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Design of Catalysts for Site-Selective and Enantioselective Functionalization of Non-Activated Primary C–H Bonds

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Abstract

The rapid and streamlined synthesis of complex molecules has been a long-standing challenge in organic chemistry. Improved procedures make accessible a broader array of potential chemical targets that can be applied in many fields, such as pharmaceuticals, agrochemicals and material science. The established approach for the synthesis of complex molecules relies on the use of functional groups, which are considered as the reactive functionality within an organic compound. In recent years, there has been considerable interest in exploring a different approach in which the carbon–hydrogen (C–H) bonds are selectively functionalized.[1–5] Several new reagents and catalysts have been recently developed to render selective C–H functionalization a viable proposition. The most widely used C–H functionalization methods rely on the use of substrates that have an inherent preference for functionalization at specific C–H bonds,[6–8] often employing directing groups[9–11] or conducting intramolecular reactions.[12–14] An alternative approach relies on catalyst control. In the ideal situation, a suite of catalysts would be available to achieve specific site-selective C–H functionalization at will and overcome the normal reactivity preference of the substrate. We recently introduced two dirhodium catalysts capable of inducing site-selective C–H functionalization at the most accessible secondary[15] and tertiary C–H bonds.[16] In this paper, we describe the design and optimization of a new dirhodium catalyst that is capable of high levels of site-selectivity and enantioselectivity for the most accessible primary C–H bond.

The development of reagents that are sufficiently reactive to functionalize non-activated sp^3 C–H bonds and still be susceptible to the controlling influence of a catalyst is a major challenge. Some notable examples included C–H oxidation with metal oxo intermediates,[17] C–H amination with metal nitrene intermediates,[18–20] C–H azidation[21–22] and C–H

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HMLD is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued March 10, 2015). The other authors have no competing financial interests.

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

borylation[23]. We have focused on the use of donor/acceptor metal carbenes as the reactive intermediates (Figure 1A).[24–25] The presence of the donor group attenuates the reactivity of the carbene compared to those with just acceptor groups, leading to the possibility of effective catalyst control of site-selectivity. The C–H functionalization proceeds through a concerted but asynchronous process, in which positive charge build-up at carbon occurs in the transition state, electronically favoring tertiary C–H functionalization. The donor/acceptor carbene intermediate, however, is sterically demanding and thus, the steric influence would tend to favor primary C–H functionalization. Therefore, the opportunity exists to control site-selectivity by modifying the size of the catalyst; a very bulky catalyst would favor primary C–H functionalization, whereas a less sterically constrained catalyst would prefer secondary or even tertiary C–H functionalization. Recently, we designed a D_2 symmetric dirhodium catalyst, Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$, that selectively functionalizes the most accessible secondary C–H bond[15] and a second catalyst, Rh_2(*R*-TCPTAD)$_4$, that selectively functionalizes the most accessible tertiary C–H bond[16] (Figure 1B). Che and co-workers have explored the use of bulky rhodium-porphyrin catalysts for selective functionalization of hydrocarbons with donor/acceptor carbenes at the primary C–H bonds, however, the site- and enantioselectivity was relatively limited.[26] Here, we report that a new dirhodium catalyst, Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$, is highly effective for the functionalization of non-activated primary C–H bonds with extremely high levels of site-selectivity and enantioselectivity.

The evaluation of the site-selectivity of new catalysts for unactivated C–H bonds was conducted with the reference reaction between 2-methylpentane and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**1a**) (Figure 2). Even though 2-methylpentane is a relatively simple substrate, it has eight distinct C–H bonds. The donor/acceptor carbenes, however, are sufficiently selective that only four sites can be functionalized, the most sterically accessible primary-, the most sterically accessible diastereotopic secondary-, and the tertiary C–H bonds, to generate the products **2**, **3** or **4**. We have previously shown that the established chiral catalysts such as Rh_2(*R*-DOSP)$_4$ (**A**) gave preferentially the tertiary C–H insertion product **4**, with Rh_2(*S*-TCPTAD)$_4$ (**B**) being the optimum catalyst for the tertiary site.[16] In the case of 2-methylpentane, Rh_2(*R*-DOSP)$_4$ gave a n.d.:19:81 ratio, whereas Rh_2(*S*-TCPTAD)$_4$ gave a n.d.:11:89 ratio favoring the tertiary site. The bulky dirhodium tetrakis-triarylcyclopropanecarboxylates [Rh_2(TPCP)$_4$] have been shown to be much more bulky catalysts than the more established catalysts and tend to favor C–H functionalization at less crowded sites. Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**C**) is exceptional for selective functionalization at the most accessible secondary C–H bond of *n*-alkanes[15] and gave a 7:75:18 ratio favoring the secondary site with 2-methylpentane. During the development of Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP], a related catalyst, Rh_2(*R*-*p*-PhTPCP)$_4$ (**D**), with a biphenyl substituent was observed to give a mixture of primary and secondary C–H insertion products with *n*-pentane[15] and in the reaction with 2-methylbutane it gave a 39:45:16 ratio. As this was the first TPCP catalyst to give significant amounts of primary C–H insertion product it became the scaffold for the design of more selective catalysts for primary C–H functionalization.

