LETTER

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Site-selective and stereoselective functionalization of unactivated C–H bonds

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The laboratory synthesis of complex organic molecules relies heavily on the introduction and manipulation of functional groups, such as carbon–oxygen or carbon–halogen bonds; carbon–hydrogen bonds are far less reactive and harder to functionalize selectively. The idea of C–H functionalization, in which C–H bonds are modified at will instead of the functional groups, represents a paradigm shift in the standard logic of organic synthesis[1–3]. For this approach to be generally useful, effective strategies for site-selective C–H functionalization need to be developed. The most practical solutions to the site-selectivity problem rely on either intramolecular reactions[4] or the use of directing groups within the substrate[5–8]. A challenging, but potentially more flexible approach, would be to use catalyst control to determine which site in a particular substrate would be functionalized[9–11]. Here we describe the use of dirhodium catalysts to achieve highly site-selective, diastereoselective and enantioselective C–H functionalization of *n*-alkanes and terminally substituted *n*-alkyl compounds. The reactions proceed in high yield, and functional groups such as halides, silanes and esters are compatible with this chemistry. These studies demonstrate that high site selectivity is possible in C–H functionalization reactions without the need for a directing or anchoring group present in the molecule.

We have demonstrated that catalyst-controlled site selectivity is possible in the dirhodium-catalysed intermolecular reactions of donor/acceptor carbenes with relatively activated C–H bonds, such as those at benzylic and allylic positions[12] and α to oxygen[13]. The carbene-induced C–H functionalization is initiated by a hydride transfer event, and consequently the reaction is favoured at sites capable of stabilizing a build-up of positive charge; thus, tertiary C–H bonds are electronically preferred (Fig. 1a)[14]. However, the dirhodium–carbene

