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# Beyond the Limits of Atropochirality: Design of Highly Conformationally Restrained Biaryls with Bridgehead Phosphine Oxide

Lucas Mele,[a] Rachida Babouri,[a] Jean-Luc Pirat,[a] Eder Tomás-Mendivil,[b] David Martin,[b] Tahar Ayad,\*[a] and David Virieux\*[a]

**Abstract:** In the last three decades, reacting sterically congested ortho-substituted arenes to form atropochiral biaryls is an appealing venture and a challenging subject that has garnered significant attention. Therefore, there is interest in developing methods to prepare these compounds. In this study, an efficient approach to produce a new class 2,2' disubstituted biaryls bridgehead phosphine oxides with an unusual topology and exceptional conformational stability is presented. Our methodology demonstrates that depending on the substitution pattern on the aryl moieties, the methanophosphocine backbone could be rigid enough to observe a double atropochirality, resulting in an under covered class of molecules. Notably, our studies revealed that replacing only one hydrogen at the ortho position by a fluorine atom led to sufficiently restricted rotation at temperatures below 80 °C, extending “far away” the limits of atropostability. Finally, our investigations, which employed variable-temperature NMR spectroscopy and DFT calculations, yielded unique insights into the isomerisation mechanism, indicating that the two biaryl motifs are fully independent in spite of their proximity

## Introduction

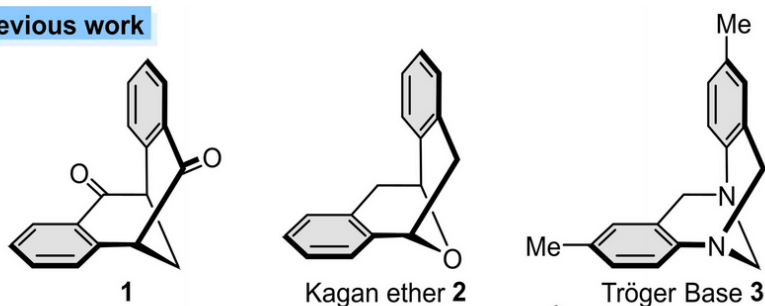
Since the discovery of molecular asymmetry, chemists have been fascinated with unconventional chiral topologies.<sup>1</sup> In recent years, molecules with seemingly exotic chirality have become more common, sparking interest in their synthesis and chemical properties. Atropisomerism, one such chiral topology, has garnered attention from several groups, particularly since the emergence of BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) which is now considered as a privileged ligand in asymmetric synthesis.<sup>2</sup> The literature is also replete with naturally occurring bioactive compounds or materials that exhibit axis of chirality.<sup>3</sup> Although initially seen as a source of complexity by medicinal chemists, modern asymmetric methods<sup>4</sup> have allowed the development of conformationally stable atropisomers that are now marketed drugs or drug candidates in clinical phases.<sup>5</sup>

For all these reasons, the biaryl motif is universally recognized as a privileged scaffold that is increasingly used as a chiral inducer in numerous asymmetric catalysis.<sup>6</sup> Atropisomerism generally occurs when the rotation of a single  $\sigma$ -bond connecting two molecular fragments is restricted. This hindered rotation is usually caused by steric constraints, which can be enhanced by electronic effects, resulting in slow interconversion of the two enantiomers. Biaryl compounds are undoubtedly fundamental atropochiral building-blocks, where the size and number of *ortho-ortho'*-substituents strongly determine the conformational stability and hinder the rotation of the pivotal bond connecting the biaryl motif.<sup>7</sup> The energy barrier of atropisomerisation is then directly related to the bulkiness of the substituents. However, the reaction of sterically congested *ortho*-substituted arenes to form atropochiral biaryls is still a challenging task. Therefore, there is still need for efficient synthesis of highly conformationally constrained biaryl atropisomers.<sup>8</sup>

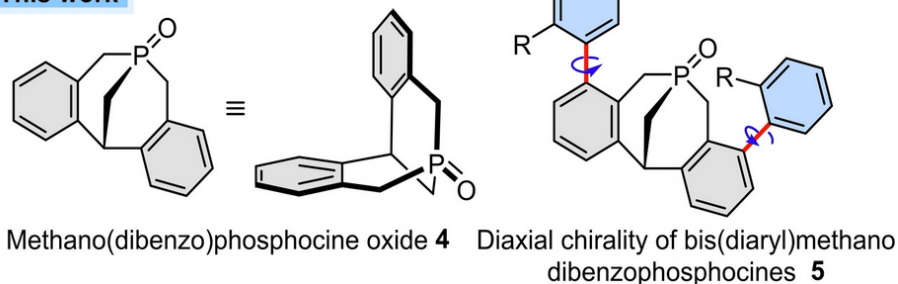
2,3 : 6,7-Dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione **1**,<sup>9</sup> Kagan ether<sup>10</sup> **2** and Tröger bases<sup>11</sup> **3** are representative examples of conformationally rigid  $\Lambda$ -shaped molecules. Among these, Tröger bases have suited significant interest in supramolecular chemistry and in ligand design.<sup>12</sup> Following our recently published synthesis of methanophosphocines **4**, a new class of P-bridgehead bicyclic molecules adopting a similar shape,<sup>13</sup> we hypothesized that aryl disubstituted methanophosphocines **5** may present an

unusual topology. Specifically, we anticipated that methanophosphocine backbone could be rigid enough to observe a double atropochirality when the biaryl motif was polysubstituted resulting that have received little attention but were recently highlighted by Bao and Bonne (Figure 1).<sup>14</sup> To the best of our knowledge, only very few papers embarked bridgeheaded structural motifs closely fused to a biaryl and none of them have discussed the asymmetric behavior of such systems.<sup>15</sup> Even the recent and elegant work of Wencel-Delord et al., who reported an efficient and tunable method to unsymmetrical bisbiaryl via a pericyclic reaction, did not highlight this feature.<sup>16</sup> In this paper, we describe how the topology of constrained biaryls bridgehead phosphine oxides, namely disubstituted methanodibenzophosphocines **5**, pushes the boundaries of axial chirality, thus paving the way for designing and developing potentially new chiral ligands.

