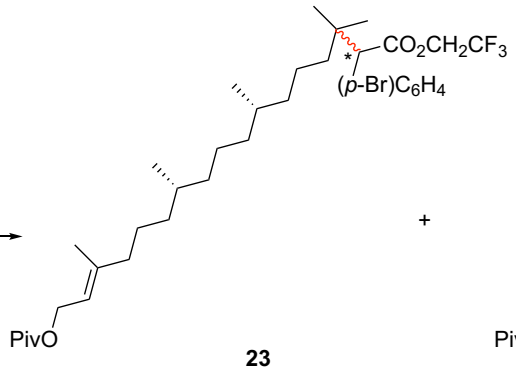
21

C



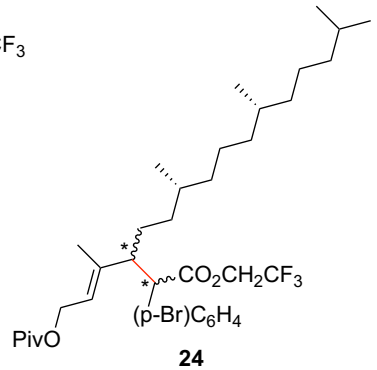
22
Phytyl pivalate
(1 *equiv.*)

1d
(1 *equiv.*)
$Rh_2(TCPTAD)_4$
(1 mol%)
CH_2Cl_2



23

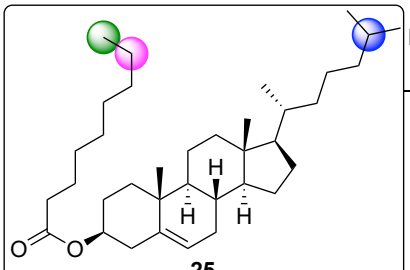
+



24

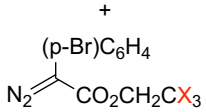
$Rh_2(TCPTAD)_4$	**22**	condition	r.r. (**23**:**24**)	d.r. (**23**)	yield (**23**, %)	yield (**24**, %)
S	*R*	39 °C	77:23	11:1	67	20
R	*S*	39 °C	78:22	12:1	69	21
R	*S*	24 °C	89:11	12:1	52	6

D



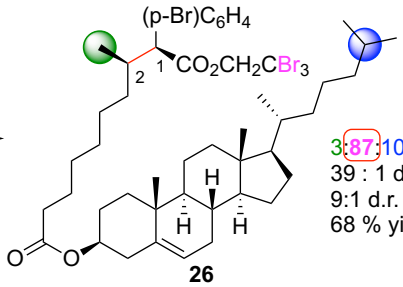
25
Cholesteryl pelargonate (1 *equiv.*)

+



1c or 1d
(1 *equiv.*)

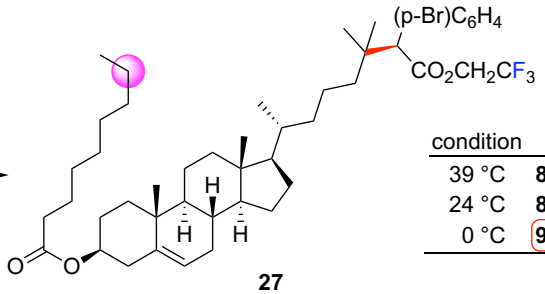
$Rh_2[R\text{-}3,5\text{-di}(p\text{-}^t\text{BuC}_6H_4)\text{TPCP}]_4$
(1 mol%)
1c, CH_2Cl_2, reflux



26

3:87:10 r.r.
39 : 1 d.r (C1/steroid)
9:1 d.r. (C1/C2)
68 % yield

$Rh_2(R\text{-TCPTAD})_4$
(1 mol%)
1d, CH_2Cl_2



27

condition	r.r.	d.r.	yield (%)
39 °C	**87**:13	6:1	74
24 °C	**89**:11	>20:1	68
0 °C	**92**: 8	>20:1	65

