Design, Synthesis and Evaluation of Extended C_4-Symmetric Dirhodium Tetracarboxylate Catalysts

Zachary J. Garlets,[#] Yannick T. Boni,[#] Jack C. Sharland, Parker R. Kirby, Jiantao Fu, John Bacsa, and Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322

KEYWORDS C—H functionalization, dirhodium, donor/acceptor carbene, catalysis, asymmetric synthesis

ABSTRACT: The synthesis and evaluation of six C_4-symmetric bowl-shaped dirhodium tetracarboxylate catalysts are described. These elaborate high symmetry catalysts are readily generated by means of the self-assembly of four C_1-symmetric ligands around the dirhodium core. These catalysts are capable of highly site-selective, diastereoselective and enantioselective C—H functionalization reactions by means of donor/acceptor carbene-induced C—H insertions.

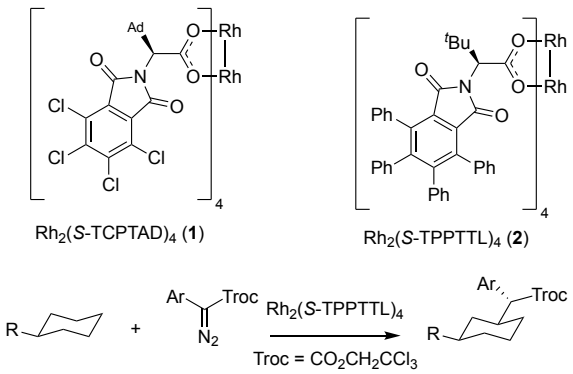
C—H Functionalization is an area of intense current interest.[1-15] A major ongoing challenge in the field is the development of methods capable of selecting which C—H bond is functionalized in substrates containing many similar C—H bonds. The majority of site-selective C—H functionalization strategies rely on the inherent reactivity preference of the substrate,[16-24] conducting the reaction intramolecularly,[25-42] or using directing groups incorporated into the substrate[43-52] to determine which C—H bond is modified. An alternative approach would be to use the catalyst as the dominant controlling element.[39, 53-63] This then calls for the design of a collection of catalysts with different properties to control which C—H bond is functionalized as illustrated in the idealized system shown in Figure 1.

Figure 1. Idealized catalyst-controlled selective C—H functionalization reactions.

Our group has focused on catalyst-controlled selective C—H functionalization by means of donor/acceptor carbene-induced C—H insertion.[64, 65] In recent years, we have developed a number of dirhodium tetracarboxylate catalysts of different shapes and sizes capable of modulating which C—H bond is functionalized.[58, 66, 67] Electronically, the rhodium carbene would preferentially attack tertiary C—H bonds. However, by making the catalysts more sterically demanding, the site selectivity can be altered from preferring the 3° C—H bonds to reacting instead at the most accessible 2° or even the most accessible 1° C—H bonds. Catalysts derived from triarylcyclopropane carboxylate ligands are especially effective because they are tunable sterically demanding catalysts.[68, 69] Our more recent work has focused on even more subtle aspects of regiocontrol by developing bowl-shaped catalysts that can distinguish between sterically similar 2° C—H bonds.[70]

A key feature of our catalyst design is to surround the dirhodium core with four identical chiral carboxylate ligands that self-assemble to generate complexes of higher symmetry (D_2, C_4, or C_2) than the ligands themselves (C_1).[65] Rh_2(*S*-TCPTAD)$_4$ (**1**),[71, 72] and Rh_2(*S*-TPPTTL)$_4$ (**2**),[70] belong to the phthalimdo amino acid catalyst scaffold, which was originally developed by Hashimoto.[73, 74] These complexes, when derived from *tert*-butyl or adamantyl alanine, adopt a C_4 symmetric bowl-shaped structure.[62, 75-77] Rh_2(*S*-TCPTAD)$_4$ (**2**) is the optimum catalyst for site selective functionalization at the most accessible 3° C—H bond.[62] Rh_2(*S*-TPPTTL)$_4$ (**1**) directs C—H functionalization of *tert*-butylcyclohexane with aryldiazoacetates **3**, cleanly at C3, forming **4** with exceptional site selectivity, diastereoselectivity, and enantioselectivity.[62] Rh_2(*S*-TPPTTL)$_4$ has a distinctive structural feature because the 16 phenyl groups on the periphery are all tilted, adding an element of helical chirality, which is considered to be an important factor for its propensity to induce high levels of asymmetric induction.[64, 70] The unusual structure and unprecedented selectivity exhibited by Rh_2(*S*-TPPTTL)$_4$ motivated us to evaluate expanded tetraarylphthalimido-derived catalysts

Scheme 2. Functionalization of *tert*-butylcyclohexane.



