



# **C2 -Symmetric atropisomeric N-heterocyclic carbene–palladium( ii ) complexes: synthesis, chiral resolution, and application in the enantioselective $\alpha$ -arylation of amides**

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# C<sub>2</sub>-Symmetric atropisomeric N-heterocyclic carbene–palladium(II) complexes: synthesis, chiral resolution, and application in the enantioselective $\alpha$ -arylation of amides†

Lingyu Kong,<sup>1</sup> Yajie Chou,<sup>2</sup> Muriel Albalat,<sup>3</sup> Marion Jean,<sup>4</sup> Nicolas Vanthuyne,<sup>5</sup> Stéphane Humbel,<sup>6</sup> Paola Nava<sup>7</sup> and Hervé Clavier<sup>1\*</sup>

The concept of atropisomeric N-heterocyclic carbene (NHC)–metal complexes was extended to NHCs possessing a C<sub>2</sub>-symmetry and implemented to prepare palladium-based complexes. An in-depth study of the NHC precursors and the screening of various NHC ligands enabled us to circumvent the issue associated with the formation of *meso* complexes. A set of 8 atropisomeric NHC–palladium complexes were prepared and then obtained with high enantiopurities, thanks to an efficient resolution by chiral HPLC at the preparative scale. These complexes displayed good activity in the intramolecular  $\alpha$ -arylation of amides and various cyclic products were isolated with excellent enantioselectivities (up to 98% ee).

## Introduction

Since the seminal work of Arduengo in 1991 disclosing stable N-heterocyclic carbenes (NHCs),<sup>1</sup> NHCs have attracted much attention in particular for their use as ancillary ligands in organometallic chemistry.<sup>2</sup> Their electronic properties (strong  $\sigma$ -donation and poor  $\pi$ -acceptor characteristics) make them more than simple phosphine mimics and allow the synthesis of a myriad of well-defined transition metal complexes bearing NHC ligands. Many of them exhibit good stability towards air and moisture. The studies on the coordinating properties of NHCs have translated into the development of a wide array of transition-metal-catalyzed transformations among which are the well-known olefin metathesis, palladium-catalyzed cross coupling reactions, and more recently C–H bond activation.<sup>3</sup> Therefore, the design of chiral NHC ligands has been the subject of intensive and fruitful research.<sup>4</sup> So far, two main strategies for the design of chiral monodentate NHC ligands have been explored: (i) the incorporation of chiral patterns as *N*-substituents, structure **A**,<sup>5</sup> including polycyclic structures, structure **B**<sup>6</sup> (Fig. 1.1); (ii) the use of a chiral backbone, structure **C**,<sup>7</sup> that can be associated with dissymmetric aryl groups

as *N*-substituents, structure **D**<sup>8</sup> (Fig. 1.2). These two designs can even be combined.<sup>5d,9</sup>

Recently, we have developed another design based on a restricted rotation of a dissymmetric *N*-aryl substituent along the C–N bond. The presence of both methyl groups on the NHC backbone and the metal enabled us to achieve high rotational barrier values and thus obtain configurationally stable complexes (Fig. 1.3).<sup>10</sup> Advantageously, this approach

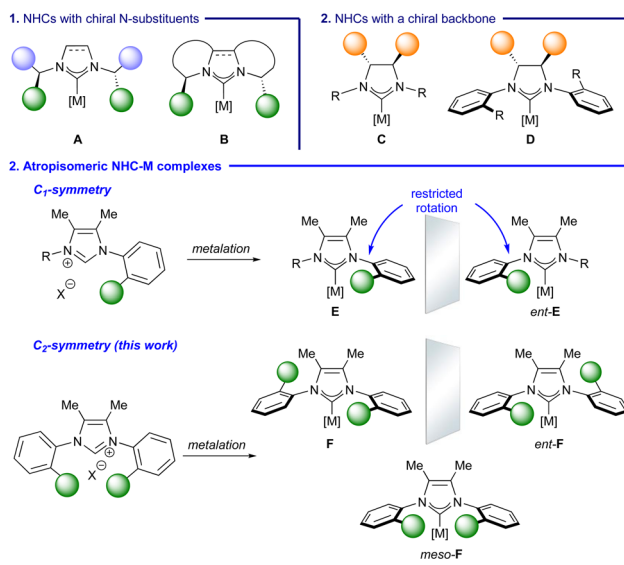


Fig. 1 Design of chiral NHC ligands.

does not require the use of enantiopure synthons since the imidazolium salts, precursors of NHC ligands, are not chiral and the metalation step creates the axis of chirality. Thus, complexes **E** are obtained as racemic mixtures. Nevertheless, thanks to the high stability of many NHC–metal complexes, in particular enabling purification by silica gel chromatography, a resolution by chiral HPLC at the preparative scale afforded complexes with excellent enantiopurities and high yields. Of note is that this technique of resolution by chiral HPLC<sup>11</sup> has been used to prepare various chiral NHC ligands<sup>6d,12</sup> and more recently was applied to obtain enantiopure metal–carbene complexes.<sup>13</sup> Complexes bearing a  $C_1$ -symmetric NHC ligand,<sup>14</sup> for which only one axis of chirality is present, are very convenient to study the rotational barrier values. Thus, they allow fine tuning of the NHC structure in order to obtain atropisomeric metal–NHC complexes displaying good configurational stability.<sup>10</sup> Nonetheless, enantiopure  $C_1$ -symmetric Pd–NHC complexes have catalyzed the intramolecular  $\alpha$ -arylation of amides with a moderate enantioselectivity (up to 64% ee).<sup>10c</sup>

