Reactive Intermediates

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Stabilization of a Chiral Dirhodium Carbene by Encapsulation and a Discussion of the Stereochemical Implications

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Abstract: *For the first time, the stereochemical course of an asymmetric cyclopropanation can be discussed on the basis of experimental structural information on a pertinent chiral dirhodium carbene intermediate. Key to success was the formation of racemic single crystals of a heterochiral [Rh_2-{(S*)-PTTL}$_4$[=C(Ar)COOMe]][Rh_2[(R*)-PTTL]$_4$] (Ar = $MeOC_6H_4$; PTTL = N-phthaloyl-tert-leucinate) capsule, which has been characterized by X-ray diffraction. NMR spectroscopic data confirm that the obtained structural portrait is also relevant in solution and provide additional information about the dynamics of this species. The chiral binding pocket is primarily defined by the conformational preferences of the N-phthaloyl-protected amino acid ligands and reinforced by a network of weak interligand interactions that get stronger when chlorinated phthalimide residues are used.*

Soon after the discovery of the remarkable catalytic properties of $Rh_2(OAc)_4$ (**1**)[1] chiral versions of this parent dirhodium paddlewheel complex appeared in the literature.[2,3] The arguably most successful designs are manifest in **2**–**8** and relatives thereof, in which the bimetallic Rh^{II}–Rh^{II} core is μ-bridged by four identical carboxylate or carboxamide ligands.[4–8] The chosen homoleptic ligand sets form chiral binding pockets about the axial coordination sites that are capable of imposing high levels of enantioselectivity on numerous mechanistically distinct transformations, including cyclopropanation and C–H activation.[4–8]

The exact reasons why these particular complexes proved effective are, however, not clear. This situation transpires from the fact that different predictive models have been proposed in the past for catalysts of type **3**–**5** pioneered by Hashimoto and co-workers.[3] Based on the X-ray structure of [**3**·(EtOAc)], these authors originally suggested that a conformation of type **A** is relevant, in which two adjacent phthalimido groups are oriented to the top and the bottom face of the complex (α,α,β,β-conformation; Figure 1).[9] In contrast, Fox and co-workers proposed an "all-up" array (**D**), such that the phthalimido groups form a C_4-symmetric chiral pocket at Rh1, while the bulky *tert*-butyl groups prevent the substrate from reaching Rh2;[10,11] in so doing, they would shut off the racemic background reaction. This rationale was based on the X-ray structure of [**4**·$(EtOAc)_2$], which features this particular conformation in the solid state (which was later also found in other paddlewheel complexes of rhodium and copper).[12,13] This proposal was supported and, at the same time, challenged by NMR data reported by the groups of Charette and Ghanem,[14,15] which suggest that the pivotal conformer **D** equilibrates with conformers such as **B**, in which (at least) one of the phthaloyl residues is flipped downward. To complicate matters further, it was found that the adduct [**4**·(NC-C_6H_4-CN)] adopts a conformation of type **C** in the solid state, in which one of the phthaloyl groups is twisted by

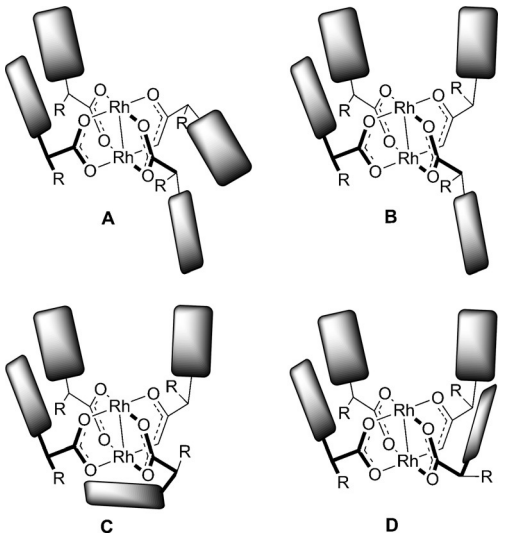
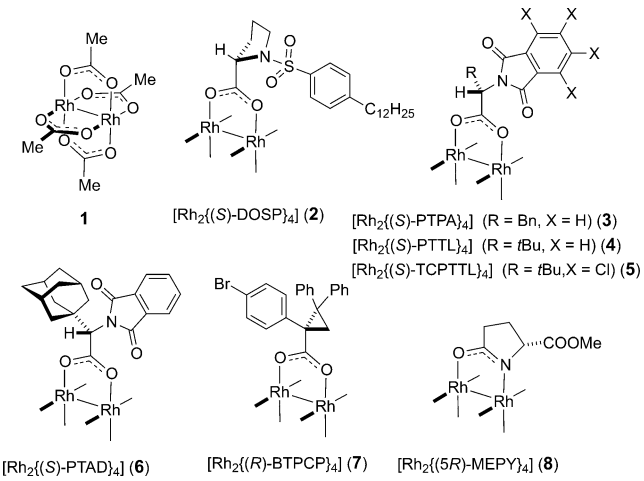