Scheme 3. Synthesis of extended tetraarylphthalimido catalysts

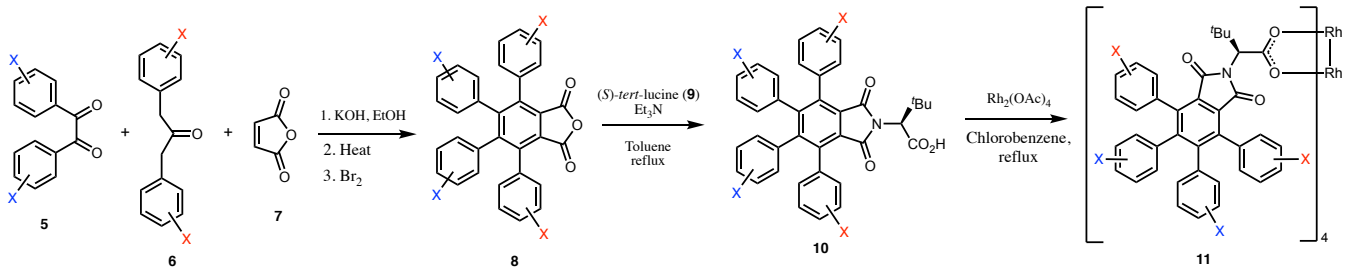
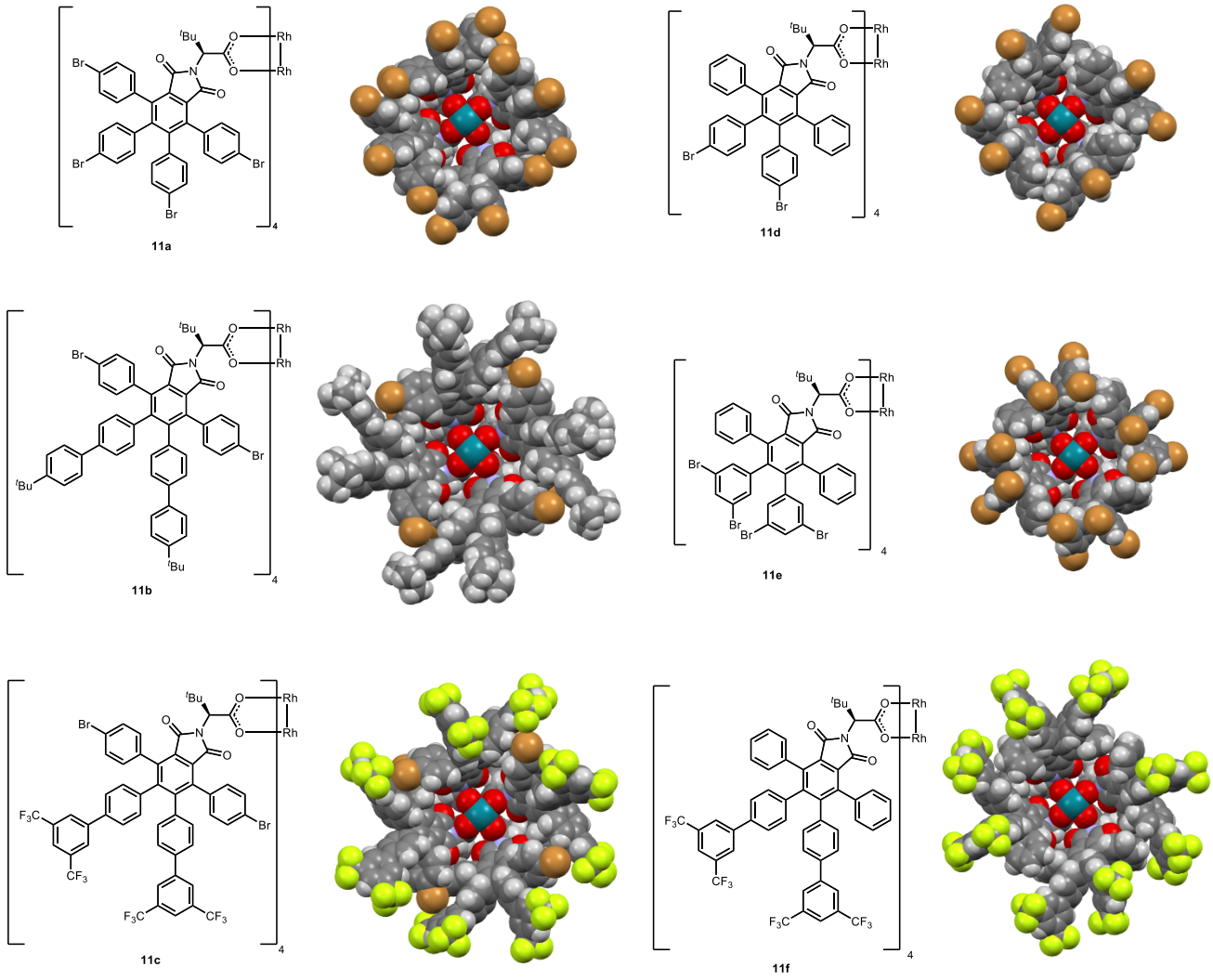


Figure 2. X-ray crystallographic structures of catalysts **11a-f**



to determine if they can further enhance the site-selective and enantioselective C—H functionalization reactions of donor/acceptor carbenes. The results of these studies are described herein.

The synthesis of the ligands (**10**) was readily achieved following established procedures (Scheme 3).[68,78] A condensation reaction between benzyl **5** and dibenzyl ketone **6** generated a cyclopentadienone, which was then subjected to a one-pot Diels-Alder/retro-Diels-Alder/oxidation sequence with maleic anhydride (**7**) to form phthalic anhydride **8**. Condensation of **8** with *tert*-leucine (**9**) generated carboxylic acid **10** which was then subjected to a ligand exchange with dirhodium tetraacetate to form the corresponding catalyst **11**. The detailed experimental procedures are described in the supplemental information. Notably, the ligand exchange was found to be very favorable, even with these very large ligands, leading to the formation of catalysts **11a-f** in 82-96% yield.

Six new dirhodium catalysts **11a-f** were generated and their structures are shown in Figure 2. When the study was initiated, it was unclear what bulky functionality could be introduced into the ligands without interfering with the self-assembly to form the bowl-shaped structures. Inspection of the X-ray structure of the parent catalyst

Rh_2(*S*-TPPTTL)$_4$ indicated that *p*-substitution of the aromatic rings had the best chance in avoiding interference with the desired self-assembly. Therefore, most of the catalysts possess *p*-substitution and additional bulky groups were introduced further away from the phthalimide. The first three catalysts **11a-c** have *p*-substituents on all four benzene rings of the tetraphenylphthalimido group, whereas **11d** and **11f** have *p*-substituents only on the two central benzene rings. A catalyst with 3,5-dibromo substitution on these central rings (**11e**) was also synthesized to investigate a structure with greater steric bulk close to the catalyst pocket. All six of the complexes generated suitable crystals for X-ray analysis and space filling views of these crystal structures are shown in Figure 2. All of the structures adopt bowl-shaped structures, and some are close to be perfectly aligned in a C_4-symmetric orientation.

Previous computational studies have shown that in this class of catalysts, the *tert*-butyl or adamantyl groups block one rhodium face.[62, 71, 72, 77, 79] Hence, the views presented in Figure 2 display the open rhodium face, looking down the bowl into the active site of the catalysts which is surrounded by the four tetraarylphthalimdo groups. A feature that is readily seen in the X-ray structure of these catalysts is the tilting of the aryl rings on the periphery of the bowl. In several of these structures, all the aryl rings are tilting in the same direction, leading to an induced helical chirality generated during the self-assembly process. The helical chirality is considered to be a major factor for the high asymmetric induction displayed by Rh_2(*S*-TPPTTL)$_4$,[70] and observing a similar structural feature in the new catalysts was a positive sign that they also would likely exhibit high asymmetric induction. The parent catalyst Rh_2(*S*-TPPTTL)$_4$ has been previously analyzed computationally.[70] These studies revealed that even though a defined bowl shape is adopted, there is some flexibility present to accommodate carbene binding and the approach of the substrate to the bound carbene. Further evidence to support the C_4-symmetric structure and the tilting of the aromatic ring was obtained from the ^{1}H NMR spectra data of the ligands and the catalyst, as illustrated for catalyst **11a** (Figure 3). The aromatic region for ligand **10a** appears relatively simple as many of the aromatic protons are equivalent. In contrast, for the catalyst **11a**, distinctive doublets for each of the 16 aromatic protons can be seen. The likely explanation for this is the tilting of the aromatic rings in the complex, which also experience hindered rotation, causing each aromatic proton to be in a different chemical environment. Indeed, the NMR signals for the aromatic signals in **11a** begin to coalesce at 60 °C, which is a good indication for the hindered rotation (See supporting information for details). Another distinction between the NMR spectra of the catalyst compared to that of its ligand is a 0.3 ppm shielding of the *tert*-butyl group of the ligand when bound in the dirhodium complex.