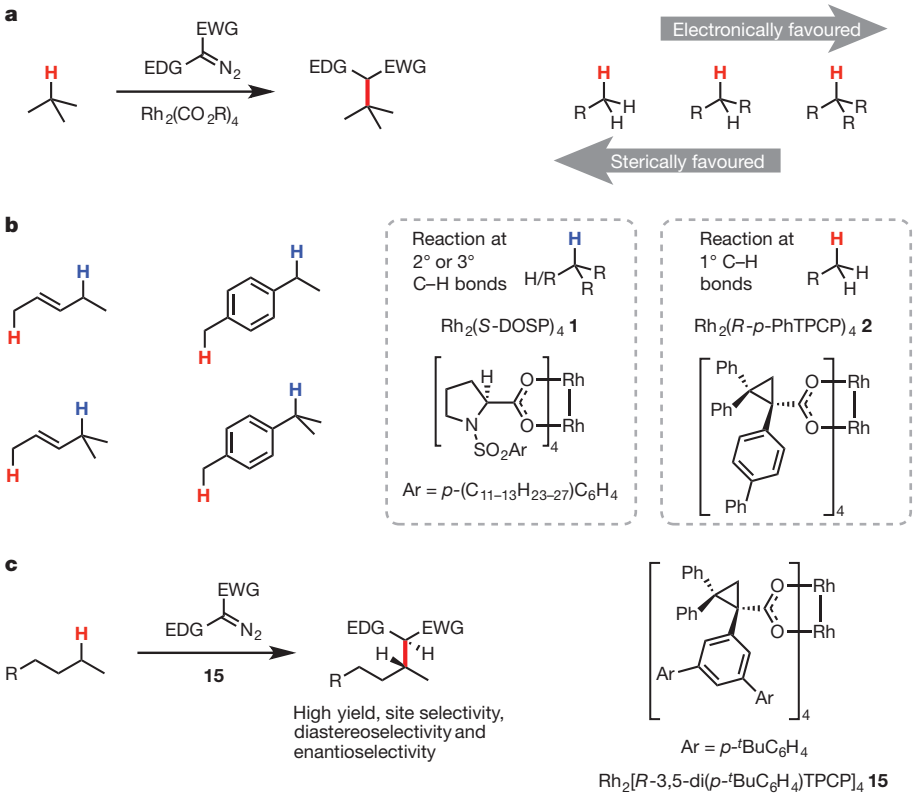

Figure 1 | Site-selective C–H functionalization by donor/acceptor carbenes. a, Site-selectivity trend in dirhodium-catalysed C–H functionalization by donor/acceptor carbenes is controlled by a delicate balance between steric and electronic effects. **b**, Previous studies showed that site selectivity at activated C–H bonds could be controlled by the nature of the catalyst. $Rh_2(S\text{-DOSP})_4$ prefers functionalization at secondary and tertiary C–H bonds, whereas $Rh_2(R\text{-}p\text{-PhTPCP})_4$ prefers functionalization at primary C–H bonds. **c**, This study demonstrates that highly site-selective and stereoselective C–H functionalization of unactivated C–H bonds can be achieved with the new catalyst $Rh_2[R\text{-}3,5\text{-di}(p\text{-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$.

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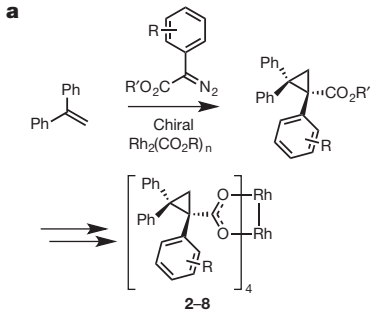
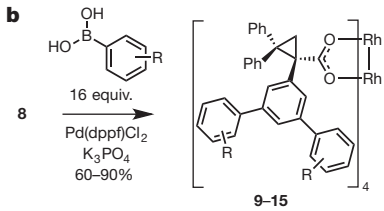


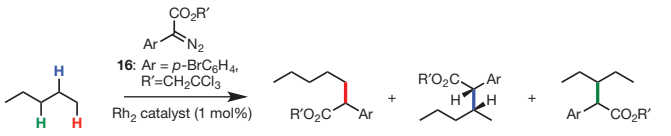
R group		Catalyst name
p-Ph	**2**	Rh_2(*R*-*p*-PhTPCP)$_4$
p-Br	**3**	Rh_2(*R*-*p*-BrTPCP)$_4$
p-^{t}Bu	**4**	Rh_2(*R*-*p*-^{t}BuTPCP)$_4$
p-NO_2	**5**	Rh_2(*R*-*p*-NO_2TPCP)$_4$
p-CF_3	**6**	Rh_2(*R*-*p*-CF_3TPCP)$_4$
3,5-diCF_3	**7**	Rh_2(*R*-3,5-di-CF_3TPCP)$_4$
3,5-diBr	**8**	Rh_2(*R*-3,5-di-BrTPCP)$_4$



R group		Catalyst name
H	**9**	Rh_2(*R*-3,5-di-PhTPCP)$_4$
3,5-diCF_3	**10**	Rh_2[*R*-3,5-di(3,5-di$CF_3C_6H_3$)TPCP]$_4$
3,5-diCH_3	**11**	Rh_2[*R*-3,5-di(3,5-di$CH_3C_6H_3$)TPCP]$_4$
3,5-diPh	**12**	Rh_2[*R*-3,5-di-(3,5-diPhC_6H_3)TPCP]$_4$
p-Ph	**13**	Rh_2[*R*-3,5-di(*p*-PhC_6H_4)TPCP]$_4$
p-CF_3	**14**	Rh_2[*R*-3,5-di(*p*-$CF_3C_6H_4$)TPCP]$_4$
p-^{t}Bu	**15**	Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$

Figure 2 | Synthesis of TPCP carboxylate dirhodium catalysts. **a**, Original synthesis of TPCP carboxylate dirhodium catalysts. **b**, New synthesis of TPCP carboxylate dirhodium catalysts using palladium-catalysed cross-coupling on a preformed dirhodium complex. See Supplementary Information for the synthetic details.