Herein, we disclose the extension of the concept of atropisomeric metal–NHC complexes to  $C_2$ -symmetric NHC ligands, which might lead to the formation of *meso* complexes (*meso*-**F**) in addition to both enantiomers (**F** and *ent*-**F**). The enantiopure  $C_2$ -symmetric NHC–Pd complexes were successfully tested in the intramolecular  $\alpha$ -arylation of amides.

## Results and discussion

Several symmetric imidazolium salts **1**·**X** containing methyl substituents at the 4 and 5 positions were synthesized according to literature procedures (Fig. 2).<sup>15,16</sup> Since the imidazolium salt possessing bulky *tert*-butyl groups as *ortho*-substituents could not be synthesized, the dissymmetric imidazolium salt **1b**·**OTf** with a *tert*-butyl group on one side and an iso-propyl group on the other side was prepared. <sup>1</sup>H NMR spectroscopy analyses indicated that these imidazolium salts possess two resonances for the characteristic proton at position 2 accounting for two isomeric forms in solution. An in-depth study on imidazolium salts **1d**–**f**·**X** demonstrated that the nature of the anion **X** (Cl, OTf, and BF<sub>4</sub>) does not influence significantly the isomeric ratios (Table S1†).<sup>15</sup> However, the NMR solvents used for these analyses led to sharp differences in the isomeric

ratios in the case of imidazolium salt **1d**·**X** spanning from 1:1.2 in CDCl<sub>3</sub> to 1:9 in acetone-*d*<sub>6</sub>. For imidazolium salts **1e**·**X** and **1f**·**X**, the isomeric ratios remain similar whatever the NMR solvent is, 1:10 and 1:5 respectively. We hypothesized that **1d**·**X** isomers are rotamers while a second *ortho*-substituent on the *N*-aryl groups, either a fluorine or a methyl group, leads to an increase in the rotational barrier values about the N–C bonds and gives rise to atropisomers (two diastereomers).

In order to gain insight into the values of the rotational barriers, theoretical calculations were run (Scheme 1).<sup>15,17</sup> According to these calculations, *cis*-conformations (*meso*) are more stable than *trans*-conformations (chiral). As expected, the more energetically favourable rotations take place with the benzhydryl groups on the side of the imidazolium proton ( $\Delta G^\ddagger_{(H)} = 69.7 \text{ kJ mol}^{-1}$ ) since the methyl groups prevent rotation on the back-bone side ( $\Delta G^\ddagger_{(BB)} = 127.3 \text{ kJ mol}^{-1}$ ). The calculated values indicate that the rotation of *N*-aryl substituents is not restricted in the case of imidazolium **1d**·**X** ( $\Delta G^\ddagger_{(H)} = 69.7 \text{ kJ mol}^{-1}$ ;  $t_{1/2} = 0.1 \text{ s}$  at 25 °C). For imidazolium salts **1e**·BF<sub>4</sub> and **1f**·BF<sub>4</sub>, containing additional *ortho* substituents on the *N*-aryl groups, either a fluorine or methyl, values of rotational barriers are substantially higher and the rotations of the *N*-aryl groups appear to be restricted,  $\Delta G^\ddagger_{(H)} = 108.7 \text{ kJ mol}^{-1}$ ;  $t_{1/2} = 7 \text{ days}$  at 25 °C and  $\Delta G^\ddagger_{(H)} = 155.9 \text{ kJ mol}^{-1}$ ;  $t_{1/2} = 4 \text{ M years}$  at 25 °C, respectively. In view of these results, we conclude that for imidazolium salts **1e**·**X** and **1f**·**X**, the two isomeric forms observed in solution are diastereomers and can be characterized using a diastereomeric ratio (dr). We attempted to isolate the major diastereomers of imidazolium salts **1e**·BF<sub>4</sub> and **1f**·BF<sub>4</sub>. Diastereomerically pure imidazolium salts were obtained by recrystallization or/and silica gel chromatography.<sup>15</sup> X-ray diffraction analyses of major diastereomers enabled us to unambiguously attribute the *trans*-conformation to these compounds (Fig. 3) and suggest that the formation of these imidazolium salts occurs under kinetic control.