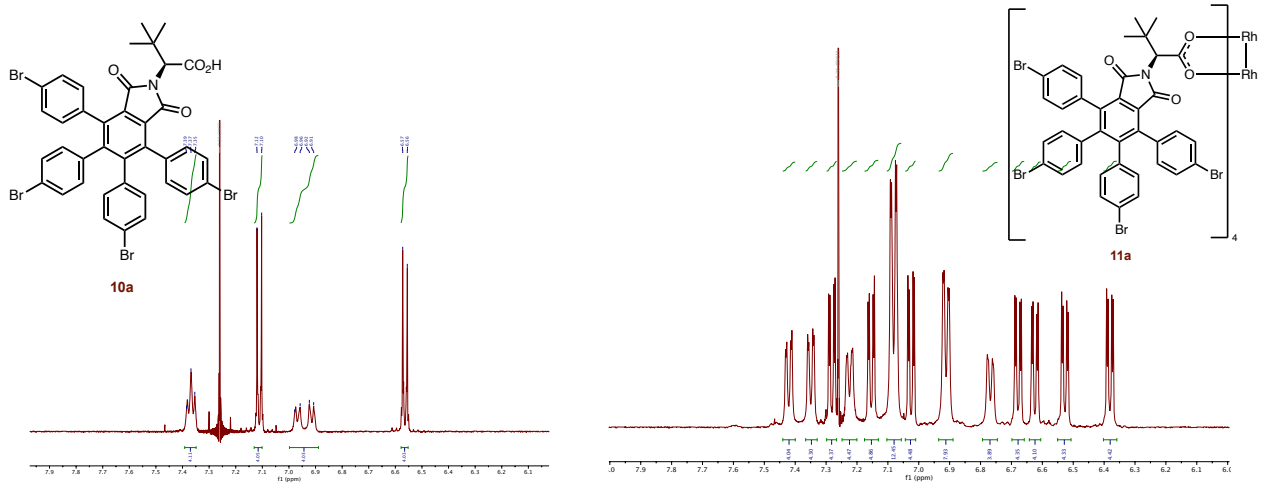


Figure 3: NMR spectra of ligand **10a** and catalyst **11a** (aromatic region)

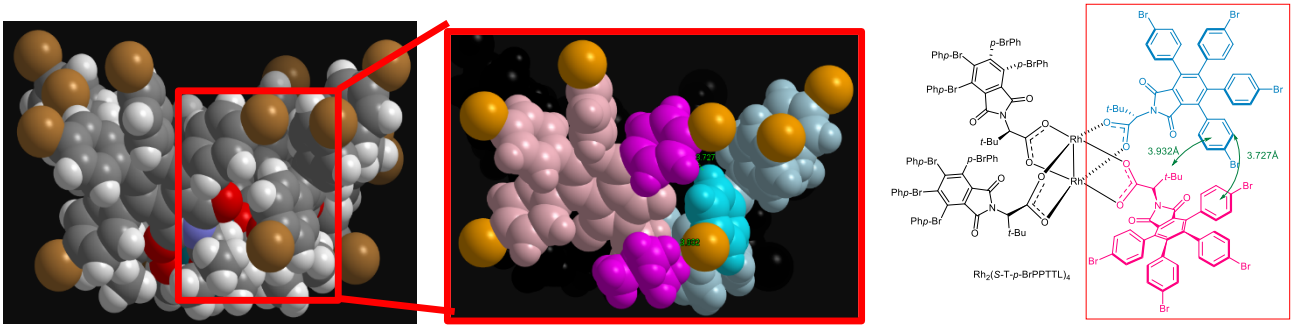
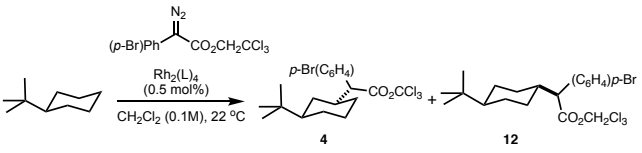


Figure 4: The rigidity of these extended bowl catalysts may be due to stabilizing C—H-*pi* interactions between adjacent phenyl and *tert*-butyl groups on neighboring ligands. The interactions are visualized in the structure above and distances are measurable on the resolved X-Ray structure of the catalyst **11a**. One ligand is in purple, and the adjacent ligand is in blue.

The cause for the dramatic difference between the ligands and the catalyst can be seen in a more detailed analysis of the X-ray structure of **11a** as illustrated in Figure 4. The *tert*-butyl group of one ligand (colored purple) is orientated very close to the first phenyl group of

the adjacent ligand (colored blue) (3.93 Å). Furthermore, a phenyl group in the first ligand is involved in T-shaped stacking to the same phenyl group of the second ligand (3.73 Å). These interactions would explain the considerable shielding influence seen in the catalyst compared to the free ligand. Also, these interactions would inhibit the rotation of the phenyl rings and could contribute to the induced helical chirality upon complex formation.

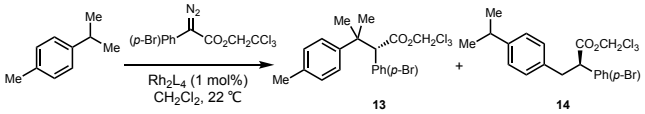
The new catalysts were then evaluated in C—H functionalization reactions with standard reference substrates to determine how they compared with established bowl-shaped catalysts, Rh_2(*R*-TCPTAD)$_4$ and Rh_2(*S*-TPPTTL)$_4$. The C—H functionalization of *tert*-butylcyclohexane with the aryldiazoacetate **3** is one of the standard reference substrates because it allows comparison of the site-selectivity, diastereoselectivity and the enantioselectivity exhibited by each catalyst (Table 1).[79] Rh_2(*R*-TCPTAD)$_4$ lacks the phenyl rings at the periphery of the bowl and is an inferior catalyst in this reaction, giving relatively poor site-selectivity for C3 (**4**) over C4 (**12**), and poor diastereoselectivity and enantioselectivity (entry 1). Rh_2(*S*-TPPTTL)$_4$ has already been shown to show exceptional selectivity in this reaction (entry 2).[79] All the new catalysts (**11a-f**) perform equally well (entries 3-8) with exceptional site selectivity (>20:1). Furthermore, they all give high levels of enantioselectivity (96-99% ee), whereas the diaryl-substituted catalysts **11e** gives the best diastereoselectivity (19:1 d. r.).