Figure 4 **Exploration of the site-selectivity of Rh_2(*R*-TCPTAD)$_4$- and Rh_2(*R*-TCPTAD)$_4$-catalyzed C–H functionalization in complex substrates. A**: The reaction occurs exclusively at the tertiary C–H bond (marked in red) of cholesteryl acetate (**18**). The absolute configuration of the new stereogenic center generated in **19** was shown by X-ray crystallography to be *R* when Rh_2(*S*-TCPTAD)$_4$ was used. The absolute configuration of other compounds are tentatively assigned in analogy with the assumption of all substrates would preferentially attacked the *Re* face of the Rh_2(*S*-TCPTAD)$_4$ bound carbene to generate an *R* configuration stereogenic center. **B**: The reaction occurs exclusively at the tertiary C–H bond (marked in red) of vitamin E acetate (**20**). **C**: The reaction occurs selectively at the tertiary C–H bond (marked in red) of phytyl pivalate (**22**) with certain competition at the secondary allylic position. **D**: The Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$-catalyzed reaction with cholesteryl pelargonate (**25**) reacts at the most sterically accessible secondary C–H bond to form **26**. The Rh_2(*R*-TCPTAD)$_4$-catalyzed reaction results in site-selective C–H functionalization at the most sterically accessible tertiary site to from **27**.

The ultimate goal of this program would be to have a collection of catalysts to control site-selectivity at will. In order to demonstrate this concept, the influence of Rh_2(*R*-TCPTAD)$_4$ and Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$, on the functionalization of cholesteryl pelargonate (**25**) was examined (Figure 4D). Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$ has been shown to be selective for the most sterically accessible secondary C–H bond, whereas Rh_2(*R*-TCPTAD)$_4$ was designed to be selective for the most sterically accessible tertiary C–H bonds. In the Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$-catalyzed reaction of the 2,2,2-tribromoethyl 2-(4-bromophenyl)-2-diazoacetate (**1c**), the methylene C–H functionalization product **26** became the dominant product by a ratio of 87:10:3. The second most prevalent isomer was the tertiary C–H insertion product formed at the tertiary position of the other branched alkyl chain (marked as blue); and the minor regioisomer was the primary C–H insertion product formed at the end of the *n*-alkyl chain (marked as green). The formation of **26** generates two new stereogenic centers but the major diastereomer is produced with high asymmetric induction (39:1 d.r.). In contrast, the Rh_2(*R*-TCPTAD)$_4$-catalyzed reaction of the 2,2,2-trifluoroethyl 2-(4-bromophenyl)-2-diazoacetate (**1d**) gave an 87:13 ratio favoring the tertiary C–H functionalization product **27** over the methylene position at the terminal side of the *n*-alkyl chain (marked as pink). The regioisomers were readily separated and **22** was isolated in 68% yield from the Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$-catalyzed reaction and **23** was isolated in 74% yield from the Rh_2(*R*-TCPTAD)$_4$-catalyzed reaction. When the Rh_2(*R*-TCPTAD)$_4$-catalyzed reaction was conducted at 0 °C, the site selectivity was improved to 92:8 r.r. and the diastereoselectivity was >20:1 dr.

These studies demonstrate that Rh_2(*S*-TCPTAD)$_4$ can achieve unprecedented site-selectivity for the most accessible tertiary C–H bonds. A dramatic difference is seen between the adamantyl catalysts Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-TCPTAD)$_4$, in which the former, lacking the chlorine functionality, gives poor site-selectivity as well as relatively low and opposite enantioselectivity. Previously, computational and experimental studies[24-29] on the related *tert*-butyl catalysts Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-TCPTTL)$_4$ developed by Hashimoto[30] showed that the tetrachloro functionality rigidifies the structure and generates a chiral crown shape with all phthalimido groups

