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Enantioselective Pd^0-Catalyzed C(sp^2)–H Arylation for the Synthesis of Chiral Warped Molecules

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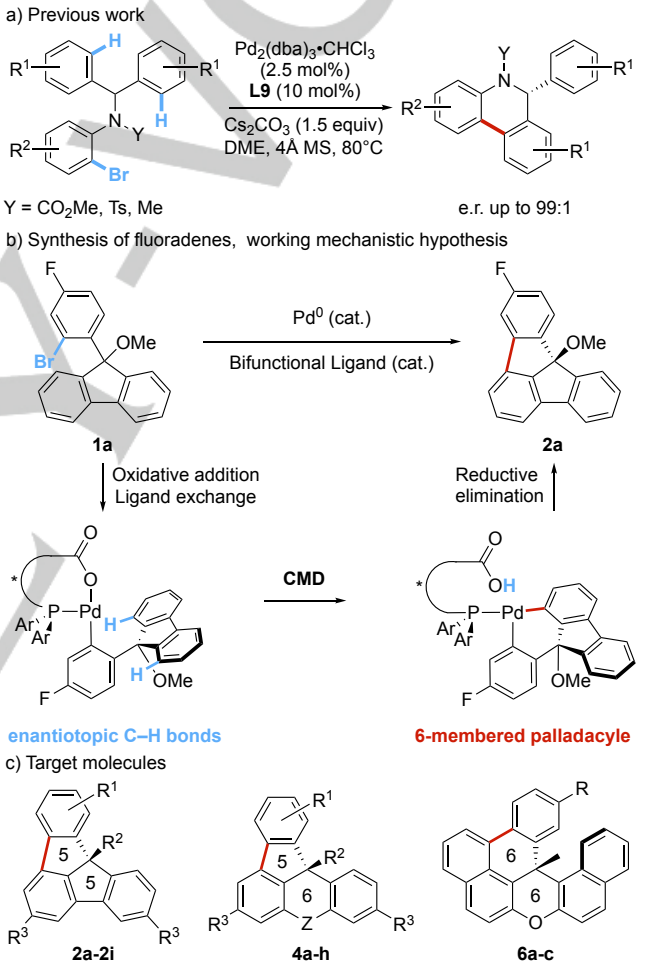
Abstract: C–H activation-based ring-forming methods constitute a powerful approach for the construction of complex molecular architectures, especially those containing a congested stereocenter. Therefore, this strategy seems perfectly suited to address the synthesis of chiral polycyclic aromatic hydrocarbons (PAHs) and bowl-shaped molecules, which are important target molecules in the field of organic electronic materials. Herein, we describe an enantioselective Pd^0-catalyzed C(sp^2)–H arylation protocol for the synthesis of chiral fluoradenes and other warped molecules, which could serve to the bottom-up construction of chiral PAHs. The current approach relies on the use of chiral bifunctional phosphine-carboxylate ligands and delivers diverse polycyclic compounds in high yield and with good to excellent enantioselectivity. The chiroptical properties of the obtained products were investigated, and some of them were found to have a strong ellipticity and an emission band located in the visible region.

The activation of C–H bonds permits the rapid construction of complex chemical architectures via ring construction events.[1] The high similarity between the products and their precursors generally translates into diminished waste generation and improved atom-economy.[2] Moreover, C–H activation-based desymmetrisation reactions constitute a powerful way of generating congested stereogenic centers, because they occur at a remote position and hence do not suffer from the steric hindrance associated to such units.[3] In this context, the use of asymmetric Pd^0/Pd^{II}-catalyzed C(sp^2)–H arylation has been the topic of many publications over the last decade, often targeting the preparation of new potential ligands, organocatalysts precursors or natural products.[4,5] The mechanism underlying these transformations usually involves an enantiodetermining concerted metalation–deprotonation (CMD) step. At the transition state of this step, both the ligand and the base are coordinated to the metal center. Therefore, a chiral ancillary ligand[5] and/or a chiral base[6,7] may be used to bring in stereocontrol over the reaction. In order to induce a more organized transition-state, and thereby to provide higher enantioselectivities in challenging cases, we recently developed a new family of chiral bifunctional phosphine-carboxylate ligands (Scheme 1a).[8] Herein, we describe the application of this approach to the enantioselective synthesis of highly symmetrical fluoradenes[9], through the selective activation of one enantiotopic C-H bond (scheme 1b), and other warped molecules, which could serve to the bottom-up preparation of buckybowls or other bowl-shaped hydrocarbons.