Imidazolium salts **1**·**X** were used to prepare the corresponding Pd(allyl)Cl(NHC) complexes **2** in order to probe the formation of chiral *vs.* *meso* complexes, respectively ( $\pm$ )-**2** and *meso*-**2** (Table 1). Imidazolium **1a**·BF<sub>4</sub> containing isopropyl

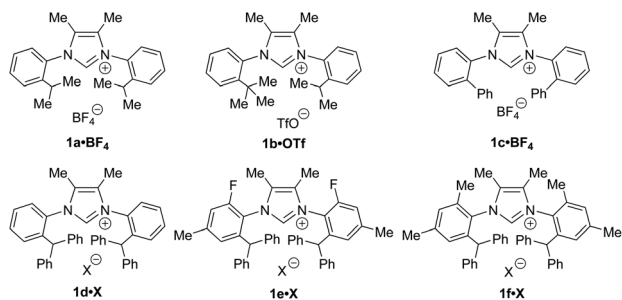
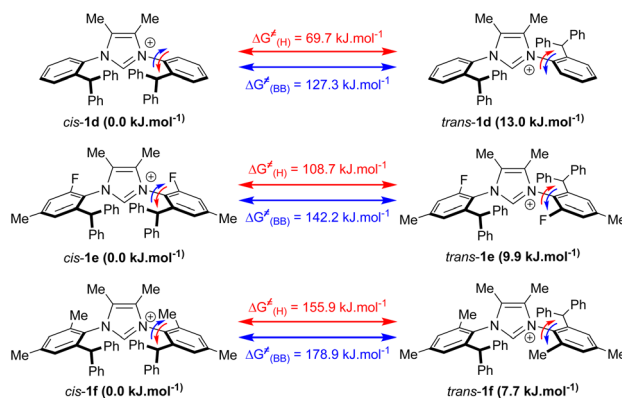
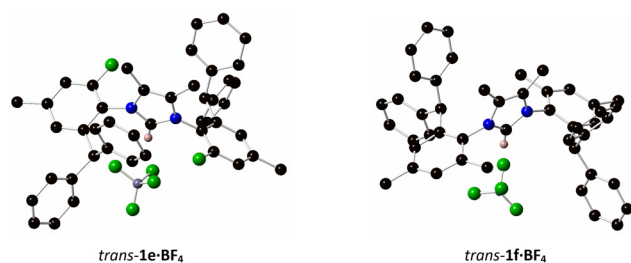


Fig. 2 Imidazolium salts used in this study (X = OTf, Cl and BF<sub>4</sub>).



Scheme 1 Configurational stabilities of imidazolium salts calculated by DFT.



**Fig. 3** Ball-and-stick representation of the major diastereomers of the imidazolium salts **1e-BF<sub>4</sub>** and **1f-BF<sub>4</sub>** (most of the hydrogens have been removed for clarity).

groups at one of the *ortho* positions of the *N*-aryl substituents treated with *t*BuOK in THF at 25 °C in the presence of [Pd(allyl)Cl]<sub>2</sub> (conditions A) gave complex *meso*-**2a** after silica gel purification with a moderate yield (49%, entry 1). The structure of *meso*-**2a** was unambiguously determined by single crystal X-ray diffraction studies (Fig. 4) and no trace of the expected chiral complex **2a** was detected. The complex formation was repeated at 60 °C and using K<sub>2</sub>CO<sub>3</sub> instead of *t*BuOK (conditions B) according to the procedure disclosed by Nolan and Cazin (entry 2).<sup>18</sup> Complex *meso*-**2a** was isolated in a higher yield (78%) but still without formation of (±)-**2a**. At this stage, we postulated that more hindered *ortho*-substituents on the aromatic side groups should favor the formation of a chiral complex. Nevertheless, with pre-ligand **1b-OTf**, the corresponding complex **2b** was obtained with a *cis* arrangement of the *tert*-butyl and isopropyl groups, even if the presence of a small amount of *trans*-**2b** cannot be ruled out.<sup>15</sup> Of note, complex *cis*-**2b** is chiral but can be considered a “pseudo *meso*” complex. At this stage, we hypothesized that the preferential formation of *meso* complexes might be the result of an induced dipole-induced dipole attraction involving alkyl groups in the *ortho* position (London dispersion forces).<sup>19</sup> Thus, we turned our attention toward imidazolium salt **1c-BF<sub>4</sub>** containing phenyl groups as *ortho*-substituents (entries 4 and 5). Conditions A allowed the formation of 2 complexes that could be separated by silica gel chromatography. The <sup>1</sup>H NMR spectrum of one of these complexes exhibited two sets of signals for the allyl pattern due to conformers resulting from the allyl orientation and we attributed them to (±)-**2c**. Whereas for *meso*-**2c**, the plane of symmetry results in only one set of signals for the allylic protons.<sup>15</sup> This statement was confirmed by single crystal X-ray diffraction studies of both complexes (Fig. 4). Under conditions A, the yields of (±)-**2c** and *meso*-**2c** were moderate and the *meso* complex was formed in higher proportions (entry 4). Conditions B improved the overall yield and the expected complex (±)-**2c** was found to be the major palladium complex (entry 5). Under conditions B, the benzhydryl containing salt **1d-BF<sub>4</sub>** led to the formation of two diastereomers which were separated by silica gel chromatography to give rise to (±)-**2d** and *meso*-**2d**, in respectively 28% and 62% yields (entry 6). The structure of *meso*-**2d** was confirmed by single crystal X-ray diffraction (Fig. 4). Because imidazolium