Figure 1. Schematic representations of different conformers previously invoked to explain the asymmetric induction of dirhodium complexes with N-protected amino acids as chiral ligands.



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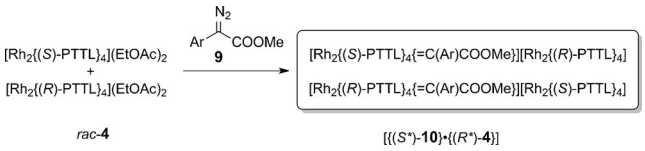
only about 80°.[12] While this fact showcases the flexibility of the complex, it also increases the conformational space that needs to be considered.

As even the closely related complexes [**3**·(EtOAc)], [**4**·(EtOAc)$_2$], and [**4**·(NC-C$_6$H$_4$-CN)] adopt different conformations in the solid state, any extrapolation drawn from the stereostructure of such precatalysts is necessarily ambiguous; direct inspection of the actual reactive intermediates is called for. As a consequence of their exceptional reactivity, however, dirhodium carbenes escaped experimental characterization for decades.[16] Only recently has our group been able to report the structures of a set of relevant rhodium carbene species in the solid state.[17–19] Although these data provided, for the first time, a detailed picture of the constitution and conformation of such intermediates, numerous attempts to grow crystals of dirhodium carbenes bearing one of the standard chiral ligand sets met with failure.

A solution was found after we started focusing our efforts on the use of racemic dirhodium tetracarboxylate complexes. Reminiscent of "Wallach's empirical rule" that racemic crystals sometimes show higher density than crystals composed of homochiral entities,[20,21] it was hoped that a better packing in the unit cell would impart the extra stability that it takes to isolate, crystallize, and fully characterize pertinent intermediates of this type. This tactic met with success when a racemic mixture of [Rh$_2$(PTTL)$_4$(EtOAc)$_2$] was treated with the diazo derivative **9** to give the corresponding complex carrying a prototype push/pull dirhodium carbene unit as the axial ligand (Scheme 1). In line with our previous experiences,[17,18] it proved necessary to prepare this species in a reaction medium containing fluorobenzene as cosolvent, which seems to exert a positive effect on the quality of the resulting single crystals.



Scheme 1. Composition of the unit cell of the product formed from *rac*-**4** and **9a**; Ar = MeOC$_6$H$_4$ (**9a**); Ar = Ph (**9b**).

The unit cell contains [{(*S*)-**10**}·{(*R*)-**4**}] and [{(*R*)-**10**}·{(*S*)-**4**}] in the centrosymmetric space group $P2_1/n$.[22] Each molecular unit comprises two dirhodium entities, which line up such that a carbene (*S*)-**10** formed on reaction of (*S*)-**4** with **9a** pairs with an unreacted (*R*)-**4** unit via the -OMe group on the aryl substituent, and vice versa (Figure 2). The outer Rh2 atoms of the resulting heterochiral adducts are end-capped by coordination to cocrystallized CH_2Cl_2, thereby forming capsules with alternatingly connected carbenes (see the Supporting Information). The phthalimido groups protruding from either side of such a heterochiral entity shield the central carbene unit; inspection of the space-filling model leaves little doubt that this effective "encapsulation" accounts for the stability of this complex in the solid state.[23] The intricacy of the unit cell with its disordered solute notwithstanding, the