Scheme 1. Previous work, working mechanistic hypothesis to design our enantioselective synthesis of fluoradenes and target molecules.

Chiral fullerene fragments such as buckybowls (including corannulene, sumanene and dicyclopentaperylene) and other polycyclic aromatic hydrocarbons (PAHs) or bowl-shaped hydrocarbons are interesting targets which have received a lot of attention due to their photophysical and chiroptical properties and their potential applications as organic electronic materials.[10,11] However, these molecules are often synthesized in racemic form, and enantiomerically pure samples obtained by chromatographic separation on a small scale. This synthetic gap drove us to

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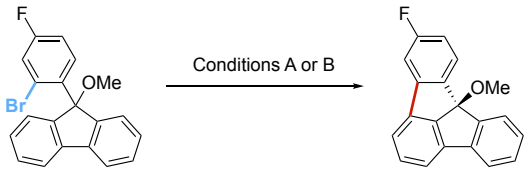
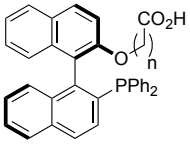
develop a general C–H activation-based protocol for the enantioselective synthesis of diverse polycyclic aromatic-rich warped molecules via the formation of ring systems of different sizes (scheme 1c).[12] We herein report the development of this method, as well as a preliminary study of the photophysical and chiroptical properties of some of the synthesized compounds.

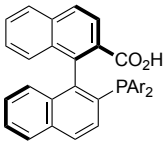


1a **2a**[a]

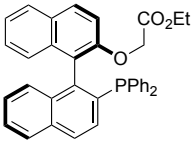
a) Initial ligand screening and control experiments (using conditions A, unless otherwise noted)



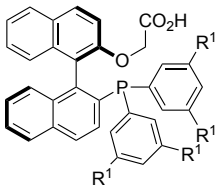
L1 n = 1, e.r. 80:20
L2 n = 2, e.r. 56:44
L3 n = 3, e.r. 57:43
L4 n = 4, e.r. 37:63
L5 n = 5, e.r. 38:62
L6 n = 6, e.r. 37:63



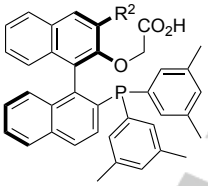
L7,[b] e.r. 50:50
Ar=4-F-3,5-diMePh



L8 +PivOH,[b,c] e.r. 63:37

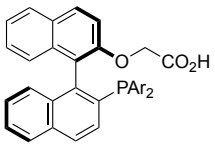


L9 R^1 = Me, e.r. 85:15
L10 R^1 = H, e.r. 80:20
L11[d] R^1 = OMe, e.r. 77:23
L12[d] R^1 = CF_3, e.r. 70:30
L13[d] R^1 = *t*-Bu, no conversion

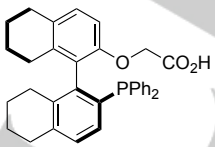


L14 R^2 = Ph, e.r. 53:47
L15 R^2 = Me, e.r. 53:47

b) Further optimization (using conditions B)



L9 Ar = 3,5-diMePh, e.r. 87:13
L16 Ar = naphtalen-2-yl, e.r. 90:10
L17 Ar = 1,1'-biphenyl-4-yl, e.r 91:9
L18 Ar = 1,1'-biphenyl-3-yl, e.r. 79:21
L19 Ar = *m*-tolyl, e.r. 89:11
L20 Ar = 4-F-3,5-diMePh, e.r. 91:9



L21, e.r. 18:82

Scheme 2. Synthesized bifunctional ligands and their effect in enantioselective C(sp^2)–H arylation. Conditions A: ligand (10 mol%), $Pd_2dba_3{\cdot}(CHCl_3)$ (5 mol%), Cs_2CO_3 (1.5 equiv), 4Å MS, DME (0.1 M), 140 °C, 18h. Conditions B: ligand (20 mol%), $Pd_2dba_3{\cdot}(CHCl_3)$ (5 mol%), Cs_2CO_3 (1.5 equiv), 4Å MS, toluene (0.1 M), 140 °C, 18h [a] The absolute configuration of **2a** was deduced from the X-ray crystal structure shown in Scheme 3. [b] Conditions B were used. [c] 20 mol%. [d] 2.5 mol% $Pd_2dba_3{\cdot}CHCl_3$. dba = dibenzylideneacetone, DME = 1,2-dimethoxyethane, MS = molecular sieves.