on the same face of the catalyst.[31] Our crystallographic and computational studies of the structural features of Rh_2(TCPTAD)$_4$ give some insight about why it is such an effective catalyst. An X-ray structure of Rh_2(*R*-TCPTAD)$_4$ showed that the catalyst adopts a structure with all the phthalimido groups on the same side but is slightly distorted from a perfect C_4 symmetric structure (see supporting information for detail). Computational studies on Rh_2(*S*-TCPTAD)$_4$ revealed that the catalyst adopts a similar orientation to the X-ray structure (Figure 5). Charette[24] has proposed that the rigidification of Rh_2(*S*-TCPTTL)$_4$ is due to chlorine oxygen bridging bonds stabilizing the system. Certainly, in the X-ray structure of Rh_2(*R*-TCPTAD)$_4$ an oxygen of one phthalimido group is close to the chlorine of another group, but the distance is too far (3.382-4.184 Å) for a normal chlorine oxygen bonding interaction (2.963-3.020 Å).[32] A recent X-ray crystallographic study by Ghanem[33] on Rh_2(*S*-PTAD)$_4$ concluded that the adamantyl groups are unable to fully block the carbene from binding to one face of the catalyst, but this argument was made on the basis of limited data, the observation of solvent coordination to both faces of Rh_2(*S*-PTAD)$_4$ in the crystal structure. In the case of Rh_2(*R*-TCPTAD)$_4$, it is clear from the X-ray structure and the computational studies that the gap for the approach of the diazo compound to the rhodium is much wider on the face with the phthalimido groups compared to the face with the adamantyl groups (16.2 Å versus 7.8 Å). Therefore, we conclude that there is a major difference in the steric environment between the two faces of the catalyst with the rhodium face containing the phthalimido groups being much more accessible.