#### Previous work



#### This work



**Figure 1** :  $\Lambda$ -shaped molecules **1–3** and methano(dibenzo)phosphocine derivatives **4–5**.

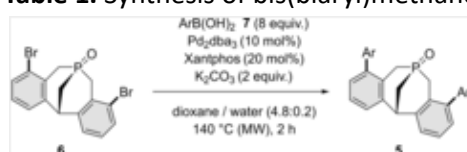
## Results and Discussion

### Synthesis of bis(diaryl)methanodibenzophosphocines **5**

Palladium catalyzed reactions are known to be sensitive to the steric bulk of the partners, and typically require high temperatures, highly reactive reagents or carefully designed catalytic systems for effective C–C bond formation.<sup>17</sup> In keeping with this knowledge, we explored the Suzuki–Miyaura coupling of 4,8-dibromo-5,7,12-trihydro-6,12-methanodibenzo[*c,f*]-phosphocine oxide **6**, which has been previously obtained by gold-catalyzed intramolecular double hydroarylation of alkynes.<sup>13</sup> To this end, bromo substituted methanophosphocine **6** was reacted with an excess of phenyl boronic acid **7 a** (Ar=Ph, 8 equivalents) in the presence of 10 mol % of palladium tetrakis(triphenylphosphine) in a mixture of dioxane/water (96:4) and potassium carbonate as a base (Table 1). The mixture was heated at 110 °C for 1

h under microwave irradiation. After purification, the expected methanophosphocine **5 a** was isolated in excellent 96 % yield (entry 1). Notably, attempts to repeat the aforementioned Suzuki–Miyaura reaction led to irreproducible results, possibly due to the high sensitivity of palladium tetrakis(triphenylphosphine) complex to oxygen. Gratifyingly, after intensive optimization, we found that this issue could be resolved by conducting the reaction with 10 mol % of the less sensitive Pd<sub>2</sub>dba<sub>3</sub> as a palladium source in the presence of 20 mol % of the bidentate Xantphos ligand, at 140 °C for 2 h under microwave irradiation, providing **5 a** in similar high yield. With the optimal conditions established, we explored the scope of the reaction using dibromo-substituted methanophosphocine **6** and various functionalized arylboronic acids. As shown in Table 1, the reactions generally proceeded smoothly, providing the corresponding bis(diaryl)methano-dibenzophosphocines **5 a–m** in yields ranging from 26 % to 96 % (entries 1–13).

**Table 1.** Synthesis of bis(biaryl)methanophosphocines **5 a–m**.<sup>[a]</sup>



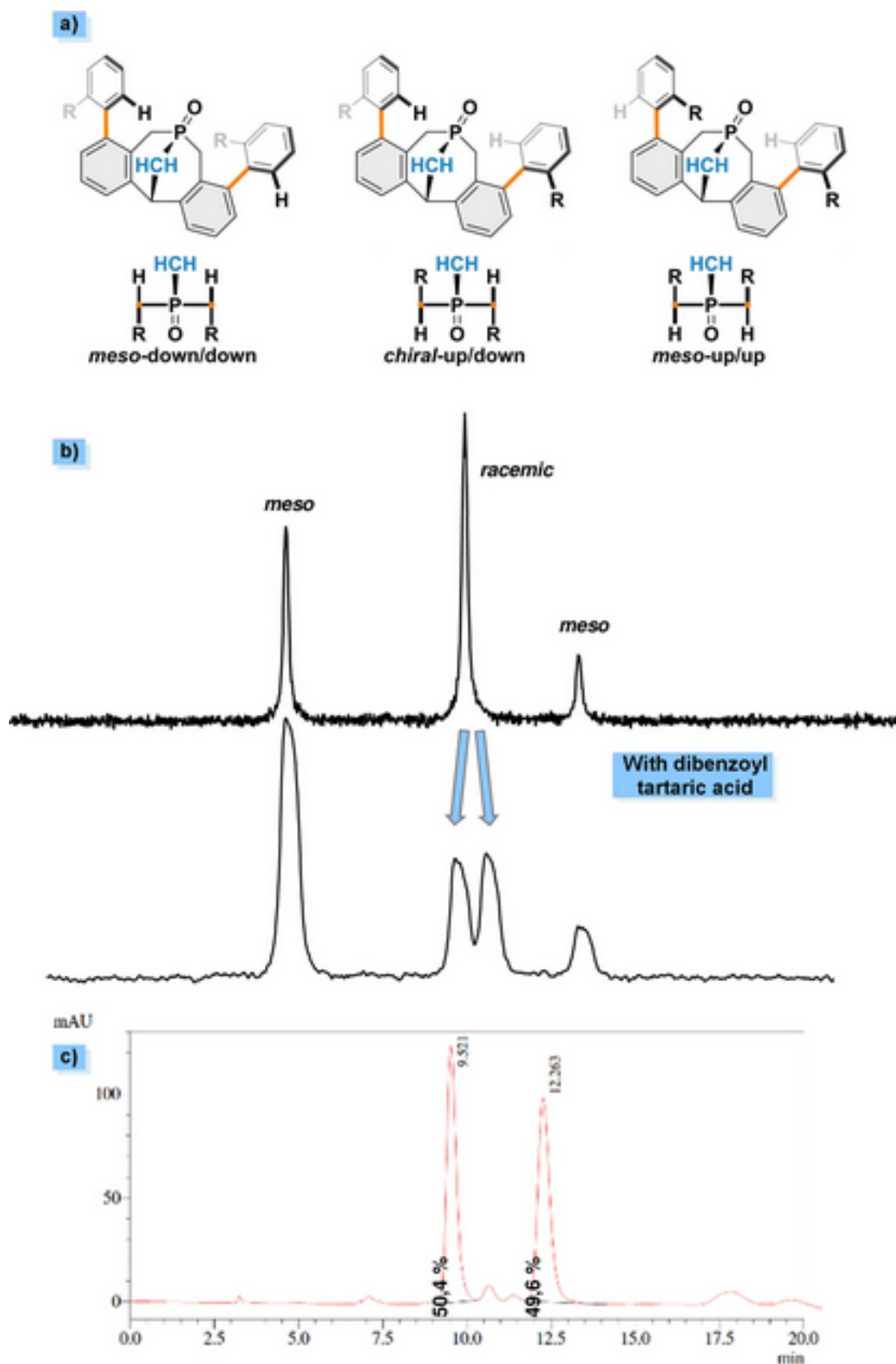
entry	Ar	yield [%] <sup>[a]</sup>
1	Ph	<b>5 a</b> 96
2	2-(6'-MeO)Naphthyl	<b>5 b</b> 81
3	4-PhC <sub>6</sub> H <sub>4</sub>	<b>5 c</b> 79
4	4-pyridyl	<b>5 d</b> 64
5	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>5 e</b> 54
6	3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>5 f</b> 27
7	3-MeOC <sub>6</sub> H <sub>4</sub>	<b>5 g</b> 70
8	2,3-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>5 h</b> 73
9	2,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>5 i</b> 26
10	2,3-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>5 j</b> 83
11	2,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>5 k</b> 52
12	1-Naphthyl	<b>5 l</b> 56
13	2,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>5 m</b> 63