Compound **1a** was chosen as a model substrate to start our optimization (Scheme 2). Standard conditions for the initial ligand screening involved a combination of the ligand (10 mol%) with $Pd_2dba_3{\cdot}(CHCl_3)$ (5 mol%), cesium carbonate (1.5 equiv) and DME as the solvent at 140 °C in the presence of molecular sieves. The yield of the desired product being excellent in most cases, we based our optimization exclusively on the observed enantiomeric ratios. The design of our bifunctional ligands allows for an easy modification of the linker attaching the carboxylic acid to the binaphthyl scaffold. Ligand **L1** with a single methylene unit in this tether gave the best results. When the length of this chain was increased (**L2**, **L3**) the enantiomeric ratio of **2a** dropped rapidly and dramatically. For longer chains (**L4-L6**), a slightly higher induction was observed, but for the opposite enantiomer, suggesting a change in the mechanism along this series. Of note, when **L7**, wherein the carboxylic acid is directly linked to the 1,1'-binaphthyl scaffold, was used, the obtained product was racemic. A control experiment with monofunctional ligand **L8**, used in combination with pivalic acid, confirmed the superiority of our bifunctional ligand for this transformation compared to a bimolecular approach. We then turned our attention to the modification of the substituents on the phosphorous atom. Different 3,5-disubtituted aryl groups were introduced (**L9-L13**), with dimethyl substituted ligand **L9** giving the highest enantiomeric ratio. Introducing a phenyl (**L14**) or methyl (**L15**) substituent at the 3' position of the binaphthyl scaffold was found to be detrimental to the selectivity of this transformation. At this point, a new round of condition optimization was conducted (see the Supporting Information for details). Optimized conditions involved a combination of the ligand (20 mol%) with $Pd_2dba_3{\cdot}CHCl_3$ (5 mol%), cesium carbonate (1.5 equiv) and toluene as the solvent at 140 °C, in the presence of molecular sieves. Using this new set of conditions, the effect of the substituents on the phosphorous atom was further investigated. Ligands **L16-L18** possessing an increased aromatic surface attached to the phosphine moiety were prepared and tested. Whereas the use of ligand **L18** did not give satisfactory results, ligands **L16** and **L17** both performed very well. Removing one methyl substituent from **L9** to get **L19** was slightly beneficial, but **L19** failed to outcompete **L17.** However, ligand **L20**, retaining the 3,5-dimethyl substitution with an additional fluorine substituent at the *para* position to the phosphorous atom gave the same selectivity as **L17** on this model substrate. Finally, replacing the 1,1'-binaphthyl scaffold with its octahydro analogue (**L21**) did not furnish a promising way to improve the selectivity.

Next, the best ligands **L17** and **L20** were chosen to study the reaction scope to generate different types of scalemic warped molecules, starting with fluoradenes (Scheme 3). The diversity and accessibility were the main criteria underlying the choice of employed substrates. Model substrate **1a** was transformed into **2a** in excellent yield and with good enantioselectivity under the optimized conditions employing ligand **L20**. The absolute configuration of **2a** was determined by X-ray diffraction analysis.[13] The latter also revealed that fluoradene **2a** adopts a bowl-like structure with a bowl depth of 1.36 Å, measured between the stereogenic carbon atom and the plane defined by the 3 most remote carbon atoms (see Scheme 3). An additional phenyl ring at the *para* position of the bromine of substrate **1b** was well tolerated to furnish product **2b**, which contains a quaterphenyl substructure. An electron-donating group at the same position was also tolerated, as demonstrated by the synthesis of **2c**, albeit with a reduced enantioselectivity.[14] Modification of the fluorene scaffold did not impact the reactivity nor the selectivity (**2d**) and it was possible to replace the methoxy group on the stereocenter by a larger propoxy substituent (**2e**).