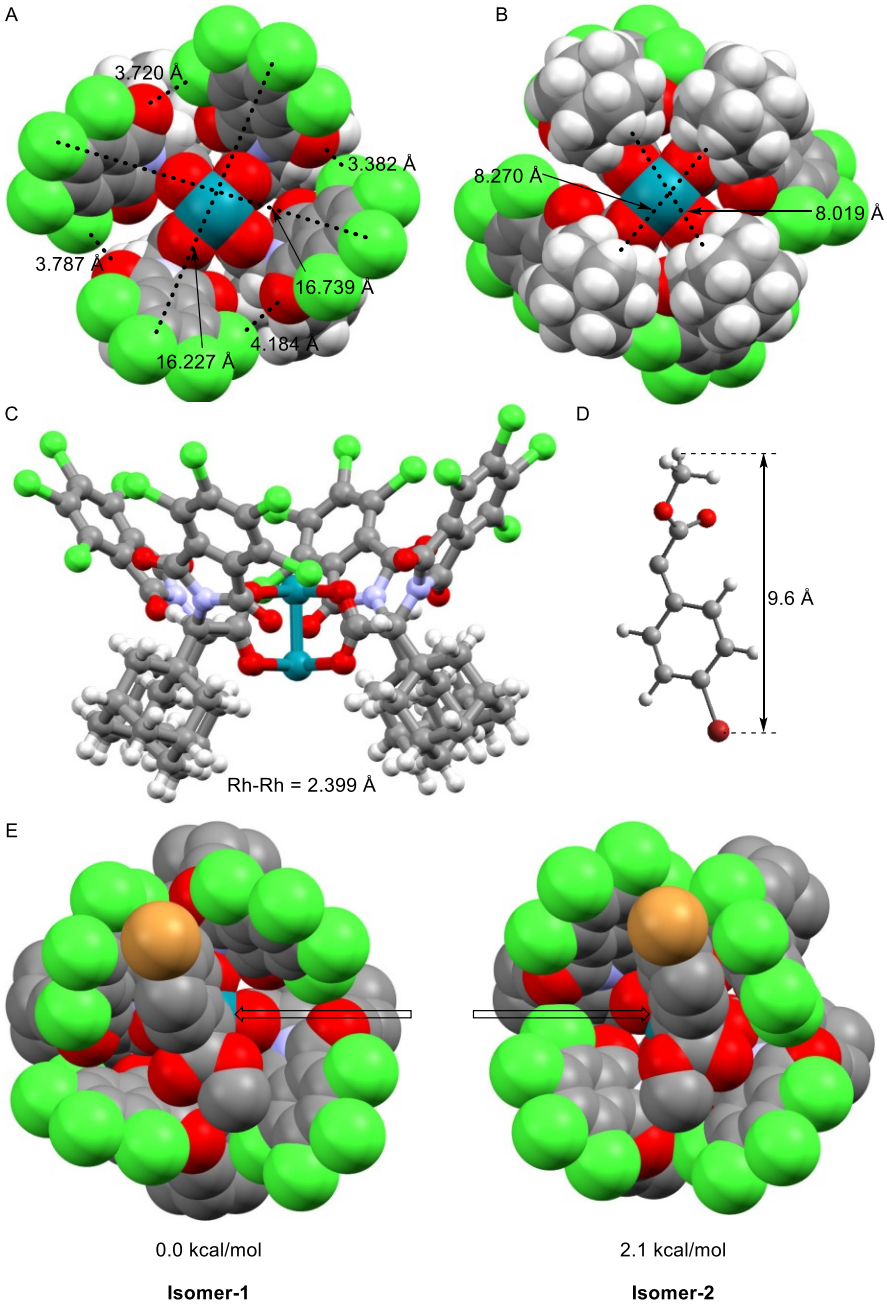


Figure 5 **Computational study of Rh_2(*S*-TCPTAD)$_4$ and the corresponding carbene structures.** A-C: calculated structure of Rh_2(*S*-TCPTAD)$_4$. A: a top view shows the chiral bowl with the dimensions of 17.5 Å and 16.2 Å. B: a bottom view shows the gap dimensions are 7.9 Å and 7.8 Å. C: a side view shows four tetrachlorophthalimido groups on the top face and four adamantyl groups on the bottom face. D: the dimensions of carbene intermediate (9.6 Å) indicates that the carbene will preferentially bind to the top face. E: two energetically most stable isomers of Rh_2(*S*-TCPTAD)$_4$[(*p*-Br-C_6H_4)C(COOMe)] carbene. In both structures, one tetrachlorophthalimido groups bent to engage in π-π stacking interaction with the carbene aryl ring. Isomer-1 is 2.1 kcal/mol more stable than isomer-2. Assuming substrate attack on the open side opposite to the π-π stacking interaction, isomer-1 would predict that the carbene *Re* face would be attacked, leading to the formation of the *R* configuration of the new stereogenic center, as was observed in the Rh_2(*S*-TCPTAD)$_4$ catalyzed reaction to form **19**.

The next level of analysis needs to explain how the catalyst, containing four blocking groups phthalimido groups controls the favored approach of the substrate to one face of the carbene, which would lead to an enantioselective reaction. Fox has conducted computational studies on the reactions of Rh_2(*S*-PTTL)$_4$-catalyzed reactions with α-alkyl-α-diazoesters, and suggested that depending on the size of the alkyl group it adopts a certain orientation within the pocket.[26] Our computational analysis of the Rh_2(*S*-TCPTAD)$_4$-donor/acceptor carbene complex revealed that even though Rh_2(*S*-TCPTAD)$_4$ is quite rigid there is a change in the ligand orientation when the carbene is bound to the complex, in which one of the phthalimido group bends forward to π-stack with the aryl ring of the carbene. Irrespective of where the carbene is positioned or the orientation of the ester group, the same face of the carbene is involved in the most favorable π-stacking interaction (by 2.1 kcal/mol), leading to a preferred attack at the *Re* face of the carbene. Even through the carbene is accessible, the substrate will still need to enter the pocket to react with the carbene; this would explain why the Rh_2(*S*-TCPTAD)$_4$ carbene complex react selectively at only the most accessible tertiary C–H bond.

These studies demonstrate that highly site-selective catalyst-controlled C–H functionalization of non-activated tertiary C–H bonds is a viable process. The dirhodium catalyst Rh_2(*S*-TCPTAD)$_4$ adopts a close C_4 symmetric shape with a relatively shallow pocket, enabling tertiary C–H bonds to approach the rhodium-bound carbene on the phthalimido face of the dirhodium complex. These results complement the outcome of Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$-catalyzed reaction, which results in site-selective functionalization at the most accessible secondary C–H bonds. The level of site-selectivity between different tertiary C–H bonds displayed by Rh_2(*S*-TCPTAD)$_4$ is unprecedented, and demonstrates that the concept of having a series of catalysts to tune site-selectivity is a viable proposition.

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

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The crystal data can be obtained free of charge from The Cambridge Crystallographic Data center at www.ccdc.cam.ac.uk. Deposition number: 1535046. Any correspondence and requests for materials should be addressed to H.M.L.D.

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