salt **1e-BF<sub>4</sub>** has been synthesized mainly as the *trans* diastereomer (dr = 10 : 1), complex *meso*-**2e** was not observed and only racemic complex (±)-**2e** was isolated in good yield (72%, entry 7). When imidazolium salt **1f-BF<sub>4</sub>** has been used as a mixture of diastereomers (dr = 5 : 1), the corresponding Pd(allyl)Cl(NHC) complexes (±)-**2f** and *meso*-**2f** were formed in overall good yield (79%) and in a 5 : 1 ratio (entry 8). Unfortunately, both diastereomers could not be efficiently separated by silica gel chromatography. However, when diastereomerically pure **1f-BF<sub>4</sub>** was employed, only complex (±)-**2f** was formed with excellent yield. Remarkably, this experiment was performed on a gram scale.<sup>15</sup>

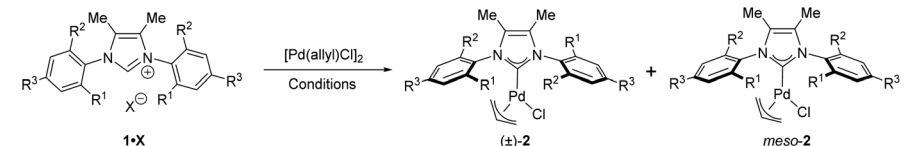
Next, we extended the complex synthesis to Pd(cinnamyl)Cl(NHC) **3** using imidazolium tetrafluoroborate **1d-f-BF<sub>4</sub>** (Table 2). The treatment of the dimeric [Pd(cinnamyl)Cl]<sub>2</sub> and **1d-BF<sub>4</sub>** with K<sub>2</sub>CO<sub>3</sub> in acetone at 60 °C gave rise to the sole formation of complex *meso*-**3d** (entry 1). The presence of the expected chiral complex could not be detected. This indicates that the nature of the allylic ligand has an influence on the diastereoselectivity of the metalation step; unfortunately, the sterically demanding cinnamyl favours the formation of the achiral complex. Configurationally stable imidazolium salts **1e-BF<sub>4</sub>** and **1f-BF<sub>4</sub>** enabled us to circumvent this issue. Solely complex (±)-**3e** was obtained starting from **1e-BF<sub>4</sub>** (dr = 10 : 1) with a moderate yield (68%, entry 2). As using **1f-BF<sub>4</sub>** with a 5 : 1 diastereomeric ratio resulted in an inseparable mixture of complexes (±)-**3f** and *meso*-**3f** with a ratio 5 : 1 (entry 3), diastereomerically pure **1f-BF<sub>4</sub>** allowed the single formation of the chiral complex (±)-**3f** with excellent yield (entry 4). Following the same protocol, chiral complex (±)-**4f** containing a *tert*-butyl-indenyl group as an ancillary ligand was prepared in moderate yield starting from diastereomerically pure imidazolium salt **1f-BF<sub>4</sub>** (Scheme 2).

Having a series of 8 chiral palladium–NHC complexes, we studied the racemate resolution by chiral HPLC at a preparative scale (Scheme 3). Various chiral columns were screened and the detection of enantiomers was performed with an UV-vis detector connected to a circular dichroism detector, giving the CD sign at 254 nm for each enantiomer. The chiralpak IG column enabled the efficient resolution of all palladium complexes.<sup>15</sup> Using a 1 cm diameter column, batches from 15 to 850 mg were purified in several hours affording both enantiomers with excellent enantiopurities, superior to 99.5% ee for most of the complexes. Yields of the resolution step span from 23 to 97% as a function of the complex.

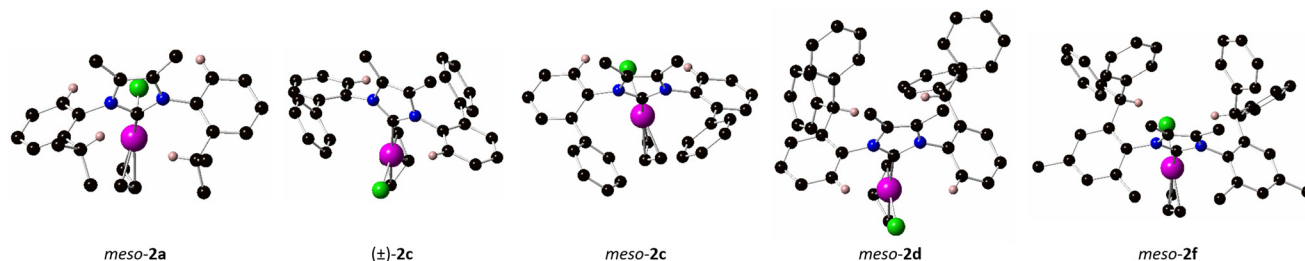
The configurational stability of these chiral complexes was found to be good, as attempts to determine experimentally the diastereomerization barriers require prolonged heating at 130 °C or at a higher temperature which causes a complex degradation faster than the diastereomerization process.