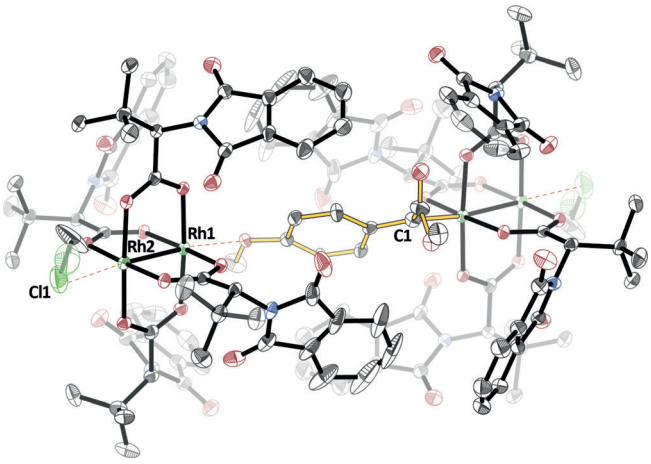


Figure 2. Structure of the heterochiral adduct [{(*S*)-**10**}·{(*R*)-**4**}], showing the encapsulation of the carbene unit and the end-capping of the outer Rh2 atoms with cocrystallized CH_2Cl_2; Ar = MeOC$_6$H$_4$. Disordered solute in the unit cell is not shown for clarity.

structure could be anisotropically refined to an *R*-factor of 5.9%.

A closer look at [Rh$_2${(*S*)-PTTL}$_4${=C(Ar)COOMe}] {(*S*)-**10**} as one of the asymmetric constituents shows that the bonding within the push/pull carbene unit is largely similar to what has previously been observed for its achiral siblings (Figure 3).[17,18,24] Characteristic is the remarkably long Rh1–C1 bond (2.004(9) Å), which is indicative of a low bond order. In contrast, the short distance between C1 and the *ipso* atom of the adjacent arene (C1–C4 1.430(18) Å) as well as the alignment of the aromatic ring and the carbene illustrate the crucial role of the ligand backbone in stabilizing the reactive site through orbital overlap with the π-cloud. In line with this notion, the ester is orthogonally disposed, which cuts off any destabilizing influence on the already highly electron-deficient carbene center. Even the particular orientation of the -COOMe group is readily understood on the basis of the X-ray structure: the -OMe unit points toward the more open quadrant in the front, whereas the smaller carbonyl group occupies the crowded backside (Figure 3A); inspection of the space-filling model shows that the inverse disposition is sterically much less favorable. The orthogonal alignment of the ester, in turn, is thought to have important consequences because it determines the trajectory by which a nucleophile approaches the reactive carbene center: it provides an efficient stereoelectronic road block that forces the incoming partner to glide in an "end-on" manner[25] alongside the arene, which is no obstacle in the almost coplanar orientation that it adopts.[18,26]

The entire push/pull carbene is staggered relative to the O-Rh-O axes of the bimetallic cage (Figure 3B). It resides within a narrow cleft formed by all four *N*-phthalimido groups, which adopt an α,α,α,α-orientation. The overall situation is, therefore, in good accord with the model proposed by Fox and co-workers.[10] The chiral calyx in the solid state is closer to C_2 rather than C_4 symmetry, as its aperture clearly has a long and a short dimension of approximately 7.8 and 8.8 Å, respectively.[27]