Entry	$Rh_2(L)_4$	Yield (%)	r.r. (4:12)	d.r. (4)	e.e. (%)
1	Rh_2(*R*-TCPTAD)$_4$	81	1.5:1	6:1	20
2	Rh_2(*S*-TPPTTL)$_4$	72	>20:1	11:1	-95
3	**11a**	70	>20:1	12:1	-96
4	**11b**	73	>20:1	11:1	-97
5	**11c**	70	>20:1	12:1	-99
6	**11d**	77	>20:1	16:1	-96
7	**11e**	69	>20:1	19:1	-98
8	**11f**	71	>20:1	10:1	-97

Table 1. C—H functionalization of *tert*-butylcyclohexane

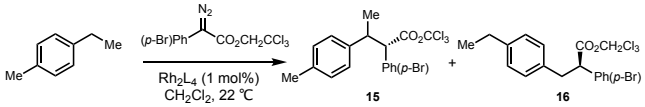
Even though the phthalimido catalysts are large they are not considered to be especially sterically demanding near the rhodium-bound carbene.[62] Indeed, Rh_2(*R*-TCPTAD)$_4$ was developed as the optimum catalyst for C—H functionalization at the most accessible 3° C—H bond.[62] In order to test the steric demand of these catalysts, a competition between benzylic 1°, 2° and 3° was conducted. *p*-Cymene is a good reference substrate to distinguish between site selectivity between 1° and 3° C—H bonds.[62, 67, 80, 81] The results for this system are presented in Table 2. As expected, Rh_2(*R*-TCPTAD)$_4$ preferentially reacted at the 3° C—H bond with a site selectivity of 7.6:1 for **13:14** (entry 1). Rh_2(*S*-TPPTTL)$_4$ performed better with a site selectivity of 10:1 (entry 2). With this system, the tetraaryl-substituted catalysts performed best, all favoring the 3° site by >20:1 r.r. (entries 3-5). All three catalysts gave very similar levels of enantioinduction ranging from 86-90% ee. These studies reveal that none of the catalysts behave as if they are sterically demanding around the carbene, strongly favoring reaction at the tertiary C—H bond.



Entry	$Rh_2(L)_4$	Yield (%)	r.r. (13:14)	e.e. (%)
1	Rh_2(*R*-TCPTAD)$_4$	89	7.6:1	-77
2	Rh_2(*S*-TPPTTL)$_4$	68	10:1	90
3	**11a**	70	>20:1	87
4	**11b**	65	>20:1	90
5	**11c**	78	>20:1	86
6	**11d**	74	8:1	74
7	**11e**	80	14:1	73
8	**11f**	56	8:1	52

Table 2. C—H Functionalization of *p*-cymene

The reference substrate for comparing the selectivity for C—H functionalization between 1° and 2° sites is 4-ethyltoluene.[67, 82, 83] The results for the series of bowl catalysts are shown in Table 3. The reaction catalyzed by Rh_2(*R*-TCPTAD)$_4$, generating preferentially the 2° functionalized product **15** over the primary product **16**, but with moderate diastereoselectivity and enantioselectivity (5.8:1 d.r. and 71% ee)(entry 1). Rh_2(*S*-TPPTTL)$_4$ performed better (20:1 d.r. And 88% ee) but the extended catalysts were uniformly superior in terms of asymmetric induction (91-97% ee). Three of the catalysts, **11a**, **11b** and **11f** gave superior levels of diastereoselectivity (>20:1 d.r.) compared to Rh_2(*S*-TPPTTL)$_4$.

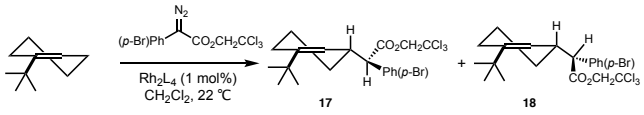


Entry	$Rh_2(L)_4$	Yield (%)	r.r. (15:16)	d.r. (15)	e.e. (%)
1	Rh_2(R-TCPTAD)$_4$	86	>20:1	5.8:1	71
2	Rh_2(S-TPPTTL)$_4$	72	>20:1	20:1	-88
3	**11a**	70	>20:1	>20:1	-97
4	**11b**	65	>20:1	>20:1	-96
5	**11c**	67	>20:1	15:1	-95
6	**11d**	79	>20:1	14:1	-91
7	**11e**	98	>20:1	13:1	-95
8	**11f**	71	>20:1	>20:1	-92

Table 3. C—H Functionalization of 4-ethyltoluene

Beyond probing the selectivity profile of the new extended tetraarylphthalimido catalysts in 1°, 2° and 3° C—H bonds functionalization, we also sought to study their selectivity in the allylic C—H bond functionalization of 1-*tert*-butyl-1-cyclohexene (Table 4).[70] Our earlier attempts at functionalizing the accessible allylic C—H

bond of 1-*tert*-butyl-1-cyclohexene and related substrates using Rh_2(*S*-DOSP)$_4$ were poor in terms of diastereoselectivity (62:38 **17:18**) and achieved only 46% combined yield for both diastereomers. The more open bowl Rh_2(*R*-TCPTAD)$_4$ catalyzed the transformation but with poor diastereoselectivity (2:1 d.r.) Rh_2(*S*-TPPTTL)$_4$ as well as the new extended tetraarylphthalimido catalysts all achieved excellent diastereoselectivity (>20:1 d.r.) favoring the *trans*-isomer (**17**) whose absolute stereochemistry was confirmed by single crystal X-ray crystallographic analysis of the hydrolyzed C—H functionalization ester product. The enantioselectivity was relatively moderate for Rh_2(*S*-TPPTTL)$_4$ catalysis (entries 1, 77% ee) but the tetraarylphthalimido catalysts performed considerably better (entries 3-8, 80-86% e.e).