The low stability of complex (±)-**2c** in solution and in the solid state explains the low yields of enantiopure complexes (29 and 21%). To illustrate the efficiency of the resolution by chiral HPLC at a preparative scale, a batch of 850 mg of (±)-**2f** afforded 420 mg (49%) and 401 mg (48%) of both enantiomers after 45 injections every 5 min (about 4 h for the complete resolution). Crystals of first eluted complexes *cis*-**2b** and **2e**

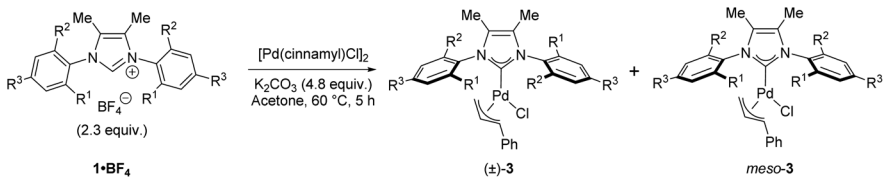
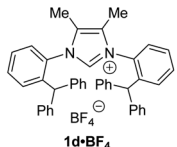
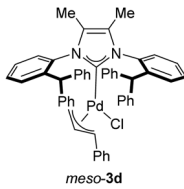
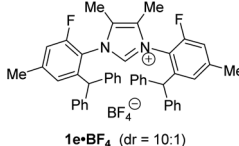
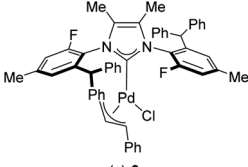
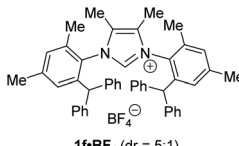
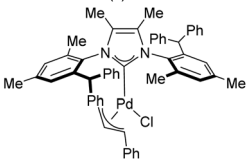
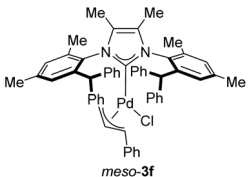
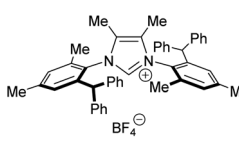
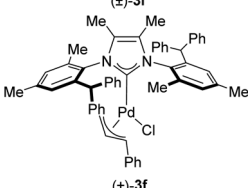
**Table 1** Synthesis of Pd(allyl)Cl(NHC) complexes bearing C<sub>2</sub>-symmetric NHC ligands<sup>a</sup>

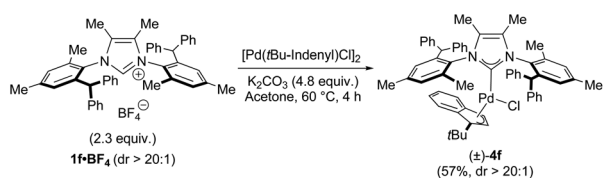
					
Entry	Imidazolium salt 1-X	Conditions	Complex (±)-2	Complex meso-2	Overall yield (ratio (±)/meso)
1		A	Not observed		49% 49% (<1 : 20)
2	<b>1a</b> ·BF <sub>4</sub>	B	Not observed		78% 78% (<1 : 20)
3		A	Trace		87% 87% (<1 : 20)
4		A		18%	31% 49% (1 : 1.5)
5	<b>1c</b> ·BF <sub>4</sub>	B		57%	42% 99% (1.35 : 1)
6		B		28%	62% 90% (1 : 2.2)
	<b>1d</b> ·BF <sub>4</sub>				
7		B		72% Not observed	72% (>20 : 1)
	<b>1e</b> ·BF <sub>4</sub> (dr = 10:1)				
8		B			79% (5 : 1)
	<b>1f</b> ·BF <sub>4</sub> (dr = 5:1)				
9		B		92% Not observed	92% (>20 : 1)
	<b>1f</b> ·BF <sub>4</sub> (dr > 20:1)				

<sup>a</sup> Conditions A: [Pd(allyl)Cl]<sub>2</sub>, (1 equiv.); imidazolium salt 1-X (2.3 equiv.), *t*BuOK (3 equiv.), THF, 25 °C, 6 h. Conditions B: [Pd(allyl)Cl]<sub>2</sub>, (1 equiv.); imidazolium salt 1-X (2.3 equiv.), K<sub>2</sub>CO<sub>3</sub> (4.8 equiv.), acetone, 60 °C, 5 h.

**Fig. 4** Ball-and-stick representation of the *meso* complexes 2a, 2c, 2d and 2f and the chiral complex (±)-2c (most of the hydrogens have been omitted for clarity).