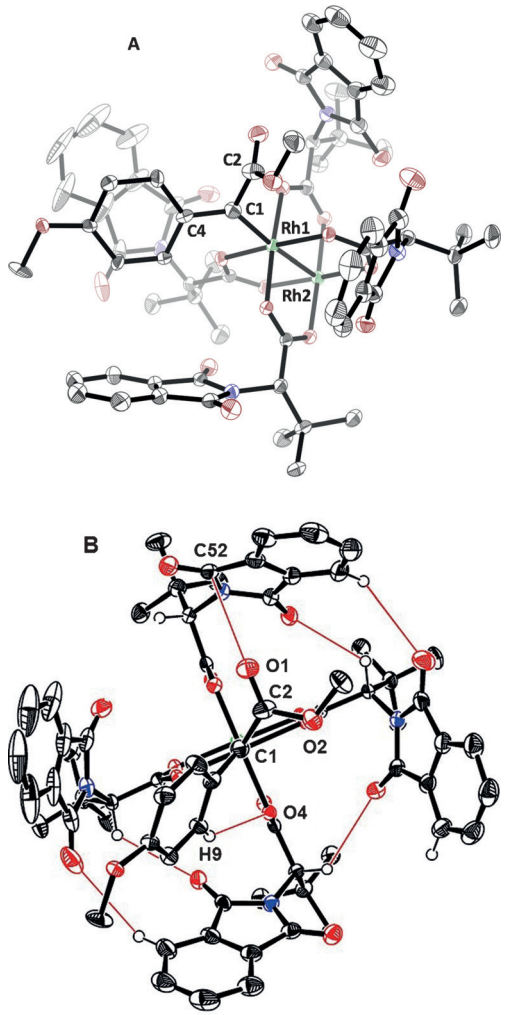


Figure 3. Structure of the [Rh_2{(*S*)-PTTL}$_4${=C(Ar)COOMe}] {(*S*)-**10**} unit in the solid state: A) projection from which the stereochemical course of a (cyclopropanation) reaction can be deduced; B) Newman-type projection along the C1-Rh1-Rh2 axis, which shows the staggered conformation of the carbene unit relative to the O-Rh-O axes and the C_2-symmetry of the asymmetric binding pocket; the red lines indicate likely weak peripheral interactions.

The projection shown in Figure 3 A allows conclusions to be drawn about the favored stereochemical course of an ensuing (cyclopropanation) reaction. Under the premise that a nucleophilic partner passes over the arene, it is clear that the backside of the carbene is shielded by the phthalimido substituent that has a π-stacking interaction with the adjacent *p*-methoxyphenyl ring (the shortest C···C contact is 3.6 Å); in contrast, the *Si*-face in the front is open to attack. For styrene as a prototypical reaction partner, the orientation shown in Figure 4 A is likely favorable, whereas exposure of the opposite face results in a clash with the ester and is hence disfavored on stereoelectronic and steric grounds (Figure 4 B). This model predicts that the reaction of diazoester **9a** with styrene in the presence of (*S*)-**4** as the precatalyst affords cyclopropane **11** as the major enantio- and diastereomer; data from the literature prove this to be the case (78 % *ee*, 84 % yield at 1 mol % loading).[28]

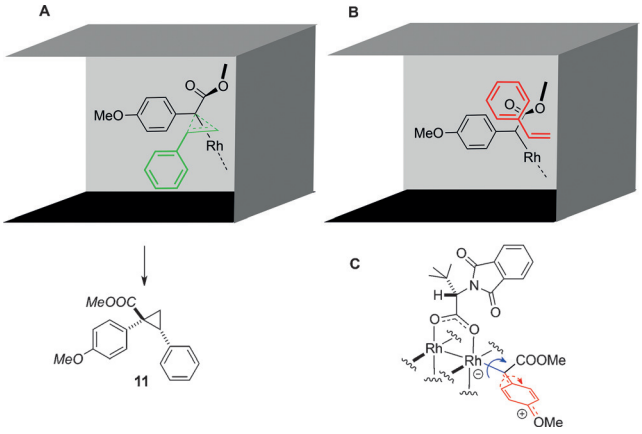


Figure 4. Selectivity mnemonic scheme for cyclopropanations catalyzed by [Rh_2{(*S*)-PTTL}$_4$] {(*S*)-**4**}: A) favored alignment; B) unfavored alignment; C) dynamic behavior of (*S*)-**10** deduced from the NMR data.

To validate this interpretation, we checked whether the static pose of the carbene and its chiral ligand environment portrayed in the X-ray structure has any bearing on the conformation in solution. The carbene signal at $\delta_C =$ 240.7 ppm indicates a notably electrophilic but not overly deshielded center.[16–18] The NMR data (CD_2Cl_2, −50 °C) show a single set of signals for the four μ-bridging chiral ligands, which is in excellent accord with a (close to) C_4-symmetric binding site. The spectra also infer a largely unrestricted rotation of the carbene about the Rh1−C1 bond (> tens of μs), which concurs with the low bond order deduced from the diffraction data. In contrast, the *p*-methoxyphenyl ring presents two inequivalent, slowly exchanging halves, as determined by NOESY/EXSY (that is, rotation must be slower than tens of ms). This finding mirrors the partial double bond character of the short C1−C4 bond and implies a largely coplanar orientation of the arene and the carbene center in solution (Figure 4 C). These structural attributes once again have their correspondence in the solid state. Since the symmetric halves of the individual phthalimide groups are magnetically inequivalent, the C–N bond and the C–COORh bonds must be relatively rigid on the NMR time scale. Importantly, distinct NOE contacts between aromatic phthalimide protons and the -COOMe group of the carbene unit corroborate the α,α,α,α-conformation in solution. While the NMR spectra reveal a malleable structure in solution with regard to the carbene dynamics, the gross features of the X-ray structure are all well retained. Hence, the stereochemical implications outlined above are deemed relevant, at least for reactions in solvents that are unlikely to interfere with the observed arrangement.