[a] Reaction conditions: **6** (1 mmol), ArB(OH)<sub>2</sub> · **7** (8 equiv.), Pd<sub>2</sub>dba<sub>3</sub> (10 mol %), Xantphos (20 mol %), K<sub>2</sub>CO<sub>3</sub> (2 equiv.), dioxane/H<sub>2</sub>O (1.98:0.02 mL), 140 °C (MW), 2 h. [b] Isolated yields.

### Atropisomery in bis(diaryl) methanodibenzophosphocines **5**

To investigate the presence of different diastereomers, <sup>31</sup>P{<sup>1</sup>H} NMR analyses were performed. Results showed that only one <sup>31</sup>P NMR signal was observed for bis(aryl)methanophosphocine derivatives **5 a–g** which were unsubstituted in *ortho*-positions. It is generally accepted that most of tri- and tetra-substituted biphenyls exhibit atropochirality. Interestingly, bis(aryl)methano-dibenzophosphocines **5 h–m** that only possessed *ortho* substituents on the aryl moieties displayed the presence of three signals in <sup>31</sup>P NMR in a ratio 1:2:1 (Figure 2). This result indicated the presence of three diastereomers and clearly demonstrated that *ortho* substituted derivatives **5 h–m** were constrained enough to adopt non-planar ground states. The

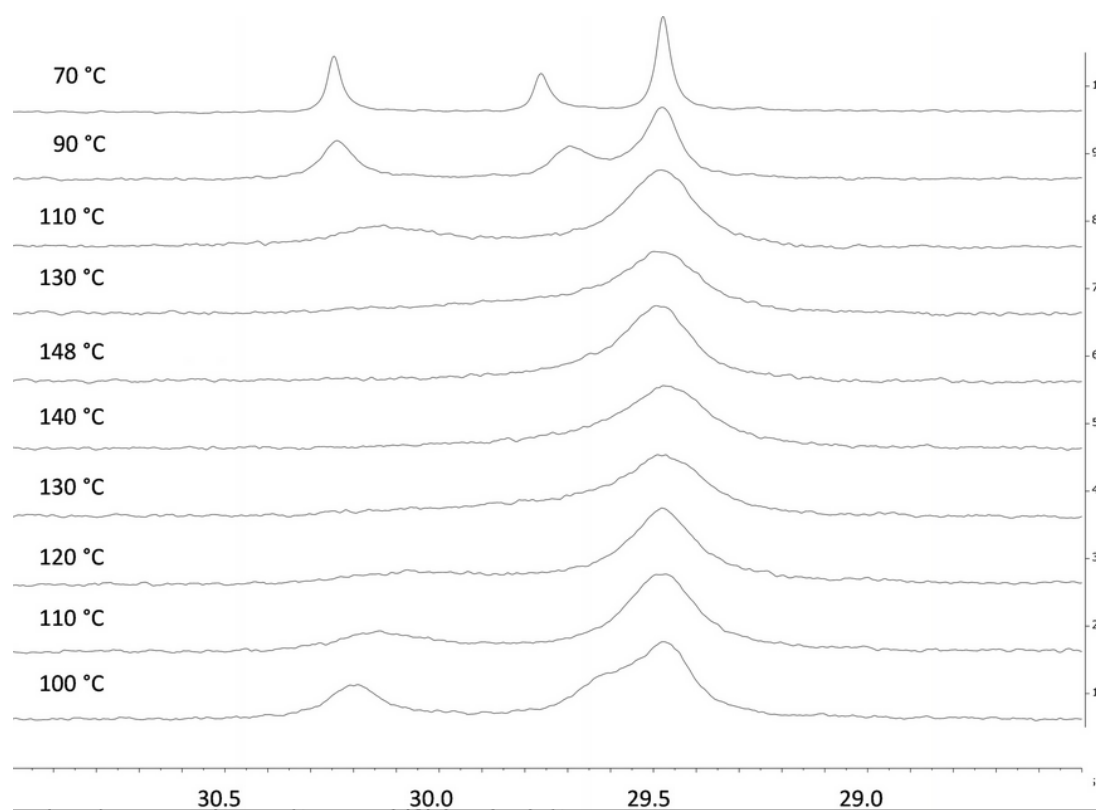
nature of these diastereomers depended solely on the relative orientation of the *ortho*-substitution of biaryl-substituents. Considering the methylene CH<sub>2</sub>-bridge, two meso-diastereomers (meso-down/down and meso-up/up) could be formed whereas the latter was the racemic chiral derivative (chiral-up/down or chiral-down/up) (Figure [2a](#)). The existence of four different stereoisomers was confirmed by the presence of the corresponding four signals when the <sup>31</sup>P NMR was recorded in the presence of *L*-dibenzoyl tartaric acid as a chiral resolver (Figure [2b](#)). The two extreme signals were assigned to the meso derivatives while the signal of chiral enantiomers was split into two singlets. Notably, this splitting was also confirmed by chiral HPLC analysis of the racemic 1-naphthyl derivative **51** as illustrated in Figure [2c](#). Indeed, for compound **51**, we were able to separate the two meso compounds from the racemic chiral derivative by flash column chromatography thus opening the way to access enantiopure chiral ligands with this unusual topology. From a stereochemical perspective, this system shares some similarities with 2,3,4-trihydroxyglutaric acid.<sup>18</sup> By analogy, the two meso stereoisomers are achiral and the central phosphorus atom is stereogenic but not chirotopic. For the two enantiomers, although chirotopic, the phosphorus atom is not a stereogenic center as it bears two identical ligands. This situation is not common for molecules bearing chiral centers, and to our knowledge, has never been described for axially chiral systems.



**Figure 2 :** a) Structure of the stereoisomers ( $R \neq H$ ), b)  $^{31}\text{P}\{^1\text{H}\}$  NMR of stereoisomers and splitting of enantiomers in the presence of *L*-dibenzoyl tartaric acid, c) Chiral HPLC (IA, 85/15: cyclohexane/isopropanol 1.0 mL/min, 25 °C) of racemic **5** I.