**Table 2** Synthesis of Pd(cinnamyl)Cl(NHC) complexes bearing C<sub>2</sub>-symmetric NHC ligands

				
Entry	Imidazolium salt <b>1-BF<sub>4</sub></b>	Complex (±)-3	Complex <i>meso</i> -3	Overall yield (ratio (±)/ <i>meso</i> )
1	 <b>1d-BF<sub>4</sub></b>	Not observed	 <i>meso</i> -3d	78% 78% (<1 : 20)
2	 <b>1e-BF<sub>4</sub></b> (dr = 10:1)	 (±)-3e	68% Not observed	68% (>20 : 1)
3	 <b>1f-BF<sub>4</sub></b> (dr = 5:1)	 (±)-3f	 <i>meso</i> -3f	82% (5 : 1)
4	 <b>1f-BF<sub>4</sub></b> (dr > 20:1)	 (±)-3f	90% Not observed	90% (>20 : 1)

**Scheme 2** Preparation of the Pd(*t*Bu-indenyl)Cl(NHC) complex **4f**.

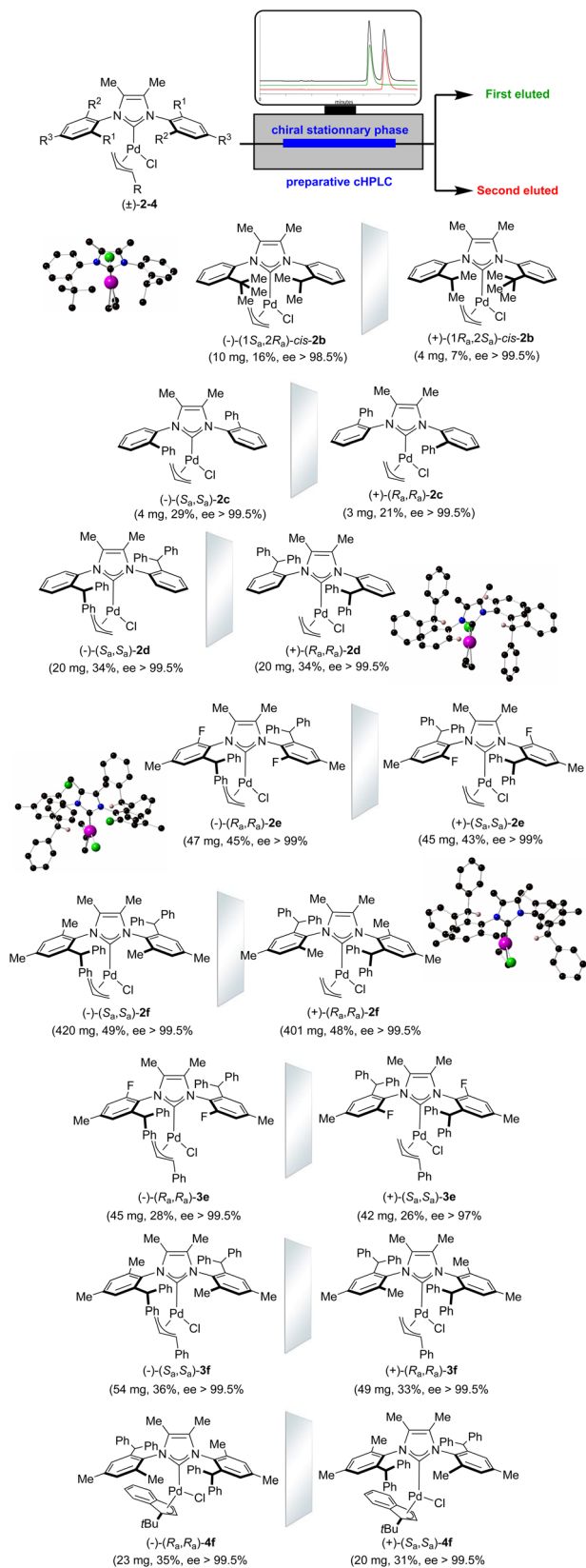
and second eluted complexes **2d** and **2f** suitable for single crystal X-ray diffraction were obtained and allowed the determination of their absolute configuration. Of note, the modification of the absolute configuration between complexes **2e** and **2f** is the result of priority changes to assess the stereodescriptors.

UV-vis and ECD spectra for both enantiomers for all complexes have been recorded in acetonitrile solutions. Individual ECD spectra, reported in the ESI,<sup>†</sup> showed expected mirror images for both enantiomers.<sup>15</sup> The comparison of ECD spectra with those of complexes that have been studied by

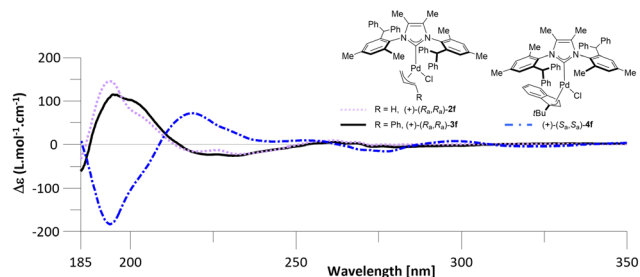
X-ray crystallography was used to assign absolute configurations of all complexes. As an example, ECD spectra of the 2<sup>nd</sup> eluted complexes **2f**, **3f** and **4f**, depicted in Fig. 5, show a similar shape for complexes **2f** and **3f** with a positive ECD-active band between 195 and 200 nm and a negative ECD-active band between 220 and 230 nm. Thus, allyl- and cinnamyl-complexes **2f** and **3f** possess the same spatial conformation. *tert*-Butyl-indenyl complex **4f** displays an ECD spectrum being the mirror image of those of complexes **2f** and **3f** indicating an inversion of the elution order, although the optical rotation values of all 2<sup>nd</sup> eluted complexes are positive (+). Enantiopure complexes **2c** and **4f** display optical rotation values of high magnitude at several wavelengths ((±)-**2c**, [ $\alpha$ ]<sub>589</sub><sup>25</sup> = ± 300; (±)-**4f**, [ $\alpha$ ]<sub>589</sub><sup>25</sup> = ± 740).