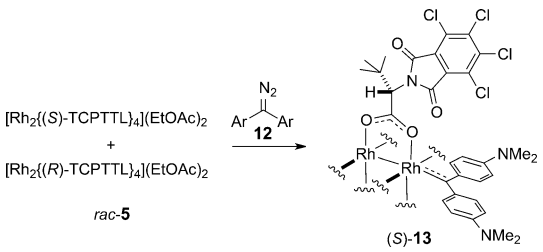
An interference of the medium seems likely for aromatic hydrocarbons able to disrupt the face-to-face π-stacking interaction between the *p*-methoxyphenyl ring and one of the phthalimido substituents. Actually, a strong solvent dependence of the enantioselectivity is documented in the literature for many rhodium-catalyzed asymmetric transformations.[4–8] While benzene was often found useless, cyclohexane and related media are privileged. Furthermore, one can argue that

the π-stacking visible in Figure 3A might be tuned to some extent by the substitution pattern in the chosen push/pull diazo derivative. In line with this notion, the reaction of diazoester **9a** (Ar = $MeOC_6H_4$) with styrene is known to result in a significantly higher *ee* value than that of the parent compound **9b** (Ar = Ph).[28]

However, π-stacking is more likely an adjuvant rather than the key structural determinant. The conformational preferences of the N-protected amino acid ligands themselves are likely more relevant (see below). Moreover, a network of peripheral contacts seems in place, most notably hydrogen-bonding interactions between the imide carbonyl groups and the slightly acidified protons α to the carboxylate groups of the ligands and/or the *peri*-protons on the phthalimide residues (Figure 3B). In addition, we note short contacts between the ester carbonyl oxygen atom and the second shielding phthalimide on the backside (O1···C52 3.24 Å), as well as between the *ortho*-H5 atom on the *p*-methoxyphenyl ring and an O-atom of the μ-bridging chiral ligand (H9···O4 2.59 Å). A larger set of experimental structures is desirable to assess the relevance of these interactions in more detail.

The attainable *ee* value is also critically dependent on whether a given substrate is able to react competitively at Rh2, the immediate environment of which is achiral. The *tert*-butyl groups in (*S*)-**10** certainly shield this center (Figure 2): this is achieved by orienting the C–C(Me_3) bonds roughly parallel to the central Rh–Rh axis; in so doing, the mutual steric interaction between these groups is minimized and access to the second axial binding site on the dirhodium cage impeded. This alignment is perhaps the single most important structure-determining factor.[29] Under this premise, it becomes clear why catalysts derived from amino acids other than *tert*-leucine deviate from the α,α,α,α-conformation (see above) more readily and, therefore, often lead to lower induction. Despite the critical positioning of the *tert*-butyl groups on the same face, a sizeable pore of ≥7.3 Å inner diameter remains, through which certain substrates might be able to penetrate and reach Rh2 given a certain conformational flexibility of the overall array. The fact that CH_2Cl_2 is docked onto Rh2 through the large chlorine atom underscores this aspect (Figure 2). Replacing the *tert*-butyl residues by even larger substituents should help disfavor a competing racemic background reaction. This design concept has already been turned to practice by Davies and co-workers who introduced the [Rh_2(PTAD)$_4$] precatalyst **6** carrying adamantyl groups, which often proved superior to the (more readily available) [Rh_2(PTTL)$_4$] series in terms of asymmetric induction.[30]

It has been shown in the literature that placement of halogen substituents on the rim of the phthalimide residues of such precatalysts can lead to higher asymmetric induction.[11a,31] Steric, stereoelectronic, and halogen-bonding effects[32] can be invoked. In an attempt to provide experimental evidence, we tried to grow crystals of the push/pull carbene analogous to (*S*)-**10** starting from the chlorinated precatalyst *rac*-**5**. While these attempts have so far met with failure, the more stable push/push carbene complex (*S*)-**13** was obtained in crystalline form when the diaryldiazo derivative **12** was used as the substrate (Scheme 2).



Scheme 2. Preparation of a push/push carbene; Ar = $Me_2NC_6H_4$. In contrast to [{(*S**)-**10**}·{(*R**)-**4**}], *rac*-**13** crystallized as a conglomerate (space group $P2_1$).