During the studies on Rh_2[*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**C**), we developed a novel strategy to generate a library of catalysts by a palladium-catalyzed eight-fold cross coupling reaction.[15] A similar strategy was used for catalyst diversifications in this project. Two series of new catalysts related to Rh_2(*R*-*p*-PhTPCP)$_4$ were generated, either by a four-fold cross coupling on Rh_2(*R*-*p*-BrTPCP)$_4$ to form catalysts **E-G** or a 12-fold cross coupling on Rh_2(*R*-tris(*p*-Br)TPCP)$_4$ to form catalysts **H-K**. All the catalysts were effective chiral catalysts, generating the primary C–H functionalization products with high asymmetric induction (≥90% e.e.). In the case of the Rh_2(*R*-*p*-BrTPCP)$_4$ derived analogs Rh_2[*R*-(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**E**) and Rh_2[*R*-(*p*-^{t}Bu$C_6H_4C_6H_4$)TPCP]$_4$ (**G**) were the best for site-selectivity, giving a 71:25:4 and 71:26:3 ratio favoring the primary C–H insertion product, which was formed with very high asymmetric induction (96% and 97% e.e.). The triphenyl derivatives **F** also gave good but slightly inferior selectivity to **E** and **G**. The four catalysts generated from Rh_2[*R*-tris(*p*-Br)TPCP]$_4$ were also evaluated and Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**I**) displayed the best characteristics with an 84:16 ratio of primary and secondary products **2** and **3** (no observable tertiary product **4**) and 98% e.e for the primary product **2**. In this series, the extended triphenyl catalysts **J** and **K** gave considerably inferior site-selectivity to Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**I**). On the basis of these studies, Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**I**) was selected as the optimum catalyst for primary C–H functionalization. The nature of the ester functionality of the donor/acceptor carbene also has a significant effect on the outcome of this chemistry (see supporting information). The methyl ester derivative failed to give any of the C–H functionalization, whilst the trifluoroethyl ester gave a poor regioisomeric mixture (54:36:10 r.r.). The tribromoethyl derivative gave slightly improved site- and enantioselectivity (87:13:n.d. r.r. and >99% e.e.) compared to the trichloroethyl derivative but the yields were lower.

Having optimized the catalyst and the ester functionality, the scope of the primary C–H functionalization was examined with a range of substrates (Figure 3). Initially a series of alkanes was examined to determine the influence of the steric environment within the substrate on site-selectivity (Figure 3, **5–12**). In contrast to 2-methylpentane, the methylene group in 2-methylbutane is not susceptible to functionalization because it is too close to the isopropyl group. The tribromoethyl product **5** is formed with better selectivity for the most accessible primary C–H bond (90:10 r.r., >99% e.e.) compared to the trichloroethyl product **6** (89:11 r.r., 90% e.e.) but the yield is lower (**5**, 40%; **6**, 82%). In the case of 3-methylpentane the tertiary site is slightly more crowded than 2-methylbutane and this is enough for the reaction to proceed cleanly for the primary C–H insertion product **7**. In contrast to the previous study in which only tertiary C–H functionalization product was observed with Rh_2(*S*-TCPTAD),[16] C–H functionalization occurred only at the most accessible primary C–H bond with Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$, the more crowded secondary site and the tertiary site were no longer functionalized. Similarly, highly selective reactions were observed in the formation of **8–11**. the reaction with 2,2-dimethylbutane to form **8** is notable because in the past 2,2-dimethylbutane has been extensively used as an “inert” solvent for donor/acceptor carbene C–H functionalization. Also, the formation of **11** with very high site-selectivity (>98:2 r.r.) and enantioselectivity (98% e.e.) shows the current system is superior to the best previously reported chiral catalyst, a rhodium-porphyrin catalyst, which formed **11** with relatively poor primary/secondary ratio (3.8:1 r.r.) and

enantioselectivity (65% e.e.).[26] These results showed that primary C–H functionalization competes favorably with reactions of secondary and tertiary C–H bonds, as long as secondary and tertiary sites are slightly sterically encumbered. The steric subtleties are readily seen in the reaction with 3,3-dimethylhexane to form **12**. Reaction at the primary C–H bond on the propyl group is favored over ethyl group (marked in green) by an 84:13 ratio and no reaction occurs at the other two methyl groups. Studies were also conducted in the presence of substrates containing functional groups to illustrate the potential versatility of this chemistry. The reaction was conducted with a series of trimethylsilyl (TMS) protected alcohols to form **13–17**. Generally, the reactions proceeded with excellent selectivity, but the yields were deceased when the inductively electron-withdrawing group was too close to the site of C–H functionalization, as seen in the case of **13** and **14**. The reactions with TMS protected 3-ethyl-3-hexanol to form **17** is a further illustration of the subtle steric effects because reaction at the propyl methyl group is strongly preferred over the six other methyl groups in the substrate. 1-Bromobutane is also a viable substrate, forming **18** with high enantioselectivity (93% e.e.) but with some competition from C–H functionalization as the secondary C–H bond marked in blue with a ratio of 84:16. As the emphasis of this study has been to determine the subtleties of the site-selectivity, the studies so far have concentrated on a single aryl group in the donor/acceptor carbene. However, the donor group can be varied and this is illustrated in the reactions of 2,2-dimehylpentane to form the boronic ester and trifluoromethyl derivatives **19** and **20**.