Entry	$Rh_2(L)_4$	Yield (%)	r.r.	d.r. (17:18)	e.e. (%)
1	Rh_2(*R*-TCPTAD)$_4$	86	>20:1	2:1	nd[a]
2	Rh_2(*S*-TPPTTL)$_4$	83	>20:1	>20:1	77
3	**11a**	98	>20:1	>20:1	86
4	**11b**	99	>20:1	>20:1	85
5	**11c**	99	>20:1	>20:1	86
6	**11d**	69	>20:1	>20:1	80
7	**11e**	85	>20:1	>20:1	84
8	**11f**	70	>20:1	>20:1	83

a: ee not determined due to overlapping peaks with the diastereomeric product.

Table 4. Allylic C—H functionalization

The studies reveal that all of the extended catalysts are capable of displaying exceptional selectivity, showing similar or superior results to the parent Rh_2(*S*-TPPTTL)$_4$ in terms of site selectivity, diastereoselectivity and/or enantioselectivity. The unique properties of these catalysts are likely due to the influence of the wall of the bowl which accommodates certain substrates better than others. The high selectivity for C3 insertion upon reaction with *tert*-butylcyclohexane is considered to be an ideal system for assessing the influence of the catalyst wall (Figure 5). When the rhodium-bound carbene reacts at C3 of *tert*-butylcyclohexane the *tert*-butyl is pointing out of the bowl (model **B**), whereas when it attacks at C4, the *tert*-butyl group is pointing into the wall of the catalyst (model **A**).[70] Even though the equatorial sites at C4 and C3 would be sterically similar, the influence of the wall causes selection bias between the two sites. The reaction with *p*-cymene further underscores this effect. The tertiary site is preferred by all the catalysts but the tetraarylphthalimido catalysts are the most selective. A reasonable explanation for this is that when attack occurs at the 1° site, the isopropyl group interferes with the wall of the bowl leading to the enhanced selectivity for the 3° over the 1° site, similar to the model described in Figure 5.

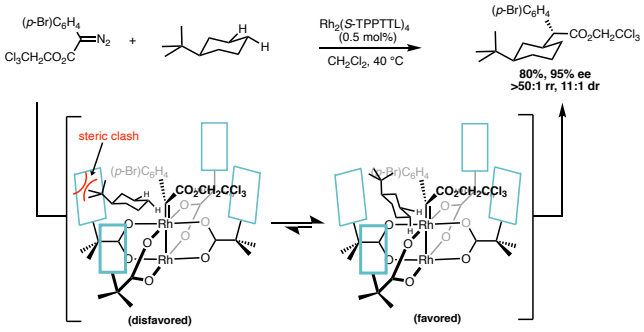


Figure 5. Model to rationalize C3 site selectivity in tetraarylphthalimido catalysts.

In conclusion, these studies demonstrate that a diverse series of large C_4-symmetric bowl-shaped catalysts can be readily generated by means of the self-assembly of four identical chiral tetraarylphthalimido-carboxylate ligands around a dirhodium core. The extended bowl shaped structures are capable of achieving highly site selective and enantioselective C—H functionalization reactions. The site-selectivity is considered to be controlled by how well substrates fit into the bowl shape of the catalysts during reactions with the rhodium-bound carbene. These extended systems can also lead to enhanced enantioselectivity and diastereoselectivity compared to the parent catalyst Rh_2(*S*-TPPTTL)$_4$. Future work will be directed towards the introduction of further functionality into the catalyst wall to refine the controlling elements beyond just steric hindrance for site-selective C—H functionalization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Complete experimental procedures, compound characterization, and computational modeling details are described in the Supporting Information. (PDF)

Accession Codes

The following crystal structures have been deposited in the Cambridge Crystallographic Data Centre: **11a** (CCDC 2156564), **11b** (CCDC 2160556), **11c** (CCDC 2161501), **11d** (CCDC 2158058), **11e** (CCDC 2160533), and **11f** (CCDC 2156513). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic DataCentre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 902 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Huw M. L. Davies; hmdavie@emory.edu

Author Contributions

# Zachary J. Garlets and Yannick T. Boni contributed equally to this work

Current Address:

Zachary J. Garlets current address: Bristol Myers Squibb, 1 Squibb Drive, New Brunswick, NJ 08903

Jiantao Fu current address: 1. Merck & Co Inc, 126 East Lincoln Ave Rahway, NJ, USA 07065

Notes

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.

ACKNOWLEDGMENT

Financial support was provided by NSF under the CCI Center for Selective C—H Functionalization (CHE-1700982) and financial support for the synthesis of the catalysts was provided by NIH (GM099142).

REFERENCES

(1) Godula, K.; Sames, D., C-H Bond Functionalization in Complex Organic Synthesis. *Science* **2006,** *312* (5770), 67-72.

(2) Gutekunst, W. R.; Baran, P. S., C—H functionalization logic in total synthesis. *Chem. Soc. Rev.* **2011,** *40* (4), 1976-1991.

(3) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S., Innate and Guided C—H Functionalization Logic. *Acc. Chem. Res.* **2012,** *45* (6), 826-839.

(4) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J., Recent applications of C—H functionalization in complex natural product synthesis. *Chem. Soc. Rev.* **2018,** *47* (23), 8925-8967.

(5) McMurray, L.; O'Hara, F.; Gaunt, M. J., Recent developments in natural product synthesis using metal-catalysed C-H bond functionalisation. *Chem. Soc. Rev.* **2011,** *40* (4), 1885-98.

(6.) Newhouse, T.; Baran, P. S., If C-H bonds could talk: selective C-H bond oxidation. *Angew. Chem. Int. Ed.* **2011,** *50* (15), 3362-74.

(7) Chen, D. Y.; Youn, S. W., C-H activation: a complementary tool in the total synthesis of complex natural products. *Chem. Eur. J.* **2012,** *18* (31), 9452-74.

(8) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K., C-H bond functionalization: emerging synthetic tools for natural products and pharmaceuticals. *Angew. Chem. Int. Ed.* **2012,** *51* (36), 8960-9009.

(9) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W., The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016,** *45* (3), 546-576.

(10) Wencel-Delord, J.; Glorius, F., C-H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat. Chem.* **2013,** *5* (5), 369-75.

(11) Upp, D. M.; Lewis, J. C., Selective C-H bond functionalization using repurposed or artificial metalloenzymes. *Curr Opin Chem Biol* **2017,** *37*, 48-55.