complex is sterically demanding, so on steric grounds the primary C–H bond would be preferred. We have shown that by altering the steric nature of the catalyst, the site selectivity of C–H functionalization can be dictated in these activated substrates from a preference for the secondary or tertiary C–H bonds using the established dirhodium catalyst Rh_2(*S*-DOSP)$_4$ (**1**), to the primary C–H bond with the more sterically encumbered triarylcyclopropanecarboxylate catalyst Rh_2(*R*-*p*-PhTPCP)$_4$ (**2**) (Fig. 1b)[12,13]. Even though intermolecular C–H functionalization with metal carbene intermediates has been a longstanding challenge[4,9,14–16], the metal-catalysed reactions of *n*-alkanes with the more traditional acceptor carbene derived from ethyl diazoacetate has been explored, furnishing mixtures of products, controlled to some extent by the nature of the catalyst, with primary C–H insertion preferred when employing larger and more electrophilic catalysts[9,15]. The reaction of *n*-alkanes with the donor/acceptor carbene derived from methyl phenyldiazoacetate showed even greater preference for primary C–H insertion when a bulky rhodium porphyrin catalyst was used[17]. We describe a new triarylcyclopropanecarboxylate catalyst, Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**15**), that can achieve highly regio-, diastereo- and enantioselective C–H functionalization at the unactivated C2 position of *n*-alkanes or terminally substituted *n*-alkyl compounds (Fig. 1c).



Rh_2 catalyst	Site selectivity (**17**:**18**:**19** ratio)	Diastereoselectivity (d.r. for **18**)	Enantioselectivity (e.e.% for **18**)	Combined yield (%)
1	n.d.:29:1	3:1	82	98
2	1:2:n.d.	14:1	92	97
3	1:4:n.d.	6:1	91	98
4	1:5:n.d.	15:1	92	95
5	13:36:1	3:1	79	82
6	1:7:n.d.	5:1	94	87
7	1:11:n.d.	8:1	81	92
8	1:26:n.d.	5:1	78	95
9	1:22:n.d.	5:1	96	95
10	1:26:n.d.	26:1	92	96
11	1:16:n.d.	29:1	99	95
12	1:5:n.d.	16:1	97	98
13	1:9:n.d.	10:1	89	91
14	1:30:n.d.	8:1	91	95
15	1:25:n.d.	20:1	99	99

Figure 3 | Catalyst optimization studies. Evaluation of the dirhodium TPCP catalysts for the C–H functionalization of pentane. The optimum catalyst for high site selectivity at C2, diastereoselectivity, enantioselectivity and yield is catalyst **15**, Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$. The standard reaction was carried out in refluxing pentane with 1 mol% catalyst loading. See Supplementary Information for experimental details. n.d., not determined.

Having discovered that the triphenylcyclopropane carboxylate (TPCP) catalysts can exert considerable influence on the site selectivity of donor/acceptor carbenes with activated substrates for C–H functionalization[12,13], we decided to explore whether these catalysts could achieve selective intermolecular C–H functionalization of unactivated C–H bonds. To initiate this project, we prepared a series of chiral dirhodium triarylcyclopropane carboxylate catalysts. The first series of dirhodium catalyst derivatives, **2**–**8**, was prepared by our standard method, which involves asymmetric cyclopropanation, hydrolysis of the resulting ester to the carboxylic acid, enantiomer enrichment, and ligand exchange (Fig. 2a)[12]. When it became clear that catalysts **7** and **8** with a 3,5-disubstituted phenyl group had promising properties (see later), we developed a new approach for catalyst diversification by conducting an eightfold palladium-catalysed cross-coupling reaction on the fully formed 3,5-dibromo complex **8** to generate a second series of catalysts (**9**–**15**) (Fig. 2b). The new approach has broad utility because the catalysts are made from a single enantiomerically pure complex, avoiding the variable yields observed in ligand exchange reactions when the ligands become sterically congested and streamlining the whole process.

The initial evaluation of the different catalysts was conducted using *n*-pentane as the test substrate. Even though *n*-pentane is a simple substrate, the challenge of C–H functionalization of this system is apparent when one considers the subtlety required in achieving a site-selective reaction. Recent studies have shown that donor/acceptor carbene reactions tend to proceed better when the trichloroethyl ester is used instead of the methyl ester[13]. Hence, 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**16**) was used as the carbene precursor for the initial evaluation (Fig. 3). The *N*-sulfonylprolinate Rh_2(*R*-DOSP)$_4$ (**1**) is the standard chiral catalyst that has been used for most of the C–H functionalization chemistry of donor/acceptor carbenes, but its reaction with *n*-alkanes has not been reported[14,16]. Therefore, it was promising to observe that when Rh_2(*R*-DOSP)$_4$ was used as the catalyst, **16** reacted with pentane to give only **18** and **19**. The products derived from insertion into methylene C–H bonds were observed in a high overall yield and good site selectivity (29:1