We have also examined the Rh_2[tris(*p*-^{t}BuC_6H_4)TPCP]$_4$-catalyzed reactions with enantiomerically pure substrates **21–23**. In these substrates, the internal methyl group is sufficient to block any C–H functionalization reactions at the methylene sites, and all the substrates react cleanly. The reactions are under catalyst control because the reaction with Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$ gives one diastereomeric series of the products **24–26**, in which the newly formed stereocenter has the S-configuration, whereas the reaction with Rh_2[*S*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$ gives the opposite diastereomeric series **27–29**.

Because Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$ (I) exhibits good selectivity for primary C–H bonds, we have conducted structural investigations on it and related catalysts. Suitable crystals of Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**I**) could not be obtained but X-ray crystallographic data of two related catalysts were obtained. Catalyst **F** adopts a D_2 symmetric structure, whereas catalyst **D** adopts a C_2 symmetric structure[27] (see Supplementary Information for details). With two different types of structures observed in the solid state, we decided to investigate with computational methods on the structure and selectivity of Rh_2[*R*-tris(*p*-^{t}BuC_6H_4)TPCP]$_4$ (**I**). Given that the catalyst contains nearly 500 atoms, we employed the two-layer ONIOM (B3LYP:UFF) approach to study the catalyst structure and C–H functionalization selectivity using the partitioning shown in Figure 5a (see Supplementary Information for computational details). These ONIOM calculations reveal that catalyst **I** has two major conformations, with a C_2-symmetric conformation favored over a C_4-symmetric conformation by an energy difference of 10.1 kcal/mol (see Supplementary Information for other higher energy symmetric conformations in Figure S4).

Figure 6 shows the ONIOM transition structures for carbene (derived from 1) insertion into the primary C–H bond. The substrate fits into the open pocket at the top of the C_2 conformer

and binds to the upper rhodium atom. The bottom rhodium atom is blocked by two biphenyl groups. The C–H functionalization step is a concerted asynchronous carbene insertion into the C–H bond, and the transition state predominantly involves movement of the hydrogen in the C–H bond towards the carbene carbon.[28] (Similar ONIOM transition structure of the C_4 catalyst is shown in Figure S5 in the Supplementary Information.) For the C2 catalyst, the transition structure for carbene insertion into the primary C–H bond from the *Si* face of the carbene, **TS1**, is energetically favored by 3.1 kcal/mol over **TS2** (primary C–H bond approached from the opposite face of the carbene), which is in excellent agreement with the experimentally observed enantioselectivity of 98% e.e. The destabilization of **TS2** arises from the alkyl substrate repulsions with the “up” biphenyl moiety. (see also Figure S7 in the Supplementary Information). Because there are significant contacts between alkyl and aryl groups, and there are likely a variety of low energy conformations, more extensive computations with dispersion and dynamic averaging are underway.