(12) Oohora, K.; Kihira, Y.; Mizohata, E.; Inoue, T.; Hayashi, T., C(sp3)-H bond hydroxylation catalyzed by myoglobin reconstituted with manganese porphycene. *J. Am. Chem. Soc.* **2013,** *135* (46), 17282-5.

(13) Zhou, A. Z.; Chen, K.; Arnold, F. H., Enzymatic Lactone-Carbene C—H Insertion to Build Contiguous Chiral Centers. *ACS Catal.* **2020,** *10* (10), 5393-5398.

(14) Hartwig, J. F., Evolution of C—H Bond Functionalization from Methane to Methodology. *J. Am. Chem. Soc.* **2016,** *138* (1), 2-24.

(15) Recent Advances in C—H Functionalization. *J. Org. Chem.* **2016,** *81* (2), 343-350.

(16.) Hartwig, J. F.; Larsen, M. A., Undirected, Homogeneous C—H Bond Functionalization: Challenges and Opportunities. *ACS Cent. Sci.* **2016,** *2* (5), 281-292.

(17) Ravelli, D.; Fagnoni, M.; Fukuyama, T.; Nishikawa, T.; Ryu, I., Site-Selective C—H Functionalization by Decatungstate Anion Photocatalysis: Synergistic Control by Polar and Steric Effects Expands the Reaction Scope. *ACS Catal.* **2018,** *8* (1), 701-713.

(18) Lanke, V.; Bettadapur, K. R.; Prabhu, K. R., Site-Selective Addition of Maleimide to Indole at the C-2 Position: Ru(II)-Catalyzed C—H Activation. *Org. Lett.* **2015,** *17* (19), 4662-4665.

(19) Neufeldt, S. R.; Sanford, M. S., Controlling Site Selectivity in Palladium-Catalyzed C—H Bond Functionalization. *Acc. Chem. Res.* **2012,** *45* (6), 936-946.

(20) Chen Mark, S.; White, M. C., A Predictably Selective Aliphatic C—H Oxidation Reaction for Complex Molecule Synthesis. *Science* **2007,** *318* (5851), 783-787.

(21) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q., Direct Sp3 α-C—H activation and functionalization of alcohol and ether. *Chem. Soc. Rev.* **2011,** *40* (4), 1937-1949.

(22) Niu, L.; Liu, J.; Liang, X.-A.; Wang, S.; Lei, A., Visible light-induced direct α C—H functionalization of alcohols. *Nat. Commun.* **2019,** *10* (1), 467.

(23) Lombard, F. J.; Coster, M. J., Rhodium(II)-catalysed intramolecular C-H insertion alpha- to oxygen: reactivity, selectivity and applications to natural product synthesis. *Org. Biomol. Chem.* **2015,** *13* (23), 6419-31.

(24) Wu, X.; Wang, M.; Huan, L.; Wang, D.; Wang, J.; Zhu, C., Tertiary-Alcohol-Directed Functionalization of Remote C(sp3)–H Bonds by Sequential Hydrogen Atom and Heteroaryl Migrations. *Angew. Chem. Int. Ed.* **2018,** *57* (6), 1640-1644.

(25) Solé, D.; Pérez-Janer, F.; Bennasar, M. L.; Fernández, I., Palladium Catalysis in the Intramolecular Carbene C-H Insertion of α-Diazo-α-(methoxycarbonyl)acetamides to Form β-Lactams. *Eur. J. Org. Chem.* **2018,** *2018* (32), 4446-4455.

(26) Doyle, M. P.; Ratnikov, M.; Liu, Y., Intramolecular catalytic asymmetric carbon-hydrogen insertion reactions. Synthetic advantages in total synthesis in comparison with alternative approaches. *Org. Biomol. Chem.* **2011,** *9* (11), 4007-16.

(27) Nakagawa, Y.; Chanthamath, S.; Liang, Y.; Shibatomi, K.; Iwasa, S., Regio- and Enantioselective Intramolecular Amide Carbene Insertion into Primary C-H Bonds Using Ru(II)-Pheox Catalyst. *J. Org. Chem.* **2019,** *84* (5), 2607-2618.

(28) Wang, J.-C.; Zhang, Y.; Xu, Z.-J.; Lo, V. K.-Y.; Che, C.-M., Enantioselective Intramolecular Carbene C—H Insertion Catalyzed by a Chiral Iridium(III) Complex ofD4-Symmetric Porphyrin Ligand. *ACS Catal.* **2013,** *3* (6), 1144-1148.

(29) Fu, L.; Wang, H.; Davies, H. M. L., Role of ortho-substituents on rhodium-catalyzed asymmetric synthesis of beta-lactones by intramolecular C-H insertions of aryldiazoacetates. *Org. Lett.* **2014,** *16* (11), 3036-9.

(30) Reddy, A. R.; Zhou, C.-Y.; Guo, Z.; Wei, J.; Che, C.-M., Ruthenium-porphyrin-catalyzed diastereoselective intramolecular alkyl carbene insertion into C-H bonds of alkyl diazomethanes generated in situ from N-tosylhydrazones. *Angew. Chem. Int. Ed.* **2014,** *53* (51), 14175-80.

(31) Soldi, C.; Lamb, K. N.; Squitieri, R. A.; Gonzalez-Lopez, M.; Di Maso, M. J.; Shaw, J. T., Enantioselective intramolecular C-H insertion reactions of donor-donor metal carbenoids. *J. Am. Chem. Soc.* **2014,** *136* (43), 15142-5.

(32) Ito, M.; Kondo, Y.; Nambu, H.; Anada, M.; Takeda, K.; Hashimoto, S., Diastereo- and enantioselective intramolecular 1,6-C—H insertion reactions of α-diazo esters catalyzed by chiral dirhodium(II) carboxylates. *Tetrahedron Lett.* **2015,** *56* (11), 1397-1400.

(33) Xu, X.; Deng, Y.; Yim, D. N.; Zavalij, P. Y.; Doyle, M. P., Enantioselective cis-beta-lactam synthesis by intramolecular C-H functionalization from enoldiazoacetamides and derivative donor-acceptor cyclopropenes. *Chem. Sci.* **2015,** *6* (4), 2196-2201.

(34) Miyazawa, T.; Minami, K.; Ito, M.; Anada, M.; Matsunaga, S.; Hashimoto, S., Enantio-and diastereoselective desymmetrization of α-alkyl-α-diazoesters by dirhodium(II)-catalyzed intramolecular C—H insertion. *Tetrahedron* **2016,** *72* (27-28), 3939-3947.

