

# Atroposelective Construction of Axially Chiral 2-Aryl-Pyrroloquinolones

Tourya Khlifi,<sup>§</sup> Chaimae Jbilou,<sup>‡</sup> Alexis Leblais,<sup>§</sup> Jérôme Marrot,<sup>§</sup> Pierrick Nun,<sup>‡</sup> Clément Ghiazza,<sup>§</sup> Isabelle Chataigner,<sup>□</sup> Vincent Coeffard,<sup>\*‡</sup> Xavier Moreau<sup>\*§</sup>

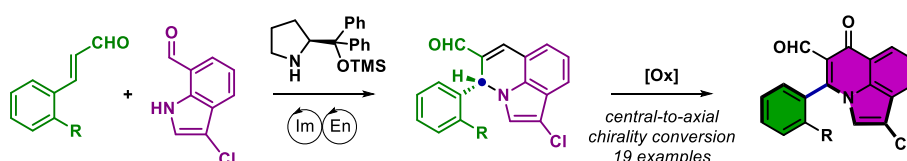
<sup>§</sup>Université Paris-Saclay, UVSQ, CNRS, UMR 8180 Institut Lavoisier de Versailles, 78035 Versailles Cedex, France

<sup>‡</sup>Nantes Université CNRS, CEISAM, UMR 6230, 44000 Nantes, France

<sup>□</sup>Univ Rouen Normandie, INSA Rouen Normandie, CNRS, Normandie Univ, COBRA, 76000 Rouen, France

Sorbonne Université, CNRS, Laboratoire de Chimie Théorique, LCT UMR7616, 75005 Paris, France

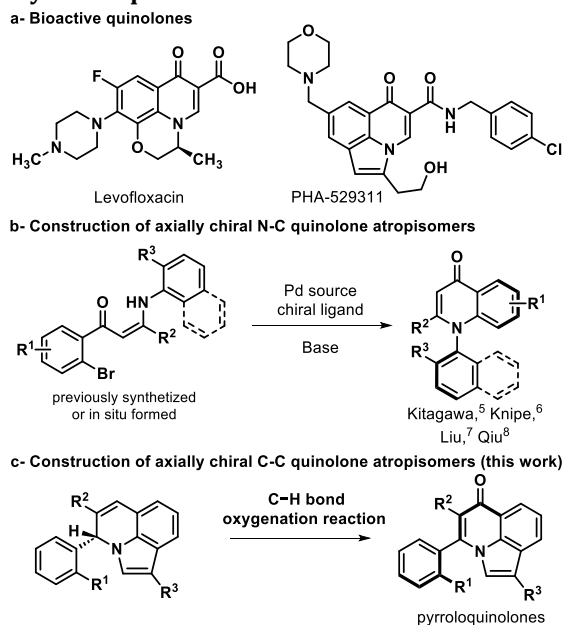
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**ABSTRACT:** A two-step protocol including an enantioselective organocatalyzed synthesis of pyrroloquinolines followed by an oxidation reaction allowed the formation of axially chiral 2-aryl-pyrroloquinolones. Thorough optimization of the experimental conditions for the second step allowed the oxygenation reaction to take place and ensured, in most cases, a central-to-axial chirality conversion with a complete retention of the enantiomeric excess.

The 4-quinolone motif is widely found in the active ingredients of many drugs with a broad range of pharmacological properties. These compounds are used in particular to treat a number of infections as they are broad-spectrum antibiotics, active against both Gram-positive and Gram-negative bacteria.<sup>1</sup> However, depending on the nature and position of the substituents decorating this azaheteroaromatic system, biological properties such as antimalarial, anti-tuberculosis, anti-HIV or anti-cancer have also been demonstrated.<sup>2</sup> As a result, quinolone derivatives have attracted considerable attention of synthetic chemists due to their wide range of potential applications. Over the years, a large number of synthetic developments have been devoted to the production of quinolone containing molecules which exhibit a high degree of structural and functional diversity.<sup>3</sup> For example, 1,8-annulated fluoroquinolone Levofloxacin is FDA-approved for the treatment of pneumonia, urinary tract infections, and abdominal infections. Pyrroloquinolone PHA-529311 exhibits activity against herpesvirus DNA polymerases.<sup>4</sup> As illustrated by Levofloxacin, there is also a growing interest in the development of enantiopure scaffolds containing one or more stereogenic centers (Scheme 1a). In stark contrast, the development of atroposelective processes giving access to chiral quinolone moieties bearing a stereogenic axis remains scarce and limited to the formation axially chiral N-C quinolone atropisomers (Scheme 1b). In 2012, Kitagawa pioneered the synthesis of axially chiral 2-aryl-4-quinolone derivatives and reported the reaction of *o*-tert-butylaniline with 2-bromophenyl arylethynyl ketone promoted by a