These and previous studies demonstrate that it is possible to obtain catalysts to achieve high site-selectivity at either primary, secondary of tertiary C–H bonds without resorting to the use of directing groups within the substrate. Previously, site-selective C–H functionalization had been achieved at the most accessible secondary[15] and tertiary[16] C–H bonds. This study demonstrates that by appropriate design of the catalyst, site-selective C–H functionalization at the most accessible primary C–H bond is also a viable process. Such selectivity is the most challenging for the donor/acceptor carbenes because it goes against the normal electronic preference of these intermediates. Considering that group transfer reactions can be conducted with a range of different types of metal carbenes beyond donor/acceptor carbenes as well as metal nitrene and metal oxo intermediates, these studies are likely to encourage further efforts in catalyst design to control site-selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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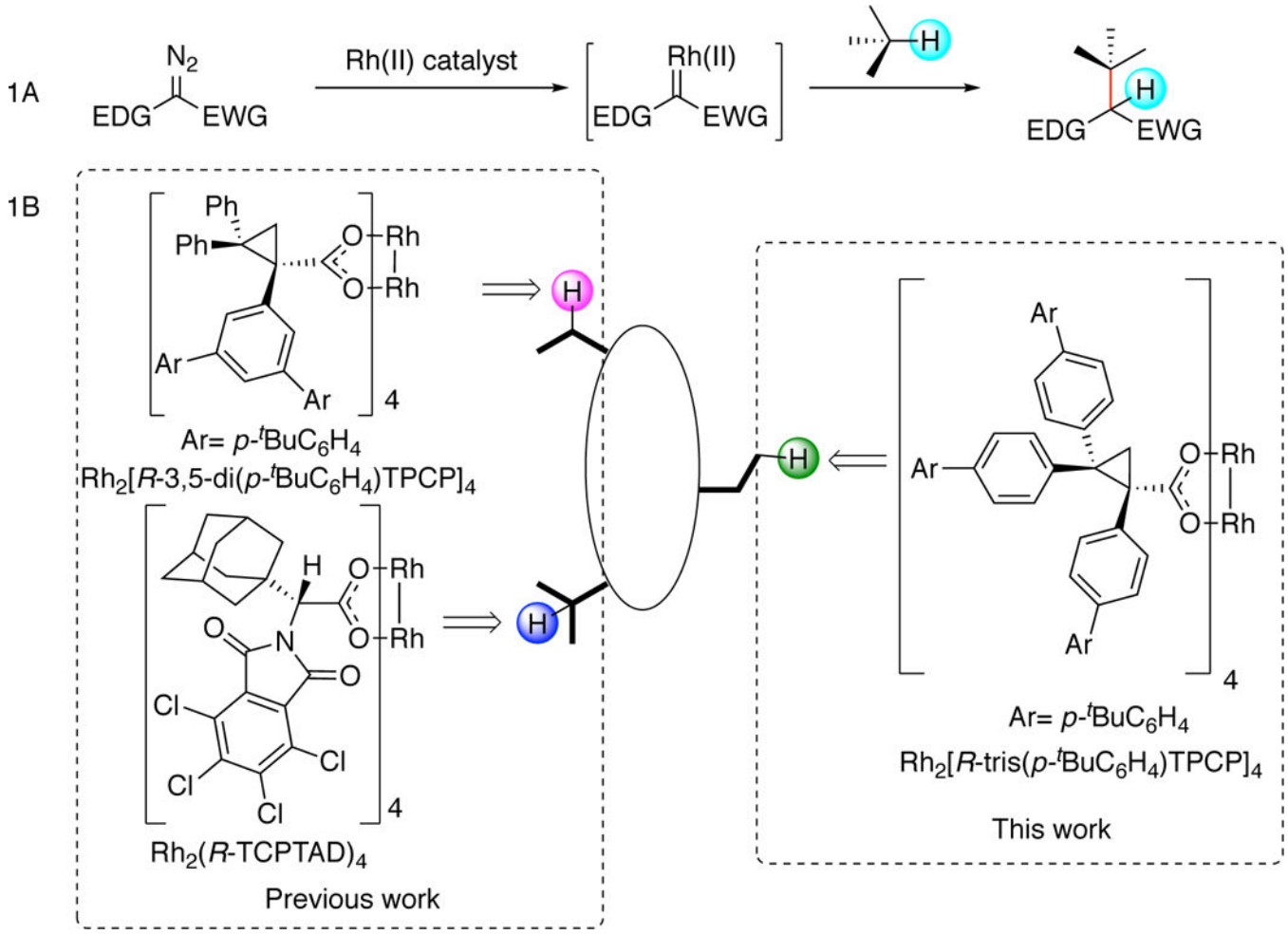
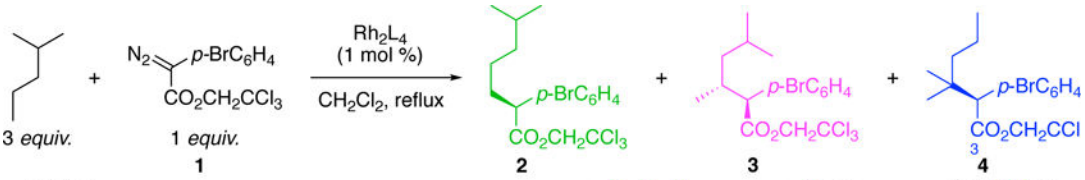
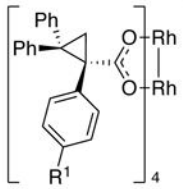
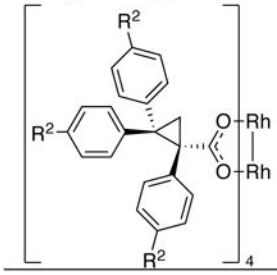


Figure 1:

Figure 1A: General scheme of the carbene-induced C–H functionalization. Figure 1B: Comparison of prior C–H functionalization studies with the current study. This study describes a catalyst that is capable of selective functionalization of the most accessible primary C–H bond.