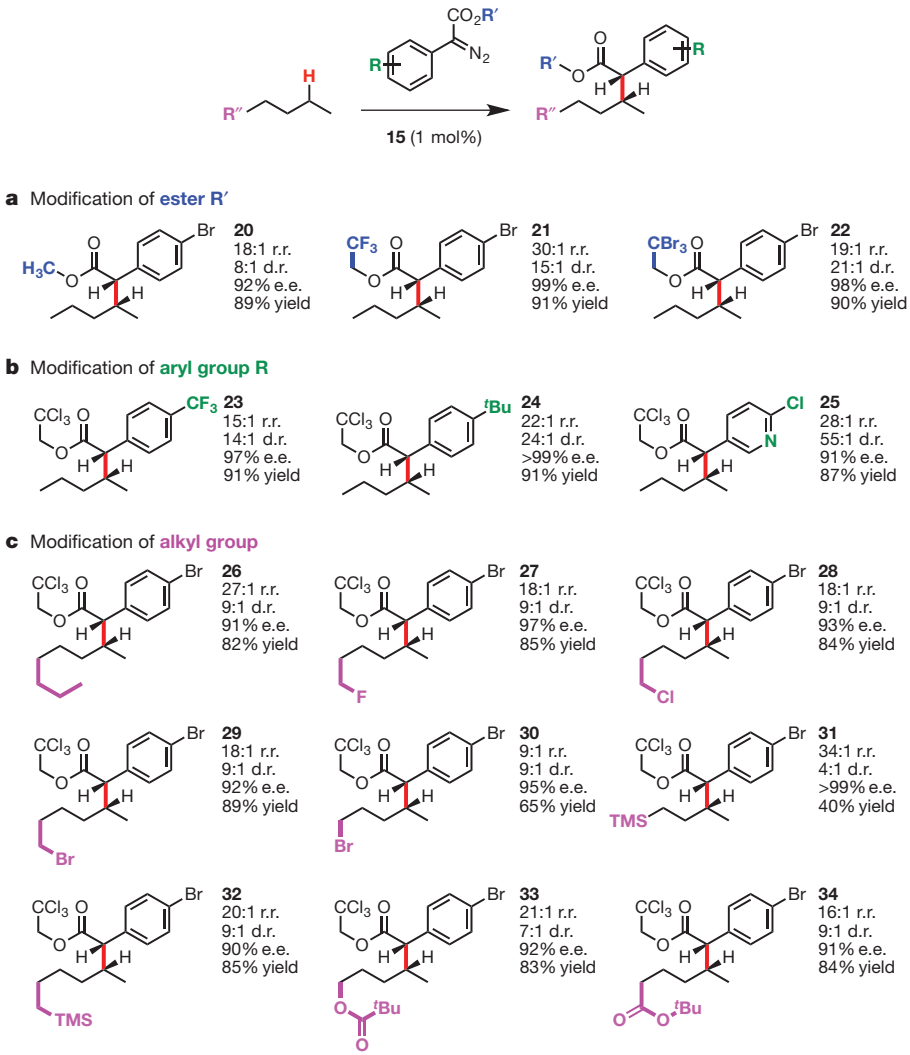


Figure 4 | C–H functionalization of alkanes and substituted *n*-alkanes. a–c, Evaluation of the scope of $Rh_2[R\text{-}3,5\text{-di}(p\text{-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$-catalysed C–H functionalization of pentane and substituted *n*-alkanes. **a**, Compounds **20–22** illustrate the effect of the ester group. **b**, Compounds **23–25** illustrate the effect of modifications to the donor group. **c**, Compounds **26–34** illustrate the effect of the alkyl substituent. Reactions with pentane were conducted in pentane as solvent. Reactions with substituted alkanes were conducted with 3 equiv. of the substituted alkane with dichloromethane as solvent. See Supplementary Information for complete experimental details.