Remarkably, beside the hindered 1-naphthyl derivative **5 l**, stable stereoisomers were also observed from mono-substituted biaryl methanophosphocines **5 i–5 k** where the *ortho*-substituents were respectively a methyl (**5 h** and **5 i**), a methoxy (**5 j** and **5 k**). Even more interestingly, the observation of diastereomers at room temperature for the bis(2,4-difluorophenyl)methanophosphocine **5 m** is noteworthy given that conformationally stable 2,2' disubstituted biphenyls remains extremely rare in literature, and only those with bulky *ortho* and *ortho'*-groups do not racemize at room temperature.<sup>19</sup> The apparent size of *ortho*-substituent (steric hindrance) determines the atropostability. With a Van der Waals effective radius of 1.47 Å, fluorine as individual atom is slightly larger than hydrogen (1.20 Å) and quasi isosteric to the “naked” oxygen (1.52 Å). For these reasons, fluorine is considered as a good isostere of a hydrogen atom while being smaller than a hydroxyl group.<sup>20</sup>

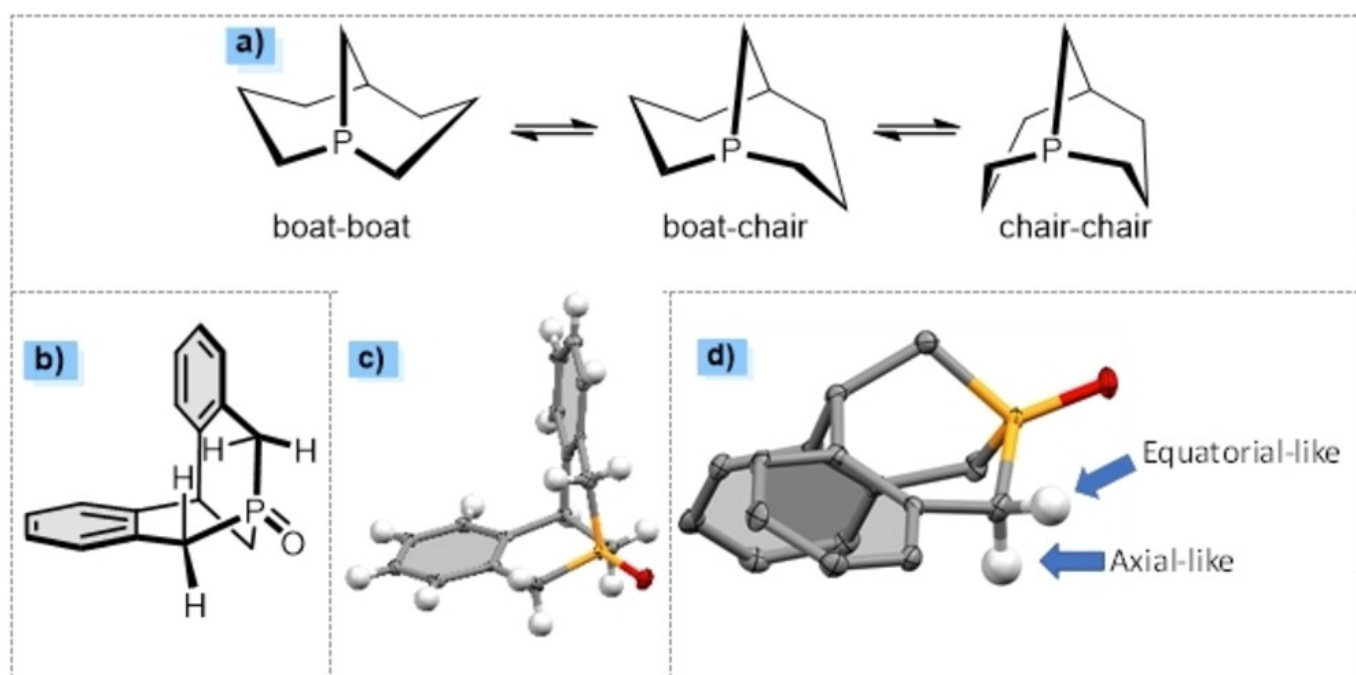
Variable-temperature NMR spectroscopy is considered as the most convenient and sensitive technique to detect and measure the rotational barrier of biaryl compounds.<sup>21</sup> Due to the presence of phosphorus atom, investigation of the aryl-aryl rotational barrier was accomplished directly by  $^{31}\text{P}\{^1\text{H}\}$  NMR experiments. To study the dynamic behavior of methanophosphocines, the *ortho*-methoxy-substituted compound **5 k** was used as a model substrate in deuterated DMSO as solvent. The sample was heated from 25 °C to 148 °C and the barrier of rotation was calculated by measuring changes in the shape of NMR spectra as a function of temperature (Figure 3). At room temperature, the line shape is constituted by the three NMR signals, indicating that no equilibration occurred at NMR timescale. Broadening of the signals was observed when the temperature rose to 90 °C. At 110 °C, only two broad singlets were visible in the NMR spectra. The complete coalescence was achieved at 130 °C and rising the temperature to 148 °C resulted in a sharper singlet signal. Cooling down to room temperature, clearly showed the reversibility of the phenomenon and resulted in the recovery of the three singlets confirming that they were related to the same molecule with different configuration/conformation.



**Figure 3** : Variable temperature  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra of methanophosphocine **5 k** in  $[\text{D}_6]\text{DMSO}$ .