Catalyst		r.r. (2 : 3 : 4)	e.e. (2, %)	yield (2+3, %)
Rh_2(*R*-DOSP)$_4$ (**A**)		n.d. : 19 : 81	–	10
Rh_2(*S*-TCPTAD)$_4$ (**B**)		n.d. : 11 : 89	–	10
Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$ (**C**)		7 : 75 : 18	81	75
	R^1= Ph (**D**)	39 : 45 : 16	97	75
	p-^{t}BuC$_6$H$_4$ (**E**)	71 : 25 : 4	96	74
	p-PhC$_6$H$_4$ (**F**)	70 : 27 : 4	98	70
	p-^{t}BuC$_6$H$_4$C$_6$H$_4$ (**G**)	71 : 26 : 3	97	72
	R^2= Ph (**H**)	68 : 25 : 7	90	71
	p-^{t}BuC$_6$H$_4$ (**I**)	84 : 16 : n.d.	98	90
	p-PhC$_6$H$_4$ (**J**)	68 : 25 : 7	92	83
	p-^{t}BuC$_6$H$_4$C$_6$H$_4$ (**K**)	48 : 35 : 17	97	55

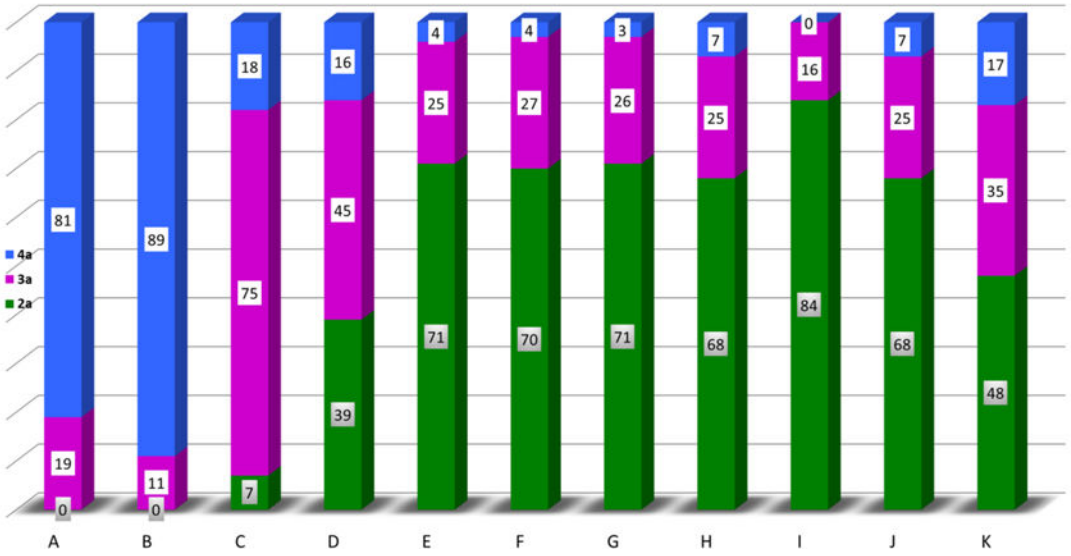


Figure 2:

Numerical and graphical representations of the catalysts optimization studies for selective primary C–H functionalization. The green product **2** is the desired product and Rh_2[*R*-tris(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$ (**I**) is the optimum catalyst. Abbreviations: r.r., regioisomeric ratio; e.e., enantiomeric excess, n.d., not detected.