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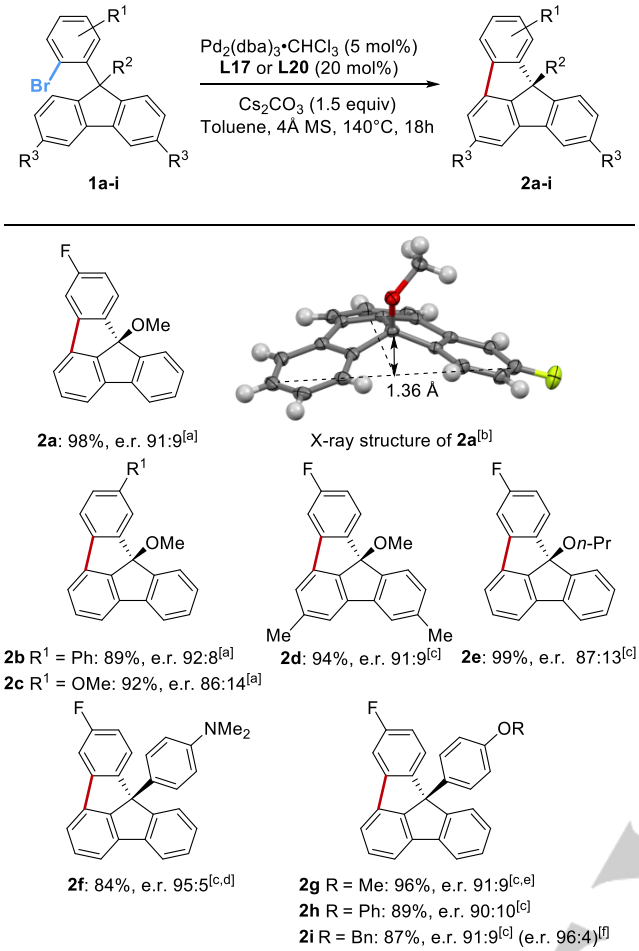
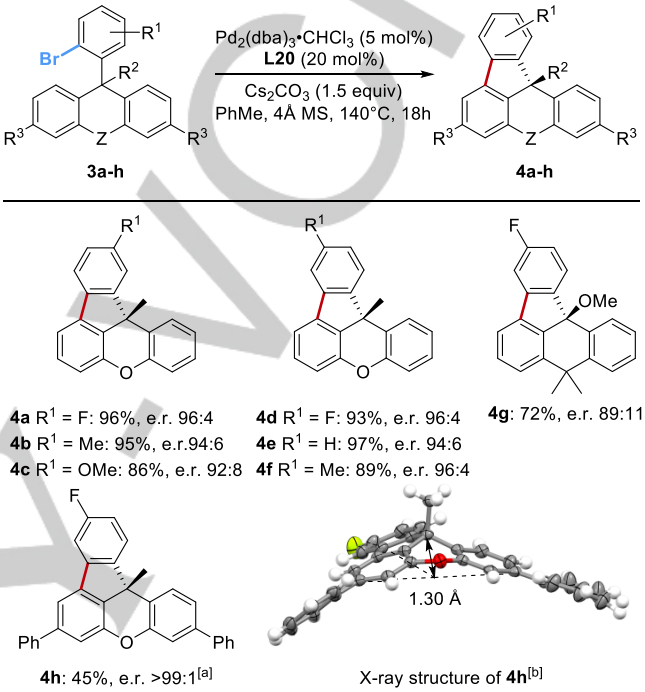


Scheme 3. Scope of the enantioselective synthesis of fluoradenes. Reactions were performed on a 0.1 mmol scale. [a] Using **L20**. [b] Thermal ellipsoids shown at 50% probability. The absolute configurations of other products were assigned by analogy to **2a**. [c] Using **L17**. [d] Determined from the corresponding monodemethylated aniline. [e] Determined form the corresponding free phenol. [f] After recrystallization from *i*-PrOH.

Four fluoradenes containing a quaternary all-carbon stereocenter were also prepared (**2f-2i**). In these cases, ligand **L17** was found to provide higher enantiomeric ratios than **L20**. Pleasingly, aniline **2f** was obtained in good yield and excellent enantiomeric ratio. The oxygen-containing fused tetraphenylmethane products **2g-2i** were also obtained in excellent yield and good enantioselectivity, and the methoxy group of **2g** was readily cleaved to afford the corresponding phenol, which could serve as a handle for further functionalization. Furthermore, the enantiomeric ratio of **2i** could be easily increased to 96:4 upon recrystallisation from isopropanol.

In addition to fluorenes, xanthone-derived substrates (**3a-3f, 3h**), were successfully transformed into the corresponding products (**4a-4f, 4h**), which contain an all-carbon quaternary stereocenter. An excellent enantioselectivity was achieved in most cases using **L20** as the ligand. Aryl bromides bearing electron-withdrawing (**3a**) or electron-donating (**3b, 3c**) substituents at the *para* position to the bromine atom provided good results. Meta-substituted (**3d, 3f**) and unsubstituted (**3e**) aryl bromides also gave excellent yields and enantioselectivities. Moreover, compound **4h** displaying an increased aromatic surface was isolated by recrystallization and obtained with a very high enantiomeric ratio. The structure and the absolute configuration of this compound were confirmed by X-ray diffraction analysis.[13] The latter revealed that **4h** adopts a bowl-like structure too, with a slightly shorter bowl depth (1.30 Å) compared to **2a**, due to the presence of the 6-membered pyran ring. Finally, our protocol could also be used for the preparation of anthrone-derived compound **4g**, albeit with a reduced enantioselectivity.