The gross structure of (*S*)-**13** is largely similar to that of (*S*)-**10** (Figure 5) and a comparison is, therefore, appropriate. The electron-rich *p*-dimethylaminophenyl ring flanking the carbene is π-stacked with the tetrachlorophthalimide from the ancillary ligand; as expected, this interaction seems stronger than in the nonchlorinated complex (*S*)-**10**, as

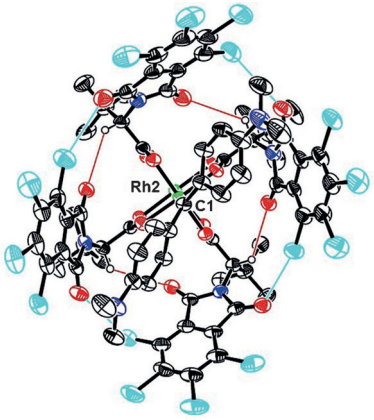


Figure 5. Structure of (*S*)-**13** in the solid state shown in a Newman-type projection along the C1-Rh1-Rh2 axis; the lines indicate inter-ligand O···Cl halogen (cyan) and C=O···H (red) bonding interactions.

evident from the shortened distance between the interacting groups (3.95 Å in (*S*)-**13** versus 4.13 Å in (*S*)-**10**). Arguably more significant, however, are the peripheral halogen-bonding interactions, which are similar to the ones previously observed for precatalysts of this type.[11a,33] Three of the four contacts between the imide carbonyl groups and an *ortho*-chlorine substituent on the adjacent halogenated phthaloyl rings (2.92, 3.12, 3.27, 3.48 Å) are (significantly) shorter than or equal to the sum of the van der Waals radii of oxygen and chlorine (3.27 Å). As a result of these cooperative effects, the chiral calyx of (*S*)-**13** is tighter and arguably more rigid than that of the nonchlorinated analogue (*S*)-**10.** The structure of (*S*)-**13**, therefore, provides a compelling rationale for the high asymmetric induction frequently obtained with catalysts of the TCPTTL series.[11a,31]

In summary, the first X-ray structures of two chiral dirhodium carbene complexes are presented. As the key structural features are retained in CD_2Cl_2 solution, they are relevant for a discussion of the absolute and relative

stereochemistry induced by dirhodium precatalysts endowed with *N*-phthaloyl-protected amino acids as ancillary ligands. The data confirm a model originally proposed by Fox and coworkers that an α,α,α,α-conformation accounts for the induced chirality.[10,12,34] The conformational preferences of the ancillary ligands together with a network of weak peripheral forces define a malleable yet effective chiral binding site about Rh1; although Rh2 is sterically decommissioned, it is thought to assist the actual bond formation as an effective electronic buffer.[24]

Keywords: asymmetric synthesis · carbenes · cyclopropanes · reactive intermediates · rhodium

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[21] This empirical observation has many exceptions, cf. Ref. [20b]; the fact that [{(*S**)-**10**}·{(*R**)-**4**}] crystallizes as a racemate whereas *rac*-**13** crystallizes as a conglomerate is one more example.

[22] CCDC 1481518 [(*S*)-**13**] and 1481519 ([{(*S**)-**10**}·{(*R**)-**4**}]) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Additional crystallographic information is contained in the Supporting Information.

[23] Once formed, these crystals are more stable than those of any other dirhodium carbene that we have managed to isolate so far, cf. refs. [17,18]; they can be stored for extended periods of time, even at ambient temperature. When dissolved in an appropriate medium, however, the carbene proved fully active and catalytic turn-over of the dirhodium cluster was restored.

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[29] Additional support for this notion comes from the fact that even carbenes unable to engage in classical π-π-stacking react with high selectivity, see Refs. [8c,10]. If the conformational preference of the *tert*-leucine-derived ancillary ligands in concert with

an ensemble of weak interligand forces is the major determinant for the shape of the chiral binding site, carbenes bearing a reasonably large aliphatic rather than aromatic substituent should adopt a similar orientation within the wider cleft of the C_2-symmetric cavity.

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[34] This assumption was also made in recent computational studies, see Y.-S. Xue, Y.-P. Cai, Z.-X. Chen, *RSC Adv.* **2015**, *5*, 57781 – 57791.

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