Enantiopure complexes were tested in the asymmetric intramolecular  $\alpha$ -arylation of amides using amide **5a** as the benchmark substrate (Table 3).<sup>8c,20</sup> Reactions were performed at 40 °C in DME using potassium *tert*-butoxide as the base. Neither complex *cis*-**2b** due to its “pseudo *meso*” structure nor **2c** due to its poor stability was evaluated. Complex (+)-(*R<sub>a</sub>*,*R<sub>a</sub>*)-





**Scheme 3** Resolution of racemic complexes by chPLC at a preparative scale.



**Fig. 5** ECD spectra of the second eluted complexes (+)-2f, (+)-3f and (+)-4f.

**Table 3** Catalysts screening for the palladium-catalyzed intermolecular  $\alpha$ -arylation of amide **6a**

Entry	Catalyst	<i>T</i> (°C)	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
1	(+)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-2d	40	44	77 ( <i>S</i> )
2	(-)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-2e	40	73	72 ( <i>R</i> )
3	(-)-(1 <i>S</i> <sub>a</sub> ,2 <i>S</i> <sub>a</sub> )-2f	40	85	95 ( <i>R</i> )
4	(+)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-2f	40	84	95 ( <i>S</i> )
5	<i>meso</i> -2f	40	54	—
6	(-)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-3e	40	65	77 ( <i>R</i> )
7	(+)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-3f	40	86	92 ( <i>S</i> )
8	(-)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-4f	40	93	92 ( <i>S</i> )
9	(+)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-2f	25	8	92 ( <i>S</i> )
10	(+)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-2f	60	84	95 ( <i>S</i> )
11 <sup>c</sup>	(+)-(1 <i>R</i> <sub>a</sub> ,2 <i>R</i> <sub>a</sub> )-2f	80	87	95 ( <i>S</i> )

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> Reaction duration 5 h (DME = 1,2-dimethoxyethane).

**2d** catalyzed the formation of product **6a** with a moderate yield (44%) and a good enantiomeric excess (77%, entry 1). In comparison, (-)-(1*R*<sub>a</sub>,2*R*<sub>a</sub>)-**2e** allowed to improve the isolated yield with a slight decrease of the enantioinduction (72%, entry 2).

Enantiopure complexes **2f** enabled us to obtain both good activity and an excellent enantioselectivity (95% ee, entries 3 and 4). From the efficiency point of view, catalysts containing bulkier NHC ligands display a high activity since they favor reductive elimination. Of note, we noticed that pre-catalyst *meso*-**2f** was significantly less efficient than chiral analogs (entry 5). It seems that having the sterically hindered benzhydryl groups on only one side of the NHC is less favorable to boosting the reductive elimination. This observation is in sharp contrast with the study disclosed by Kündig.<sup>20i</sup> Based on DFT calculations, it has been proposed that oxidative addition is the rate-determining step. Nevertheless, a recent theoretical study on palladium-catalyzed  $\alpha$ -arylation of ketones with phosphine ligands suggested that reductive elimination is the rate-limiting step.<sup>21</sup> As expected, the nature of the allyl derivative ligand has no meaningful influence on the enantioselectivity (72% ee, entry 2 vs. 77% ee, entry 6) (95% ee, entries 3 and 4

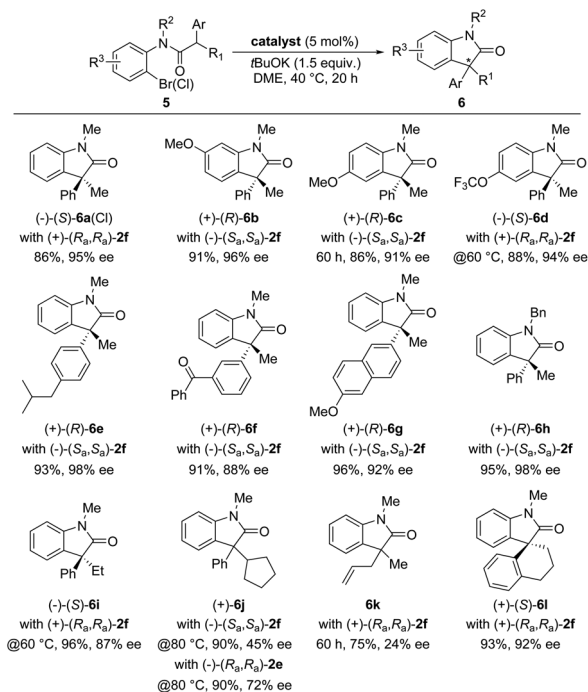
vs. 92% ee, entry 7 vs. 92%, entry 8) since the generated catalytic species is the same. As isolated yields are good to excellent, the effect of the nature of the allyl derivative ligand on catalytic activity cannot be confidently addressed. At 25 °C, using (+)-(R<sub>a</sub>,R<sub>a</sub>)-**2f**, only a tiny amount of **6a** was isolated with a similar enantiomeric excess (92%, entry 9). At higher temperatures, 60 or 80 °C, identical ees were measured (entries 10 and 11). This observation proves that not only pre-catalysts but also catalytic species possess excellent configuration stability.