## Molecular structure, conformation and DFT calculations

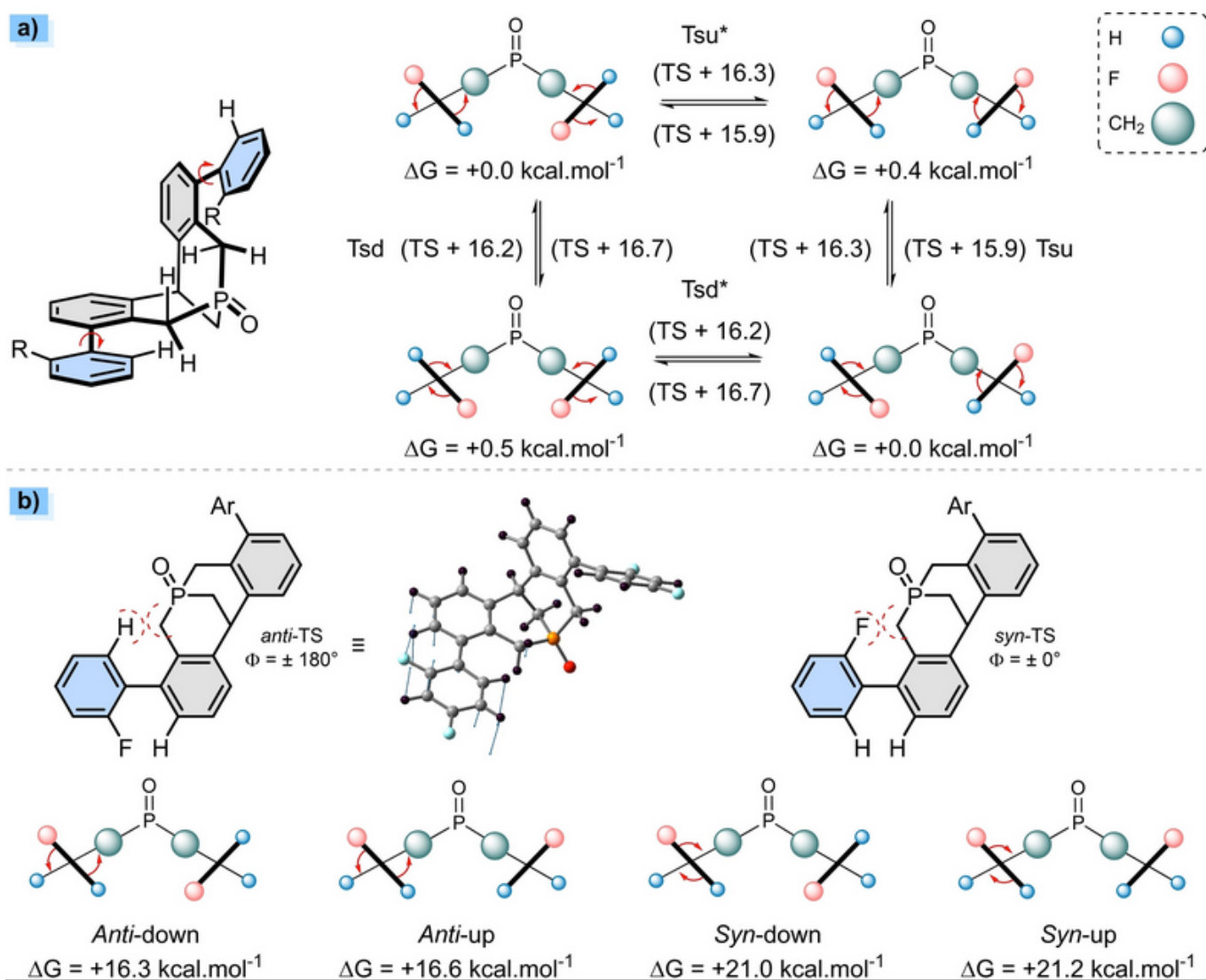
Bicyclo[3,3,1]nonane and related compounds generally exhibit conformational flexibility. As mentioned by Issleib<sup>22</sup> and later discussed,<sup>23</sup> these compounds coexist under three main conformations: boat-boat, boat-chair and chair-chair conformations (Figure 4a). However, due to the presence of fused phenyl rings, dibenzomethanophosphocines **4** exhibit a unique conformation with a cleft-like shape (Figure 4b and 4c). This strained system resulted in a specific orientation of methylene PCH<sub>2</sub>Ar where the hydrogen atoms are positioned in pseudo-axial and pseudo-equatorial positions (Figure 4d).



**Figure 4** : a) Conformations of phosphabicyclo[3,3,1]nonane vs dibenzomethanophosphocine **4**, b) and c) cleft view, d) Orientation of hydrogens of PCH<sub>2</sub> group.

Ab initio methods (B3LYP/6-311G\*\*) were used to calculate the different conformations of ground states and transition states.<sup>24</sup> First, optimized calculations were performed on the fluorine-derivative **5m** to estimate the energy difference for the smallest *ortho*-substituent (R = F). The calculations showed that the *ortho*-substituted biaryl motifs adopt an angular shape in their ground states (Figure 5a). Little energy differences were observed among all stereoisomers (0.4–0.5 kcal.mol<sup>-1</sup>), indicating that there is no preferred conformation.



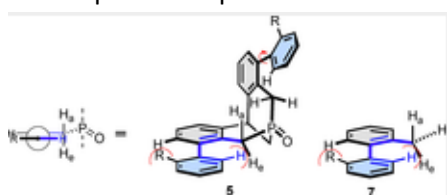


**Figure 5** : Ab initio calculation (B3LYP/6-311G\*\*), a) of the different conformations of ground states and transition states for dibenzomethanophosphocine **5 m**, b) Energy barrier for rotation for **5 m**. (DFT-calculations were accomplished at 25 °C).

To determine the energy barrier for rotation of the C–C bond, DFT calculations were performed using bis(2,4–fluorophenyl)methanophosphocine **5 m** as a model substrate (Figure 5b). The system consists of four transition states where one biaryl system is planar (in either *anti*- or *syn*-route), while the second one is an angular and stable conformation (either up or down). There are two *anti*-TS with the second fluoroaryl group oriented up or down and two *syn*-transition states. The preferred path for atropisomerisations occurs through a transition state with the minimum of energy. With a barrier of  $16.4 \text{ kcal.mol}^{-1}$ , the *anti*-routes are systematically preferred to the *syn*-paths which are  $4.1 \text{ kcal.mol}^{-1}$  higher in energy. As observed for the ground states, the conformation of the second aryl group does not affect the energy, meaning that the two biaryl-systems are fully independent, and their respective conformations do not affect each other. The exchange rate between two stereoisomers was calculated at the coalescence temperature and compared with the one extrapolated from NMR analysis. As expected, the results were consistent with a mean error of less than 10 % (see Supporting Information for details).