Scheme 4. Scope of the enantioselective C(sp^2)–H arylation of xanthone- and anthrone-derived substrates. Reactions were performed on a 0.1 mmol scale. [a] Performed on a 0.05 mmol scale, isolated by recrystallization from *i*-PrOH. [b] Thermal ellipsoids shown at 50% probability. The absolute configurations of other products were assigned by analogy to **4h**.

To further demonstrate the applicability of our protocol to the preparation of warped molecules containing an extended aromatic system, helix-shaped products **6a-6c** containing an all-carbon quaternary stereocenter and a formed 6-membered ring (vs. 5-membered for previous products **2** and **4**) were synthesized by C–H arylation from substrates **5a-5c**. Electron-donating and -withdrawing substituents were again well tolerated and did not significantly influence the selectivity of the reaction. Moreover, the enantiomeric ratio of **6a** could be increased upon recrystallization from isopropanol to reach an enantiomeric ratio of 98:2. The structure and the absolute configuration of this compound were confirmed by X-ray diffraction analysis.[13] Interestingly, **6a** adopts a right-handed helical shape induced by the stereogenic center and the extended aromatic surface, which is similar to the configurationally unstable[15] oxa[5]helicene (angle between the two edge rings: **6a**, 54°, oxa[5]helicene, 53°).[16]

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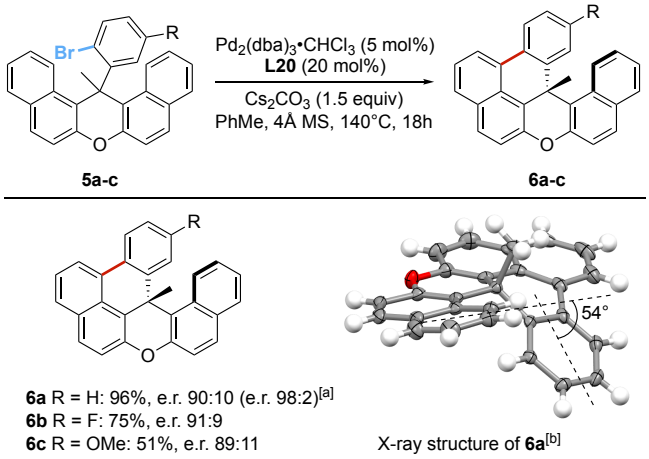

6a R = H: 96%, e.r. 90:10 (e.r. 98:2)[a]
6b R = F: 75%, e.r. 91:9
6c R = OMe: 51%, e.r. 89:11

X-ray structure of **6a**[b]

Scheme 5. Scope of the enantioselective synthesis of helix-shaped xanthone-derived products. Reactions were performed on a 0.1 mmol scale. [a] After recrystallization from *i*-PrOH. [b] Thermal ellipsoids shown at 50% probability. The absolute configurations of other products were assigned by analogy to **6a**.

A tentative model to rationalize the stereochemical outcome of the reaction furnishing fluoradene **2a** using ligand **L20** based on preliminary modelling is shown in Figure 1. At the transition state of the enantiodetermining C–H activation step, the fluorene ring of the substrate is presumably oriented inside the chiral pocket to maximize dispersion interactions with the ligand. With this orientation, the *M* configuration of the rigid bifunctional ligand **L20** imposes C–H activation to occur at the pro-*R* hydrogen atom of the fluorene ring, thereby generating product **2a** as the major *R* enantiomer after reductive elimination.

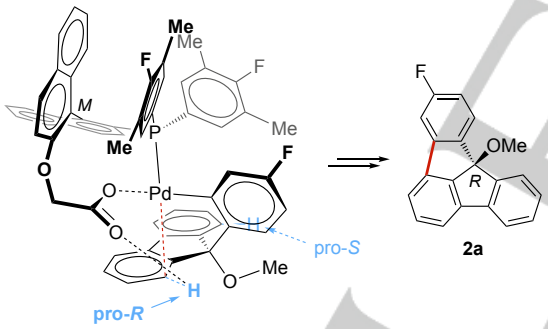

Figure 1. Proposed stereochemical model.