The scope of the intramolecular  $\alpha$ -arylation of amides was studied with several substrates using enantiopure complexes **2f**, either (+)-(R<sub>a</sub>,R<sub>a</sub>)-**2f** or (–)-(S<sub>a</sub>,S<sub>a</sub>)-**2f** (Scheme 4). Absolute configurations of products were determined based on the work of Kündig<sup>20b,i</sup> or by analogy and were tentative. With amide **5a** (Cl), the chlorinated analogue of **5a**, a similar yield of **6a**(Cl) was isolated possessing the same enantiopurity. The reaction was complete after 20 h at 40 °C with **5b** containing a methoxy group at the *para* position of the bromine. Substrates bearing electron-donating and electron-withdrawing groups at the *meta* position, OMe (**5c**) and OCF<sub>3</sub> (**5d**) respectively, were found less reactive and required either a prolonged reaction time (60 h) or an increase of the reaction temperature to 60 °C to reach completion. All these products were isolated with enantiomeric excesses superior to 90% ee. With substrates derived from ibuprofen, ketoprofen and naproxen, products **6e**, **6f** and **6g**, respectively, were isolated with excellent yields and enantioselectivities. A slightly higher enantiomeric excess was obtained with *N*-benzyl-substituted substrate **5h** (**6h**, 98% ee) compared to *N*-methyl-substituted substrate **5a**. The nature of the alkyl group of the stereogenic center has an influence on

the enantioselectivity related to its steric bulk: methyl (**6a**, 95% ee), ethyl (**6i**, 87% ee) and cyclopentyl (**6j**, 45% ee). Of note, substrate **5j** has been previously investigated by Trapp and co-workers and up to 55% ee for **6j** was reported.<sup>20h</sup> We screened again several enantiopure atropisomeric Pd–NHC complexes and using the fluorine containing complex (–)-(R<sub>a</sub>,R<sub>a</sub>)-**2e** the enantiomeric excess was increased up to 72% ee. Substrate **5k** containing a methyl and an allyl group on the stereogenic center represents a very challenging substrate. Despite the full conversion of the substrate at 60 °C and the good isolated yield of product **6k**, only a low enantiomeric excess (24% ee) was reached. To our delight, the highly enantio-enriched spiro compound **6l** (92% ee) was isolated in high yield (92%) under the same conditions with catalyst (+)-(R<sub>a</sub>,R<sub>a</sub>)-**2f**.

## Conclusions

In conclusion, we successfully applied the concept of atropisomeric NHC–metal complexes to C<sub>2</sub>-symmetric NHC ligands and implemented it into the preparation of chiral palladium complexes. The use of imidazolium salts with unrestricted rotation axes (rotamers) as NHC precursors gave mostly *meso* palladium complexes, probably as thermodynamic products. To circumvent this issue, imidazolium salts containing additional *ortho*-substituents (F or Me) were found to be conformationally stable and have been prepared mainly as chiral, yet racemic. So far, we could not unambiguously point out the parameters governing the formation of either *meso* or chiral complexes; the working hypothesis involving London dispersion forces could not be clearly demonstrated. Thus, several chiral palladium(II) complexes containing an allyl, a cinnamyl or a *t*Bu-indenyl group as an ancillary ligand were synthesized. These racemic complexes exhibited good chemical stability and could be resolved using chiral HPLC at the preparative scale. Both enantiomers of each palladium complex were obtained with excellent enantiopurities and overall good yields and this strategy could be efficiently implemented up to 850 mg scale. The absolute configuration of the enantiopure complexes was determined by single crystal X-ray diffraction and comparison of the ECD spectra. Enantiopure complexes were tested in the intramolecular  $\alpha$ -arylation of amides and excellent enantioselectivities (up to 98% ee) can be achieved with some of the enantiopure atropisomeric palladium complexes that have been designed and prepared. This finding is in sharp contrast to results obtained with analogue C<sub>1</sub>-symmetric NHC–palladium complexes (up to 54% ee).<sup>10b</sup> Having in hand a new and efficient design of chiral catalysts, further development of new enantioselective reactions is currently underway in our laboratory.



**Scheme 4** Scope investigation on asymmetric  $\alpha$ -arylation of amides **5** (absolute configurations were assigned by analogy and were tentative).

## Author contributions

Lingyu Kong and Yajie Chou: organic synthesis, complex preparation, and asymmetric catalysis; Muriel Albalat, Marion



Jean, and Nicolas Vanthuyne: chiral HPLC analyses, preparative chiral HPLC, determination of the chiroptic properties, and ee measurements; Paola Nava and Stéphane Humbel: theoretical calculations; Hervé Clavier: conceptualization, writing – reviewing and editing, and supervision.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

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