We hypothesized that atropisomerization in methano-phosphocines **5** could be compared to the same phenomenon in 2,2'-disubstituted biaryls **7** (Table 2). The lowest energy transition states for substituted methanodibenzophosphocines **5 h–m** (*anti* vs *syn*-route) showed that the two phenyl rings of a biphenyl motif are almost in the same plane. The *ortho*-hydrogen (blue H) bisects the hydrogen atoms of PCH<sub>a</sub>H<sub>c</sub> group, and the system is rigidified by the bicyclic core. The phosphoryl is then rejected in the *anti*-position and it does not interact with the biaryl motif. On the other hand, 2-methyl-biphenyls **7** with variable R-group in position 2' have a methyl substituent that is free to move and has no fixed conformation. The difference of transition state energy between methanophosphocines **5 h–m** and biaryls **7** is directly linked to the rigidification induced by the bicyclic core. DFT calculations were extended to the bis(diaryl)methanophosphocines **5 h–m** and their rotational barriers were compared with reported data for the 2,2'-disubstituted biaryls.<sup>25</sup> The structural strain resulted in an increase in energy of around 5 kcal.mol<sup>-1</sup>. This difference is observed even for substituents as small as fluorine and is significant enough to observe an atropostability for Me- and naphthyl- substituted methanophosphocines **5 h–i** and **5–l**.

**Table 2.** Compared atropisomerization barriers of 2,2'-disubstituted biaryls **7** vs methanophosphocines **5**.

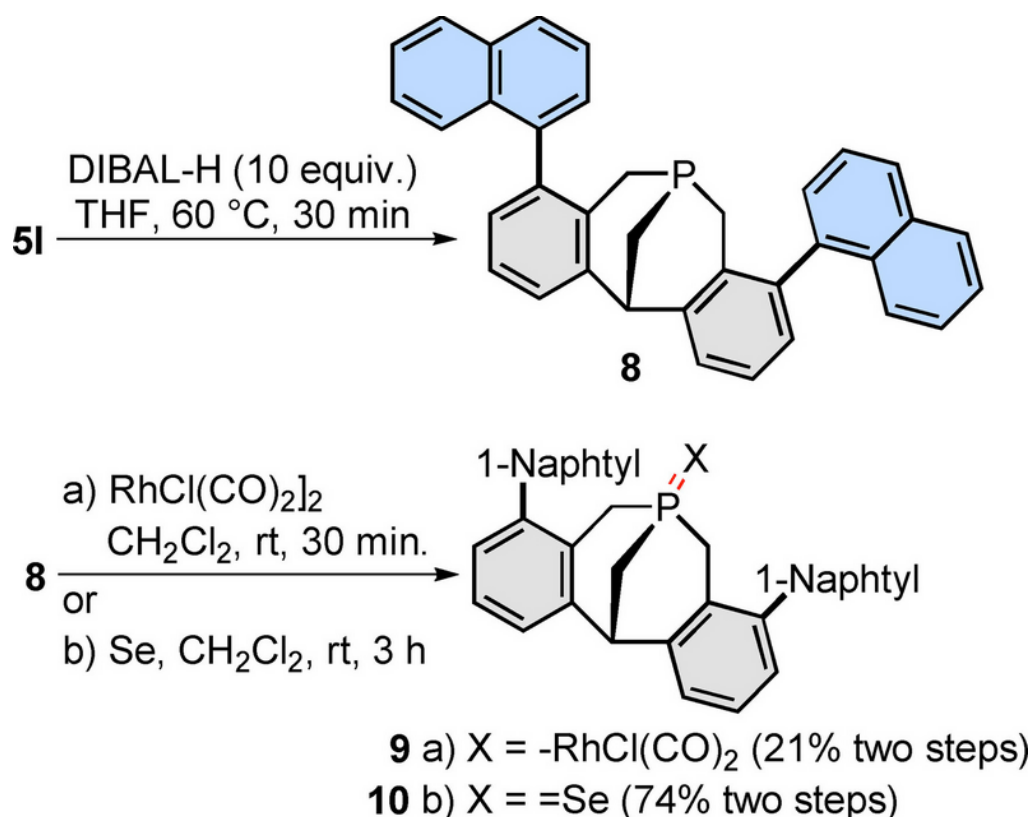


R	[kcal.mol <sup>-1</sup> ]		T °C <sup>[c]</sup>	t <sub>1/2</sub>
	biaryl <b>7</b> <sup>[a]</sup>	<b>5</b> <sup>[b]</sup>		
H	7.4	12	<-70 °C	7.10–5 s
F	12.4	17	80 °C	60 ms
MeO	14.7	19	125 °C	10 s
Me	19.4	25	>150 °C	7 d
1-Naph. /	/	31	>150 °C	500 y

[a] Experimental barrier of disubstituted-biphenyls at 25 °C. [b] Calculated rotational barrier. [c] Temperature of atropimerization for **5**.

In order to investigate the electronic properties of methanodibenzophosphocines, complementary experiments were investigated. First, we examined the proton-decoupled <sup>31</sup>P NMR spectrum of the phosphine **8** which was synthesized by reducing dinaphthyl methanophosphocine oxide **5 l** with DIBAL-H (scheme 1).<sup>26</sup> The spectrum showed three singlets at very high field at -77.8, -77.9 and -78.0 ppm (CDCl<sub>3</sub>), respectively. The chemical shifts of resulting phosphine **8** felt well upfield from those of simple trialkylphosphines (δ<sub>PMe<sub>3</sub></sub> = -62 ppm, δ<sub>PnBu<sub>3</sub></sub> = -32.3 ppm, δ<sub>PiPr<sub>3</sub></sub> = -19.4 ppm)<sup>27</sup> as well as for strained phosphatrypticenes (δ = -64.8 ppm)<sup>28</sup> and the simplest methanophosphocine (phospha bicyclo[3,3,1]nonane, δ = -62.0 ppm).<sup>29</sup> The rhodium(I) complex **9** [ClRh(CO)<sub>2</sub>(**8**)] was also prepared by reaction of **8** with [RhCl(CO)<sub>2</sub>]<sub>2</sub>.<sup>30</sup> The <sup>31</sup>P NMR spectrum of complex **9** displayed three doublets corresponding to the three diastereoisomers at δ 3.3, 3.0 and 2.8 ppm, with an identical <sup>1</sup>J<sub>PRh</sub> coupling constant of 170 Hz. The infrared stretching frequencies, which reflects the π-acceptor character, were found to be 2024.8 and 1999.0 cm<sup>-1</sup>. Next, we examined the reaction between methanophosphocines **8** with powdered elemental selenium, using a protocol compatible with strongly donating phosphine.<sup>31</sup> Following the reaction by <sup>31</sup>P{<sup>1</sup>H}NMR, we observed the disappearance of the signals at -77.8 to -78.0 ppm and the

rise of 2 new signals centered at 2.7 and 2.6 ppm. The signal at 2.7 ppm was the superposition of two diastereoisomers. The  $^{31}\text{P}$ - $^{77}\text{Se}$  coupling constants were measured and found to be 725 and 723 Hz, respectively. They were close to those observed by Stammer for phosphabicyclo[3,3,1]nonane (721.4 Hz).<sup>29</sup>