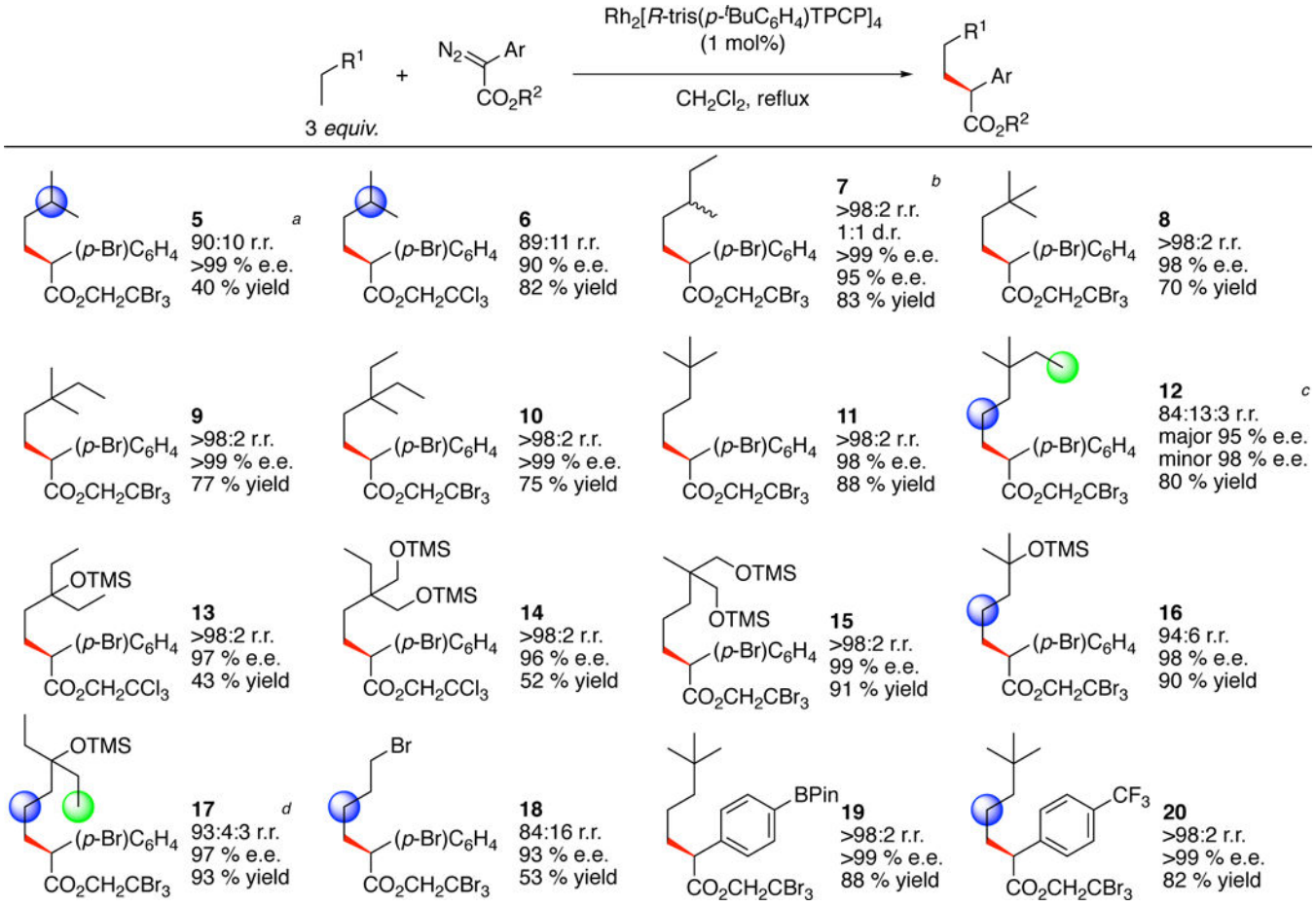


Figure 3:

Examples of selective primary C–H functionalization. In some instances regioisomer products are formed: [a] When forming the following compounds, a small amount of a secondary C–H functionalization product was formed at the position marked as blue: **5** (10%), **6** (11%), **16** (6%), **18** (16%) [b] A value of >98:2 r.r. means no other regioisomer was detected in the ^{1}H NMR spectra of the crude reaction mixtures; [c] C–H functionalization took place at other positions of 3,3-dimethylhexane (**12**): 13% at the position marked green (1° site), 3% at the position marked blue (2° site); [d] C–H functionalization took place at other positions of ((2,2-diethylpentyl)oxy)trimethylsilane (**17**): 4% at the position marked green (1° site), 3% at the position marked blue (2° site).