regioisomeric ratio (r.r.) of C2 to C3). The enantiocontrol was also reasonable (82% enantiomeric excess (e.e.)), but the diastereocontrol was moderate (3:1 diastereomeric ratio (d.r.)). Even though the reaction displayed exceptional site selectivity considering that both reacting sites are methylene sites with only a slight difference in steric environment, we recognized that the competition with the internal methylene sites would probably lead to complex mixtures when longer *n*-alkanes were used as substrates. Therefore, we examined the reaction with the triarylcyclopropanecarboxylate catalysts, as previous studies had shown that these catalysts behave as more sterically encumbered catalysts and drive the C–H functionalization site selectivity towards the less sterically hindered positions[12,13]. This expected trend was followed by the *p*-substituted catalysts **2–6**, which generated a considerable amount of the C1 insertion product **17** in addition to C2 **18** (1:3 to 1:7 ratio), without any C3 insertion product **19** being formed. The diastereo- and/or enantioselectivity of the C–H functionalization with catalysts **2–6** is influenced by the nature of the aryl substituent on the ligand, with the *p*-Ph derivative **2** giving the highest level of enantioselectivity (92% e.e.) and the *p*-tert-butyl derivative **4** giving the highest diastereoselectivity (15:1 d.r.). When the reaction was extended to the 3,5-di-CF_3-substituted catalyst **7**, we expected increased formation of the C1 insertion product. However, this was not the case, and a strong preference for C2 over C1 functionalization (11:1 ratio) was observed without any formation of the C3 functionalized product **19**. Furthermore, the diastereoselectivity and enantioselectivity for the formation of **18** was quite high (8:1 d.r., 81% e.e.). A similar effect was also seen with the 3,5-di-Br-substituted catalyst **8**, which gave an even higher C2 to C1 ratio (26:1), but slightly lower levels of diastereoselectivity and enantioselectivity (5:1 d.r., 78% e.e.). On the basis of these results, the study was extended to the 3,5-diaryl-substituted catalysts **9–15**, prepared from the cross-coupling strategy on the dirhodium complex **8**. Many of these catalysts gave a strong preference for C–H functionalization at C2 over C1 (up to 30:1), some generated the C2 product **18** with exceptional diastereoselectivity (up to 29:1 d.r.), and all gave high levels of enantioselectivity (89–99% e.e.). The optimum catalyst in terms of overall performance was the 3,5-di(*p*-*tert*-butylphenyl)phenyl-derived catalyst **15**, $Rh_2[R\text{-}3,5\text{-di}(p\text{-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$, which gave the C2 product **18** in 99% overall yield with high site selectivity favouring C2 over C1 (25:1 ratio), diastereoselectivity (20:1 d.r.) and enantioselectivity (99% e.e.).

The $Rh_2[R\text{-}3,5\text{-di}(p\text{-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$-catalysed reactions with pentane were then examined with a variety of donor/acceptor carbene precursors (Fig. 4a, b). All of the reactions proceeded in high yield (87–91%) and with high levels of enantioselectivity (91% to >99% e.e.). The first three substrates were chosen to examine the nature of the ester substituent (Fig. 4a). The methyl ester derivative

was quite effective in the C–H functionalization to form **20**, but overall its performance in terms of yield and selectivity was lower than the trichloroethyl ester **16**. Larger alkyl esters are best avoided when attempting intermolecular C–H functionalization reactions, as intramolecular C–H functionalization will tend to compete. However, the trifluoroethyl and tribromoethyl esters are effective ester groups and perform comparatively to the trichloroethyl derivatives to form **21** and **22**. In specific cases, the trifluoroethyl group may be worth considering further because the site selectivity for C2 for **21** is better than with the trichloroethyl derivative (30:1 versus 25:1 r.r.), although the diastereoselectivity is lower (15:1 versus 20:1 d.r.). The reaction was extended to a series of phenyl-substituted carbenes (Fig. 4b). They all performed well in these reactions, but the site selectivity and diastereoselectivity were somewhat reduced for the *p*-trifluoromethyl derivative **23** (14:1 C2 versus C1, 15:1 d.r.). The potential breadth of utility of the C–H functionalization is illustrated with a pyridine system, which is an effective substrate for this chemistry. Indeed, the C–H functionalization product **25** was produced with the highest diastereoselectivity to date (55:1 d.r.).