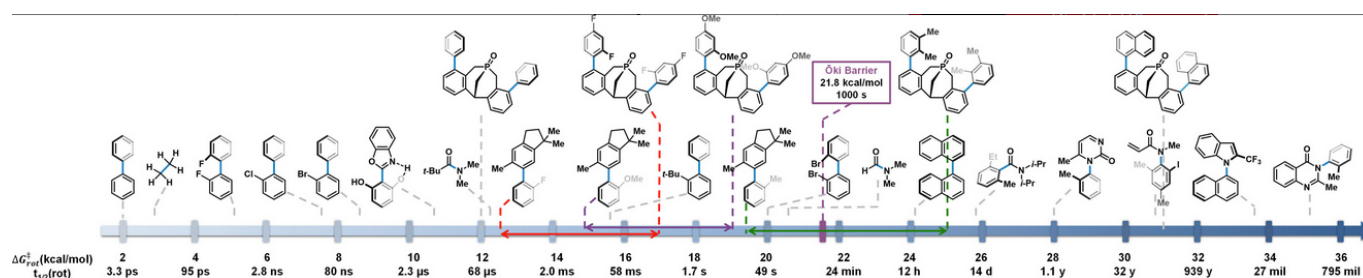


**Scheme 1** : Reduction of **5I** into phosphine **8**; rhodium complex **9** and phosphine selenide **10** synthesis.

The percent buried volume ( $\%V_{\text{bur}}$ ) was calculated to gauge the steric properties of such new phosphine **8**. It was found to be 26.1%.<sup>32</sup> Surprisingly, the accessibility of the phosphorus center appeared to be similar to trimethylphosphine with a  $\%V_{\text{bur}}$  of 26.1 for a metal-phosphorus bond length of 2.28 Å.

## Conclusion

In summary, we have developed an efficient entry into a new class of highly conformationally rigid [3.3.1] biaryls bridgehead phosphine oxides. The procedure involves a double Suzuki–Miyaura coupling reaction of readily available dibromo-substituted methanodibenzophosphocine **6** with various arylboronic acids, leading to the formation of diversely substituted bis(diaryl) methano-dibenzophosphocines **5** that possess an unusual topology. Depending on the substitution pattern on the aryl moieties, the methanophosphocine backbone could be rigid enough to observe a double atropochirality, resulting in an under covered class of compounds. Our study revealed that even small ortho substituents, such as methyl, methoxy, and fused-phenyl groups induced hindrance large enough to observe stable configurations. Surprisingly, replacing just one hydrogen at the *ortho* position with a fluorine atom led to sufficiently restricted rotation at temperature below 80 °C pushing “far far away” the limits of atropostability as illustrated in Figure 6. DFT computations (B3LYP/6-311G\*\*) were used to probe the mechanism of isomerisation, which showed that the two biaryl motifs are fully independent despite their proximity and that the isomerization proceeds through the *anti*-pathway which exhibits the lowest energy. We are continuing our experimental work to explore the potential of these compounds as novel classes of ligands and are also investigating further modifications to improve their atropostability. We will report on these findings in due course.



**Figure 6** : Compared  $\Delta G_{rot}^{\ddagger}$  and half-life of rotational stereoisomers according to their structures at 25 °C.

## Experimental Section

All experimental and DFT-calculation data associated with this work are available in the Supporting Information. Were included synthetic procedures, structural analyses, variable temperature NMR and DFT computational results as well as the spectral data of the new compounds.

## Acknowledgments

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## References

- [1] J. Simon, *Topology* 1986, 25, 229–235.
- [2] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* 1980, 102, 7932–7934.
- [3] a) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* 2015, 44, 3418–3430; b) J. E. Smyth, N. M. Butler, P. A. Keller, *Nat. Prod. Rep.* 2015, 32, 1562–1583; c) E. Kumarasamy, R. Raghunathan, M. P. Sibi, J. Sivaguru, *Chem. Rev.* 2015, 115, 11239–11300; d) P. Loxq, E. Manoury, R. Poli, E. Deydier, A. Labande, *Coord. Chem. Rev.* 2016, 308, 131–190; e) Y.-B. Wang, B. Tan, *Acc. Chem. Res.* 2018, 51, 534–547.
- [4] J. K. Cheng, S.-H. Xiang, S. Li, L. Ye, B. Tan, *Chem. Rev.* 2021, 121, 4805–4902.
- [5] M. C. Kozłowski, S. J. Miller, S. Perreault, *Acc. Chem. Res.* 2023, 56, 187–188.
- [6] J. A. Carmona, C. Rodriguez-Franco, R. Fernandez, V. Hornillos, J. M. Lassaletta, *Chem. Soc. Rev.* 2021, 50, 2968–2983.
- [7] a) S. Yuan, J. Chang, B. Yu, *Top. Curr. Chem.* 2020, 378, pp23–70; b) G. Bott, L. D. Field, S. Sternhell, *J. Am. Chem. Soc.* 1980, 102, 5618–5626.
- [8] J. Wencel-Delord, F. Colobert, *SynOpen* 2020, 4, 107–115.
- [9] a) H. Tatemitsu, F. Ogura, Y. Nakagawa, M. Nakagawa, K. Naemura, M. Nakazaki, *Bull. Chem. Soc. Jpn.* 1975, 48, 2473–2483; b) K. Naemura, R. Fukunaga, M. Komatsu, M. Yamanaka, H. Chikamatsu, *Bull. Chem. Soc. Jpn.* 1989, 62, 83–88; c) M. Kimber, A. C. Try, L. Painter, M. M. Harding, P. Turner, *J. Org. Chem.* 2000, 65, 3042–3046; d) C. K. Y. Lee, J. L. Grone-man, P. Turner, L. M. Rendina, M. M. Harding, *Tetrahedron* 2006, 62, 4870–4878; e) J. Ju, L. Zhang, R. Hua, *Tetrahedron Lett.* 2014, 55, 3374–3376; f) N. H. Slater, B. R. Buckley, M. S. J. Elsegood, S. J. Teat, M. C. Kimber, *Cryst. Growth Des.* 2016, 16, 3846–3852.
- [10] J. Kagan, S.-Y. Chen, D. A. Jr Agdeppa, W. Waston, V. Zabel, *Tetrahedron Lett.* 1977, 18, 4469–4470.
- [11] For a review, see: a) S. Sergeev, *Helv. Chim. Acta* 2009, 92, 415–444. For recent, typical results, see: b) J. Artacho, E. Ascic, T. Rantanen, C.-J. Wallentin, S. Dawaigher, K.-E. Bergquist, M. Harmata, V. Snieckus, K. Wärnmark, *Org. Lett.* 2012, 14, 4706–4709; c) E. B. Veale, T. Gunnlaugs-son, *J. Org. Chem.* 2010, 75, 5513–5525; d) C. A. M. Abella, M. Benassi, L. S. Santos, M. N. Eberlin, F. Coelho, *J. Org. Chem.* 2007, 72, 4048–4054.
- [12] Ö. V. Rúnarsson, J. Artacho, K. Wärnmark, *Eur. J. Org. Chem.* 2012, 7015–7041.
- [13] R. Babouri, L. Traore, Y.-A. Bekro, V. I. Matveeva, Y. M. Sadykova, J. K. Voronina, A. R. Burilov, T. Ayad, J.-N. Volle, D. Virieux, J.-L. Pirat, *Org. Lett.* 2019, 21, 45–49.
- [14] X. Bao, J. Rodriguez, D. Bonne, *Angew. Chem. Int. Ed. Engl.* 2020, 59, 12623–12634.
- [15] a) G. Krishnamoorthy, S. Schieffer, J. Pescatore, R. Ulsh, R. S. H. Liu, J. Liu, *Photochem. Photobiol. Sci.* 2004, 1047–1051; b) C. He, B. Wang, M. Gao, Z. Gu, *Organometallics* 2017, 36, 1073–1078.