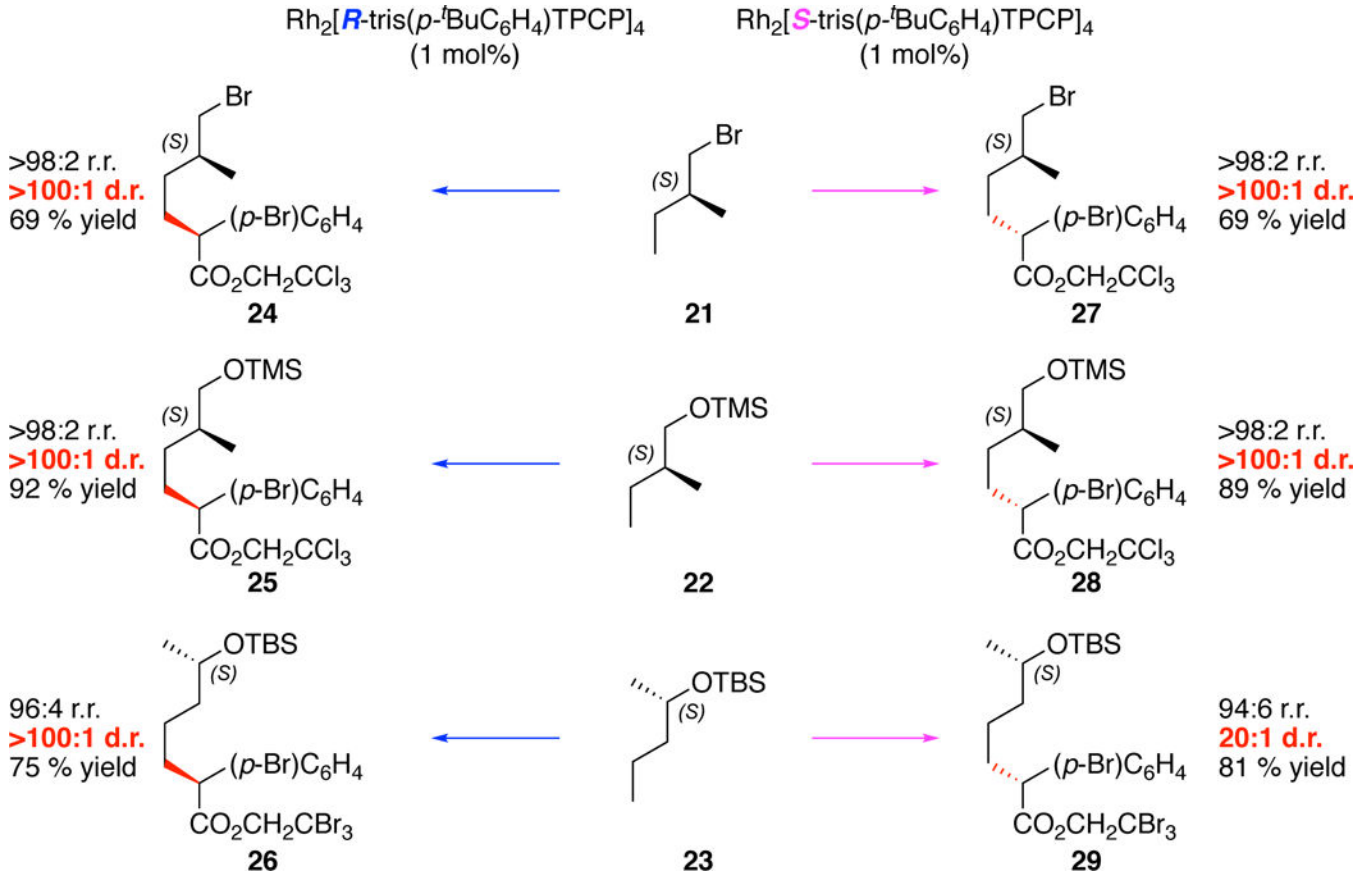


Figure 4:
Catalyst-controlled diastereoselective primary C–H functionalization

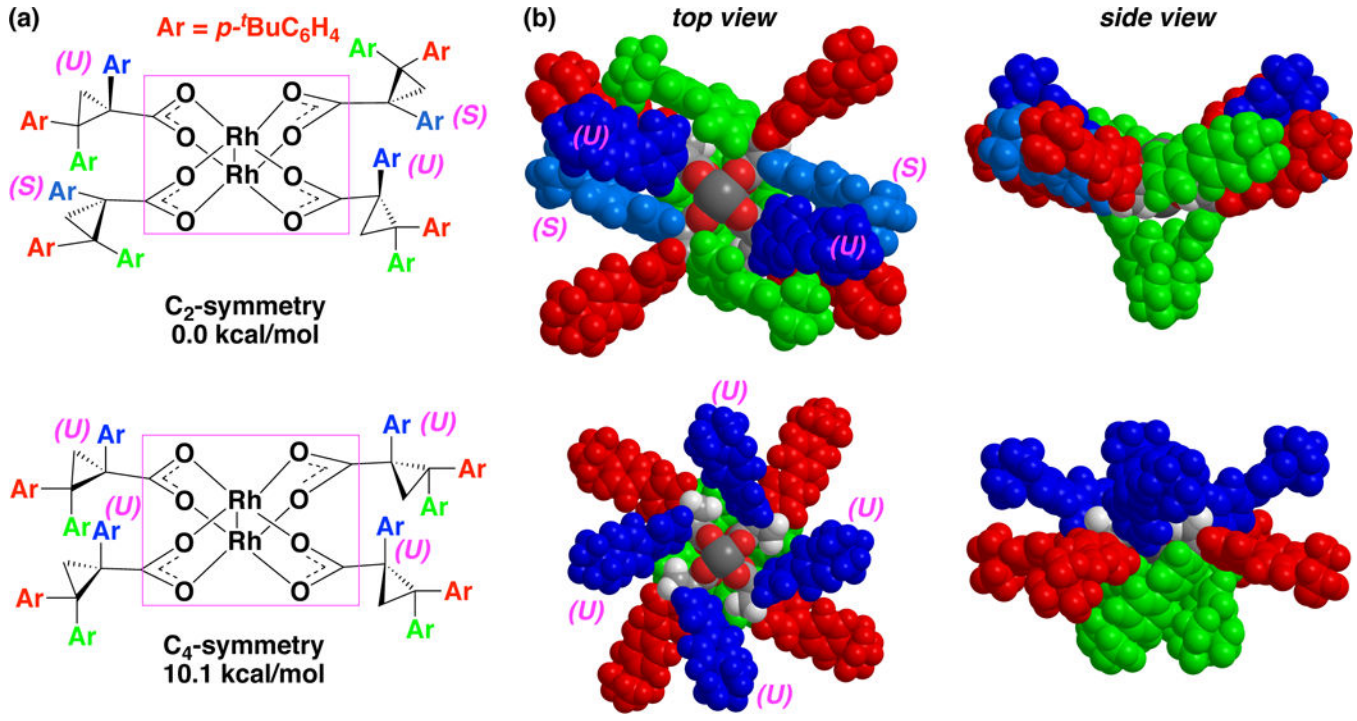


Figure 5:

Structural information about the dirhodium catalyst **I**. **a**, ONIOM partitioning of the catalyst with the atoms inside the purple rectangle modeled with DFT and the atoms outside modeled with the UFF, along with the relative energies of the C_2 and C_4 conformations (U: up; S: side). **b**, Top and side views of the C_2 and C_4 conformations. The free energies with solvation correction are given in kcal/mol.

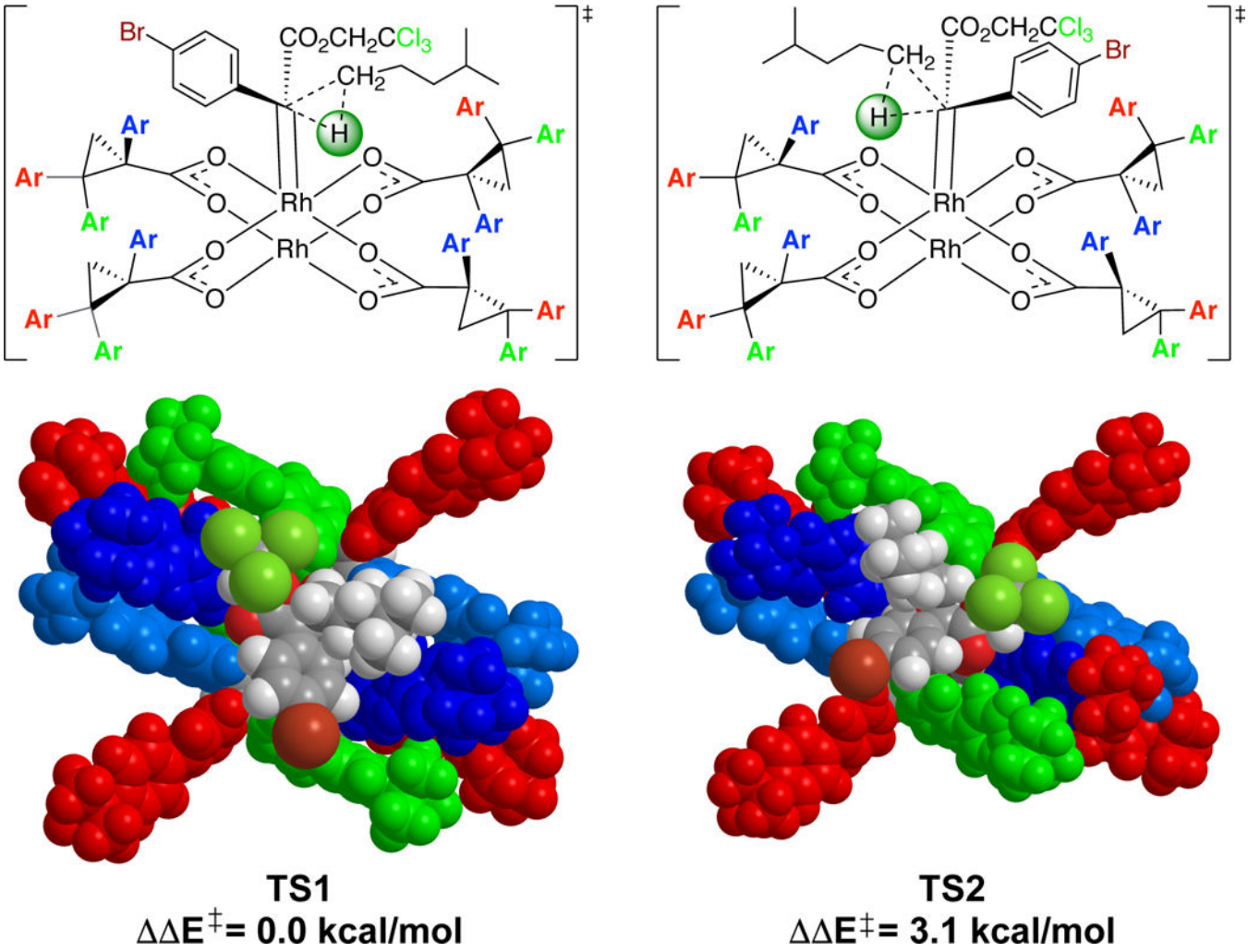


Figure 6.

Optimized transition structures for carbene insertion into the primary C–H bond. The free energies with solvation correction are given in kcal/mol. **TS1** involves attack to the Si face of the carbene and is the lowest energy, consistent with the observed asymmetric induction.