As the selectivity competition is between the C2 and C1 positions, the ratio would be expected to remain about the same for longer-chain alkanes. This was indeed the case for the reaction with *n*-octane, which generated **26** with a site selectivity of 27:1 r.r., slightly enhanced compared with pentane (Fig. 4c). One of the challenges of C–H functionalization is to conduct the reactions in the presence of functional groups. Having established that Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$ is an exceptional catalyst for C–H functionalization of *n*-pentane, we performed an initial evaluation to determine if the reaction can be conducted in the presence of terminally substituted *n*-alkyl compounds, such as alkyl halides, silanes and esters (Fig. 4c). These reactions were conducted with the bromophenyl derivative **16** and 3 equiv. of the substrate in dichloromethane as solvent under reflux conditions. Alkyl halides are versatile functionality in organic synthesis but as the dirhodium carbene is highly electrophilic we considered whether they would be compatible with the C–H functionalization chemistry. Indeed, 1-bromo-, 1-chloro- and 1-fluorohexane were found to be good substrates for the C–H functionalization. In all three cases, the levels of enantioselectivity for the formation of **27**–**29** were high (92–97% e.e.), the site selectivity for the methylene C–H bond was 18:1 but the diastereoselectivity was somewhat diminished (9:1 d.r.). The reaction with 1-bromopentane to form **30** also proceeded with high enantioselectivity (95% e.e.) but the yield was only 65% and the site selectivity was only 9:1 r.r. This result may indicate that the bromine is displaying a long-range inductive effect, which slightly deactivates the C2 position. Such a characteristic could become a useful controlling element in more complex systems. *n*-Alkyl silanes were considered to be interesting substrates because electronically the C–H bonds β to silicon should be electronically activated towards C–H functionalization. The steric influence dominates in these reactions, and preferred formation of the regioisomers **31** and **32** was observed once again. Another functional group that is compatible with this chemistry is an ester, as illustrated in the formation of **33** and **34**, again with strong preference for functionalization of the methylene C–H bond. These studies demonstrate that the Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$-catalysed reactions of donor/acceptor carbenes have a strong preference for functionalization of the methylene site at the C2 position of alkanes and terminally substituted alkanes. Presumably, the C–H functionalization at the methyl group is less favoured on electronic grounds, whereas the steric environment around the catalyst is sufficient to distinguish between the methylene sites. All of the reactions proceed with high enantioselectivity (90% to >99% e.e.), but the diastereoselectivity is variable (4:1–9:1 d.r.).

Further evidence to help understand why Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$ is such an effective catalyst was obtained from computational and X-ray crystallographic studies. We and others have previously shown that the presence of four identical chiral ligands around the dirhodium core can result in a catalyst with higher symmetry than the ligands themselves[18–22]. Computational studies on Rh_2[*S*-3,5-diPhTPCP]$_4$ revealed that the 3,5-disubstituted pattern disfavours