(35) Zhu, D.; Ma, J.; Luo, K.; Fu, H.; Zhang, L.; Zhu, S., Enantioselective Intramolecular C-H Insertion of Donor and Donor/Donor Carbenes by a Nondiazo Approach. *Angew. Chem. Int. Ed.* **2016,** *55* (29), 8452-8456.

(36) Xia, Y.; Wang, L.; Studer, A., Site-Selective Remote Radical C–H Functionalization of Unactivated C–H Bonds in Amides Using Sulfone Reagents. *Angew. Chem. Int. Ed.* **2018,** *57* (39), 12940-12944.

(37) Chen, M. S.; White, M. C., A Sulfoxide-Promoted, Catalytic Method for the Regioselective Synthesis of Allylic Acetates from Monosubstituted Olefins via C–H Oxidation. *J. Am. Chem. Soc.* **2004,** *126* (5), 1346-1347.

(38) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C., Serial Ligand Catalysis: A Highly Selective Allylic C–H Oxidation. *J. Am. Chem. Soc.* **2005,** *127* (19), 6970-6971.

(39) Alderson, J. M.; Phelps, A. M.; Scamp, R. J.; Dolan, N. S.; Schomaker, J. M., Ligand-Controlled, Tunable Silver-Catalyzed C—H Amination. *J. Am. Chem. Soc.* **2014,** *136* (48), 16720-16723.

(40) Zhu, Y.; Huang, K.; Pan, J.; Qiu, X.; Luo, X.; Qin, Q.; Wei, J.; Wen, X.; Zhang, L.; Jiao, N., Silver-catalyzed remote Csp3-H functionalization of aliphatic alcohols. *Nat. Commun.* **2018,** *9* (1), 2625.

(41) Xu, Y.; Yan, G.; Ren, Z.; Dong, G., Diverse sp3 C–H functionalization through alcohol β-sulfonyloxylation. *Nat. Chem.* **2015,** *7* (10), 829-834.

(42) Bunescu, A.; Butcher, T. W.; Hartwig, J. F., Traceless Silylation of β-C(sp3)–H Bonds of Alcohols via Perfluorinated Acetals. *J. Am. Chem. Soc.* **2018,** *140* (4), 1502-1507.

(43) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q., Weak Coordination as a Powerful Means for Developing Broadly Useful C—H Functionalization Reactions. *Acc. Chem. Res.* **2012,** *45* (6), 788-802.

(44) Liu, Y.; Ge, H., Site-selective C—H arylation of primary aliphatic amines enabled by a catalytic transient directing group. *Nat. Chem.* **2017,** *9* (1), 26-32.

(45) Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H., Cobalt-catalysed site-selective intra- and intermolecular dehydrogenative amination of unactivated sp3 carbons. *Nat. Commun.* **2015,** *6* (1), 6462.

(46) Dong, Z.; Dong, G., Ortho vs Ipso: Site-Selective Pd and Norbornene-Catalyzed Arene C—H Amination Using Aryl Halides. *J. Am. Chem. Soc.* **2013,** *135* (49), 18350-18353.

(47) Meng, G.; Szostak, M., Site-Selective C—H/C–N Activation by Cooperative Catalysis: Primary Amides as Arylating Reagents in Directed C—H Arylation. *ACS Catal.* **2017,** *7* (10), 7251-7256.

(48) Simmons, E. M.; Hartwig, J. F., Catalytic functionalization of unactivated primary C—H bonds directed by an alcohol. *Nature* **2012,** *483* (7387), 70-73.

(49) Xia, G.; Weng, J.; Liu, L.; Verma, P.; Li, Z.; Yu, J.-Q., Reversing conventional site-selectivity in C(sp3)–H bond activation. *Nat. Chem.* **2019,** *11* (6), 571-577.

(50) Tanaka, K.; Ewing, W. R.; Yu, J.-Q., Hemilabile Benzyl Ether Enables γ-C(sp3)–H Carbonylation and Olefination of Alcohols. *J. Am. Chem. Soc.* **2019,** *141* (39), 15494-15497.

(51) Shi, H.; Lu, Y.; Weng, J.; Bay, K. L.; Chen, X.; Tanaka, K.; Verma, P.; Houk, K. N.; Yu, J.-Q., Differentiation and functionalization of remote C—H bonds in adjacent positions. *Nat. Chem.* **2020,** *12* (4), 399-404.

(52) Zhuang, Z.; Yu, J.-Q., Lactonization as a general route to β-C(sp3)–H functionalization. *Nature* **2020,** *577* (7792), 656-659.

(53. Davies, H. M. L.; Beckwith, R. E. J., Catalytic Enantioselective C-H Activation by Means of Metal-Carbenoid-Induced C-H Insertion. *Chem. Rev.* **2003,** *103*, 2861-2903.

(54) Doyle, M. P., Catalytic Methods for Metal Carbene Transformations. *Chem. Rev.* **1986,** *86*, 919-939.

(55.) Doyle, M. P.; Forbes, D. C., Recent advances in asymmetric catalytic metal carbene transformations. *Chem. Rev.* **1998,** *98* (2), 911-935.

(56) Davies, H. M. L., Dirhodium tetra(N-arylsulfonylprolinates) as chiral catalysts for asymmetric transformations of vinyl- and aryldiazoacetates. *Eur. J. Org. Chem.* **1999,** *1999* (10), 2459-2469.

(57) Doyle, M. P., Perspective on Dirhodium Carboxamidates as Catalysts. *J. Org. Chem.* **2006,** *71*, 9253-9260.

(58) Davies, H. M. L.; Liao, K., Dirhodium tetracarboxylates as catalysts for selective intermolecular C—H functionalization. *Nat. Rev. Chem.* **2019,** *3* (6), 347-360.

(59) Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J.-Q., Site-Selective C(sp3)–H Functionalization of Di-, Tri-, and Tetrapeptides at the N-Terminus. *J. Am. Chem. Soc.* **2014,** *136* (48), 16940-16946.

(60) Zhang, Z.; Tanaka, K.; Yu, J.-Q., Remote site-selective C—H activation directed by a catalytic bifunctional template. *Nature* **2017,** *543* (7646), 538-542.

(61) Hartwig, J. F., Catalyst-Controlled Site-Selective Bond Activation. *Acc. Chem. Res.* **2017,** *50* (3), 549-555.

(62) Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L., Site-selective and stereoselective functionalization of non-activated tertiary C-H bonds. *Nature* **2017,** *551* (7682), 609-613.