Finally, the absorption and emission spectra of selected compounds **4h** and **6a** were obtained and are shown in Figure 2a. Interestingly, **6a** emits in the visible region with a maximum at 405 nm, and its quantum yield was determined to be 13.4% (see the Supporting Information for details). The circular dichroism spectra for compounds **2a**, **2b**, **4h** and **6a** are shown in Figure 2b. The large molar ellipticity values observed for compound **6a** in solution (–81400 M^{-1} cm^{-1} at 298 nm, +73500 M^{-1} cm^{-1} at 368 nm) seem to correlate with the helical shape observed in the solid state. Moreover, the CD spectrum of compound **2b** seems to differ significantly from those of the other synthesized fluoradenes, which could be due to its quaterphenyl substructure.

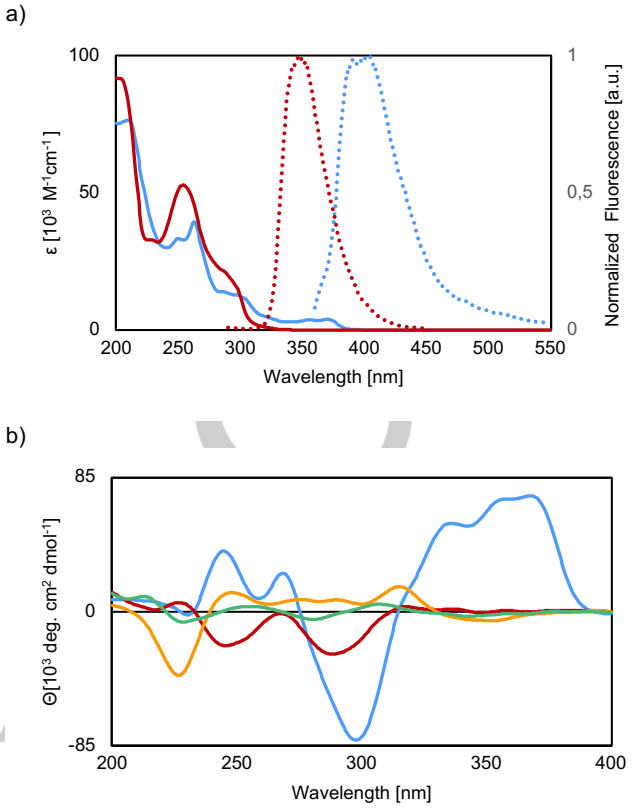

Figure 2. a) Absorption (solid trace) and emission (dotted trace) spectra of **4h** (red traces, λex = 280 nm) and **6a** (blue traces, λ_{ex} = 354 nm) recorded in de-aerated CH_3CN at 22 °C. b) Circular dichroism spectra of **2a** (green trace), **2b** (orange trace), **4h** (red trace) and **6a** (blue trace), recorded in CH_3CN at 25 °C.

In conclusion, a protocol for the enantioselective synthesis of original chiral warped molecules via Pd^0-catalyzed C(sp^2)–H arylation was developed. Our approach relies on the use of chiral bifunctional phosphine-carboxylate ligands that play a unique role in the enantiodetermining C–H activation step. A diverse array of polycyclic compounds could be synthesized in high yields and with good to excellent enantioselectivities. Moreover, the e.r. of the obtained products could easily be increased by recrystallization. The chiroptical properties of the synthesized compounds were investigated and compound **6a**, possessing a right-handed helical shape, was shown to have a strong ellipticity in solution and to emit in the visible region.

Acknowledgements

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Keywords: asymmetric catalysis • C–H activation• enantioselectivity • palladium • polycyclic aromatic hydrocarbons

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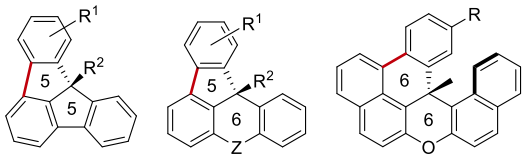

yields up to 99%, e.r. up to 96:4

Enantioselective Pd^0-catalyzed C(sp^2)–H arylation allows the synthesis of warped molecules possessing congested stereocenters. The polycyclic compounds were obtained in high yields and with good to excellent enantioselectivitiesπ using chiral bifunctional ligands, and could serve to the bottom-up construction of chiral polycyclic aromatic hydrocarbons.