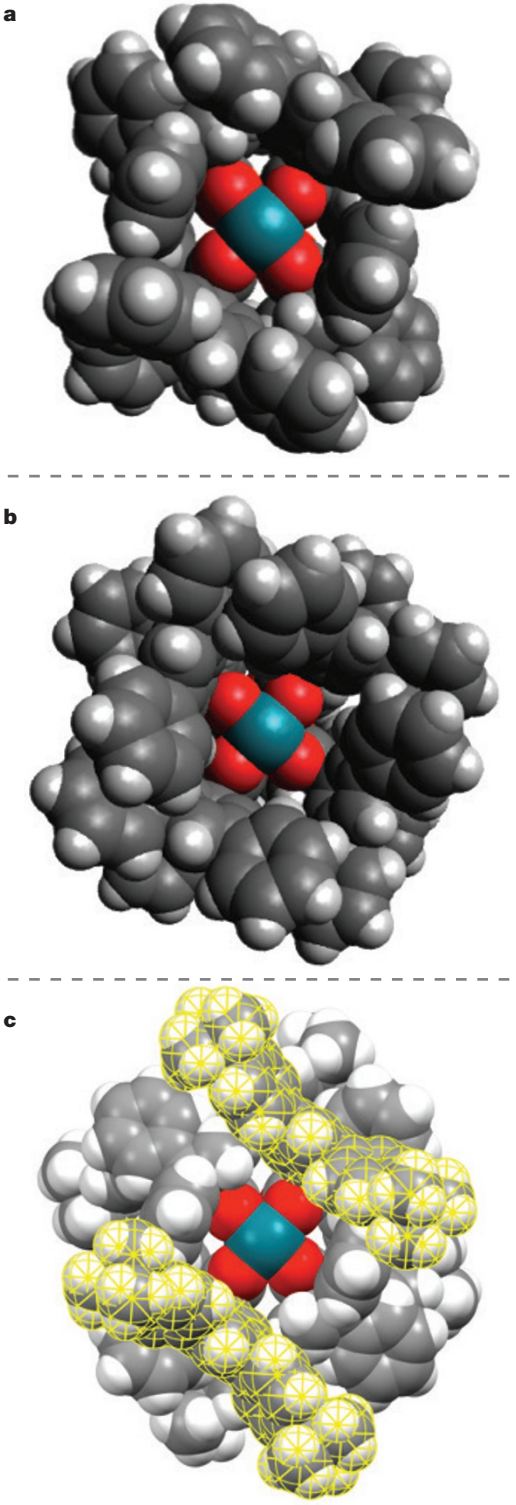


Figure 5 | Structural information about the dirhodium catalysts. **a**, Computational structure of the α, β, α, β form of Rh_2[*S*-3,5-diPhTPCP]$_4$. **b**, Computational structure of the α, α, α, α form of Rh_2(*S*-3,5-diPhTPCP)$_4$ (5.0 kcal mol^{-1} less stable than the α, β, α, β form). **c**, X-ray crystal structure of Rh_2[*S*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$, in which the two 3,5-di(*p*-^{t}BuC_6H_4)C_6H_3- groups on the top face are highlighted in yellow. For clarity, the diethyl ether molecules that were coordinated to the rhodium in the crystal structure have been removed. See the Supplementary Information for complete experimental details.

the existence of two adjacent 3,5-diphenylphenyl groups on the same face of the dirhodium catalyst. Hence the preferred orientation of the catalyst is the α, β, α, β-orientation (Fig. 5a), which is favoured over the α, α, α, α-orientation (Fig. 5b) by 5.0 kcal mol^{-1}. The results from our computational studies were consistent with data from X-ray crystallographic analysis. An X-ray crystal structure of **15** as the corresponding bis(diethyl ether) complex was solved, and the complex was found to adopt the α, β, α, β-orientation (Fig. 5c). This arrangement is D_2 symmetric, which causes both faces of the dirhodium catalyst to be the same, and limits the number of possible orientations of the carbene when it binds to the dirhodium core. The C–H functionalization has been proposed to proceed via a concerted asynchronous mechanism in which the hydrogen of the C–H bond first approaches the carbene site[23]. It has been previously demonstrated that when C–H insertion into methylene C–H bonds occurs, the reactions can be highly diastereoselective as long as there is considerable size differentiation between the two other groups at the methylene site[14]. The size difference between a methyl and an *n*-propyl group, as in the case of pentane, would not be expected to be sufficient to cause high levels of diastereoselectivity using the more traditional chiral dirhodium tetracarboxylate catalysts, but when the bulky TPCP catalysts are used, high diastereoselectivity is also possible.

These studies demonstrate that highly site-selective C–H functionalization of unactivated C–H bonds at C2 of alkanes and terminally substituted alkanes is a viable process. The reactions proceed in high yield and functional groups such as halides, silanes and esters are compatible with this chemistry. A new class of D_2-symmetric dirhodium catalysts were developed that are capable of achieving not only high site selectivity in these C–H functionalization reactions, but also high levels of diastereocontrol and enantiocontrol. These results show that high site selectivity is possible in C–H functionalization reactions without the need for a directing or anchoring group present in the molecule. The demonstration that it is possible to design catalysts with defined chiral pockets to control not only the enantioselectivity, but also the diastereo- and site selectivity of carbene-induced C–H functionalization, could have broad implications on future research directions on selective C–H functionalization.

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

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Author Contributions K.L. performed and analysed the majority of the synthetic experiments. S.N. prepared the first meta-disubstituted catalyst, D.G.M. conducted the computational studies and J.B. conducted the X-ray crystallographic studies. K.L. and H.M.L.D. designed the synthetic experiments and prepared the manuscript.

Author Information The crystal data have been deposited in the The Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk) under accession number 1445448. Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: details are available in the online version of the paper. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to H.M.L.D. (hmdavie@emory.edu).