- [16] M. Lanzi, R. AbedAli Abdine, M. De Abreu, J. Wencel-Delord, *Org. Lett.* 2021, 23, 9047–9052.
- [17] a) C. Li, D. Chen, W. Tang, *Synlett* 2016, 27, 2183–2200; b) L. Wu, E. Drinkel, F. Gaggia, S. Capolicchio, A. Linden, L. Falivene, L. Cavallo, R. Dorta, *Chem. Eur. J.* 2011, 17, 12886–12890.
- [18] a) S. Fujita, *Bull. Chem. Soc. Jpn.* 2016, 89, 987–1017; b) E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994.
- [19] a) O. Baudoin, *Eur. J. Org. Chem.* 2005, 4223–4229; b) G. Bringmann, A. J. Price-Mortimer, P. A. Keller, M. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed. Engl.* 2005, 44, 5384–5427.
- [20] M. Tredwell, V. Gouverneur, *In Comprehensive Chirality* ed. 2012, Vol. 1 (eds: E. M. Carreira, H. Yamamoto), Elsevier Ltd., pp 70–85.
- [21] a) G. P. Newsoroff, S. Sternhell, *Tetrahedron Lett.* 1967, 8, 2539–2542; b) J. M. A. Baas, A. Sinnema, *Recl. Trav. Chim. Pays-Bas* 1973, 92, 899–905; c) J. M. A. Baas, J. M. van der Toorn, B. M. Wepster, *Recl. Trav. Chim. Pays-Bas* 1974, 93, 133–135; d) D. Landman, G. P. Newsoroff, S. Sternhell, *Aust. J. Chem.* 1972, 25, 109–128; e) H. Suezawa, H. Wada, H. Watanabe, T. Yuzuri, K. Sakakibara, M. Hirota, *J. Phys. Org. Chem.* 1997, 10, 925–934; f) S. Anderson, T. Drakenberg, *Org. Magn. Reson.* 1983, 21, 730–744; g) J. S. Lomas, A. Adenier, *J. Chem. Soc. Perkin Trans.* 2 2002, 1264–1270; h) C. Wolf, L. Pranatharthiaran, R. B. Ramagosa, *Tetrahedron* 2002, 43, 8563–8567.
- [22] F. Krech, K. Issleib, *Z. Anorg. Allg. Chem.* 1976, 425, 209–216.
- [23] a) E. Marvell, S. Provant, *J. Org. Chem.* 1964, 29, 3084–3086; b) M. Chakrabarty, R. L. Ellis, J. L. Roberts, *J. Org. Chem.* 1970, 35, 541–542; c) J. Choo, S. Kim, H. Joo, Y. Kwon, *J. Mol. Struct.* 2002, 619, 113–120.
- [24] Gaussian09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.
- [25] A. Mazzanti, L. Lunazzi, M. Minzoni, J. E. Anderson, *J. Org. Chem.* 2006, 71, 5474–5481.
- [26] N. I. Rinehart, A. J. Kendall, D. R. Tyler, *Organometallics* 2018, 37, 182–190.
- [27] a) S. O. Grim, W. McFarlane, *Nature* 1965, 208, 995–996; b) R. Bosque, J. Sales, *J. Chem. Inf. Comput. Sci.* 2001, 41, 225–232.
- [28] C. Jongsma, J. P. de Kleijn, F. Bickelhaupt, *Tetrahedron* 1974, 30, 3465–3469.
- [29] A. Zschunke, C. Mügge, M. v. Löwis, F. Krech, L. Weber, H. Schumann, H. G. Stammer, *Z. Anorg. Allg. Chem.* 1992, 610, 127–134.
- [30] S. Vastag, B. Heil, L. Marko, *J. Mol. Catal.* 1979, 5, 189–195.
- [31] J. A. Werra, K. Wurst, L. B. Wilm, P. Lowe, M. B. Rothel, F. Dielmann, *Organometallics* 2023, ASAP. (10.1021/acs.organomet.3c00016).
- [32] Clavier, S. P. Nolan, *Chem. Commun.* 2010, 46, 841–861.
- [33] Buried volume was determined using SambVca2 webtool. L. Falivene, R. Credendino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano, L. Cavallo, *Organometallics* 2016, 35, 2286–2293. [34] F. P. Gasparro, N. H. Kolodny, *J. Chem. Educ.* 1977, 54, 258–26