(63) Oeschger, R.; Su, B.; Yu, I.; Ehinger, C.; Romero, E.; He, S.; Hartwig, J., Diverse functionalization of strong alkyl C—H bonds by undirected borylation. *Science* **2020,** *368* (6492), 736-741.

(64) Davies, H. M. L., Finding Opportunities from Surprises and Failures. Development of Rhodium-Stabilized Donor/Acceptor Carbenes and Their Application to Catalyst-Controlled C—H Functionalization. *J. Org. Chem.* **2019,** *84* (20), 12722-12745.

(65) Davies, H. M. L.; Morton, D. D., Guiding principles for site selective and stereoselective intermolecular C-H functionalization by donor/acceptor rhodium carbenes. *Chem. Soc. Rev.* **2011,** *40*, 1857-1869.

(66) Liao, K.; Liu, W.; Niemeyer, Z. L.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Sigman, M. S.; Davies, H. M. L., Site-Selective Carbene-Induced C—H Functionalization Catalyzed by Dirhodium Tetrakis(triarylcyclopropanecarboxylate) Complexes. *ACS Catal.* **2017,** *8* (1), 678-682.

(67) Wertz, B.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L., Comparison of 1,2-Diarylcyclopropanecarboxylates with 1,2,2-Triarylcyclopropanecarboxylates as Chiral Ligands for Dirhodium-Catalyzed Cyclopropanation and C—H Functionalization. *J. Org. Chem.* **2020,** *85* (19), 12199-12211.

(68) Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L., Site-selective and stereoselective functionalization of unactivated C—H bonds. *Nature* **2016,** *533* (7602), 230-234.

(69) Liu, W.; Ren, Z.; Bosse, A. T.; Liao, K.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stoltz, B. M.; Davies, H. M. L., Catalyst-Controlled Selective Functionalization of Unactivated C—H Bonds in the Presence of Electronically Activated C—H Bonds. *J. Am. Chem. Soc.* **2018,** *140* (38), 12247-12255.

(70) Fu, J.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L., Desymmetrization of cyclohexanes by site- and stereoselective C—H functionalization. *Nature* **2018,** *564* (7736), 395-399.

(71) Hashimoto, S.-I.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S., Enhancement of Enantioselectivlty in Intramolecular C-H Insertion Reactions of *alpha*-Diazo (*beta*-Keto Esters Catalyzed by Chiral Dlrhodlum(I1) Carboxylates. *Tetrahedron Lett.* **1993,** *34*, 5109-5112.

(72) Hashimoto, S.-I.; Watanabe, N.; Anada, M.; Ikegami, S., Site- and Enantiocontrol in Intramolecular C-H Insertion Reactions of a- Diazo Carbonyl Compounds Catalyzed by Dirhodium(H) Carboxylates. *J. Synth. Org. Chem.* **1996,** *54*, 988-999.

(73) Reddy, R. P.; Davies, H. M. L., Dirhodium tetracarboxylates derived from adamantylglycine as chiral catalysts for enantioselective C-h aminations. *Org. Lett.* **2006,** *8* (22), 5013-6.

(74) Reddy, R. P.; Lee, G. H.; Davies, H. M. L., Dirhodium Tetracarboxylate Derived from Adamantylglycine as a Chiral Catalyst for Carbenoid Reactions. *Org. Lett.* **2006,** *8*, 3437-3440.

(75) DeAngelis, A.; Boruta, D. T.; Lubin, J.-B.; Plampin, I. I. I. J. N.; Yap, G. P. A.; Fox, J. M., The chiral crown conformation in paddlewheel complexes. *Chem. Comm.* **2010,** *46* (25), 4541-4543.

(76) DeAngelis, A.; Shurtleff, V. W.; Dmitrenko, O.; Fox, J. M., Rhodium(II)-Catalyzed Enantioselective C–H Functionalization of Indoles. *J. Am. Chem. Soc.* **2011,** *133* (6), 1650-1653.

(77) Lindsay, V. N. G.; Lin, W.; Charette, A. B., Experimental Evidence for the All-Up Reactive Conformation of Chiral Rhodium(II) Carboxylate Catalysts- Enantioselective Synthesis of cis-Cyclopropane r-Amino Acids. *J. Am. Chem. Soc.* **2009,** *131*, 16383-16385.

(78) Basu, P.; Nigam, A.; Mogesa, B.; Denti, S.; Nemykin, V. N., Synthesis, characterization, spectroscopy, electronic and redox properties of a new nickel dithiolene system. *Inorganica Chim. Acta.* **2010,** *363* (12), 2857-2864.

(79) Fu, J.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L., Desymmetrization of cyclohexanes by site- and stereoselective C-H functionalization. *Nature* **2018,** *564* (7736), 395-399.

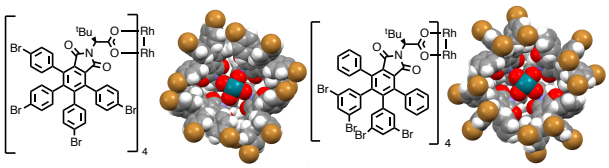
(80) Yoo, C.-J.; Rackl, D.; Liu, W.; Hoyt, C. B.; Pimentel, B.; Lively, R. P.; Davies, H. M. L.; Jones, C. W., An Immobilized-Dirhodium Hollow-Fiber Flow Reactor for Scalable and Sustainable C–H Functionalization in Continuous Flow. *Angew. Chem. Int. Ed.* **2018,** *57* (34), 10923-10927.

(81) Rackl, D.; Yoo, C.-J.; Jones, C. W.; Davies, H. M. L., Synthesis of Donor/Acceptor-Substituted Diazo Compounds in Flow and Their Application in Enantioselective Dirhodium-Catalyzed Cyclopropanation and C—H Functionalization. *Org. Lett.* **2017,** *19* (12), 3055-3058.

(82) Guptill, D. M.; Davies, H. M. L., 2,2,2-Trichloroethyl Aryldiazoacetates as Robust Reagents for the Enantioselective C—H Functionalization of Methyl Ethers. *J. Am. Chem. Soc.* **2014,** *136* (51), 17718-17721.

(83) Tortoreto, C.; Rackl, D.; Davies, H. M. L., Metal-Free C—H Functionalization of Alkanes by Aryldiazoacetates. *Org. Lett.* **2017,** *19* (4), 770-773.

SYNOPSIS TOC



- Ligands self assemble to generate C_4 symmetric catalysts
- High regio-, diastereo,- and enantioselectivity in catalyst-controlled C-H functionalization