## Scheme 1. Atroposelective strategies for the synthesis axially chiral quinolones.



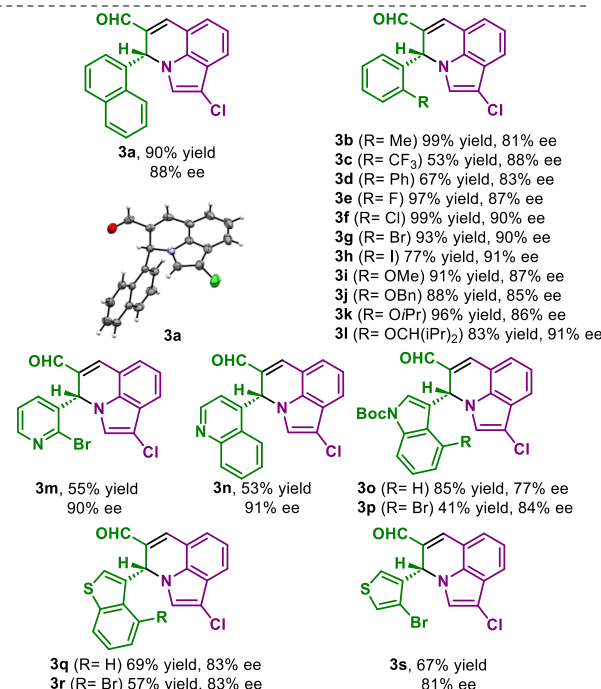
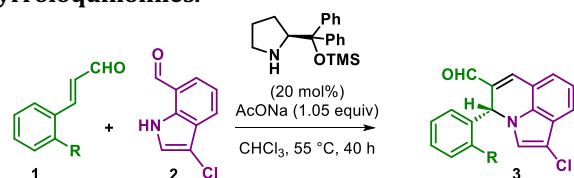
chiral Pd-based catalytic system.<sup>5</sup> Almost ten years later, Knipe extended the scope of the reaction to the construction of chiral 2-naphthyl-4-quinolone derivatives.<sup>6</sup> Very recently, Liu<sup>7</sup> and Qiu<sup>8</sup> independently reported the same Pd-catalyzed coupling with a substantial improvement in the enantioselectivity of the reaction by screening different chiral ligands. While these scant advances describe

asymmetric synthesis of axially chiral C–N atropisomers, to the best of our knowledge, no report describe the atroposelective construction of axially chiral C–C quinolone derivatives. In recent years, methods for the atroposelective formation of biaryl or heterobiaryl scaffolds with a C–C, C–N or N–N axial chirality have blossomed in the literature.<sup>9</sup> The most widely explored synthetic strategies include: i) atroposelective axis construction;<sup>10</sup> ii) atroposelective ring construction;<sup>11</sup> iii) kinetic dynamic resolution or desymmetrisation;<sup>12</sup> iv) central-to-axial chirality conversion.<sup>13</sup> This last strategy, consisting in converting a molecule or a transient intermediate containing a stereogenic center to an axially chiral compounds while preserving the enantiomeric purity of the former molecule, has recently aroused a notable attention. Among diverse biaryl or heterobiaryl compounds obtained via this route, elegant stereoselective syntheses of axially chiral pyridine or quinoline atropisomers have been documented. In these methodologies, the key step for the chirality conversion is commonly an elimination reaction under acidic conditions<sup>14</sup> or an oxidative aromatization.<sup>15</sup> In contrast to the formation of quinolines and pyridines, the atroposelective formation of chiral quinolone scaffolds further requires a C–H bond oxygenation reaction to incorporate the additional oxygen atom (Scheme 1c). Herein, we envisaged to capitalize on this sequence, scarcely described in the literature,<sup>16</sup> to afford valuable axially chiral 2-arylquinolones.

We first synthesized a series of enantioenriched pyrroloquinoline molecules using our previously described asymmetric organocatalyzed methodology (scheme 2).<sup>17</sup> A vast array of cinnamaldehyde derivatives **1** were engaged in the organocatalyzed cascade reaction involving an aza-Michael addition of the 3-chloro-7-formylindole **2** to the in situ formed chiral  $\alpha,\beta$ -unsaturated iminium followed by an intramolecular aldol condensation reaction giving tricycles **3**. The steric nature of the R group of compounds **1** has been carefully chosen to gain insights on its influence regarding the efficiency of the central-to-axial chirality conversion that will occur during the transformation of pyrroloquinolines **3** to quinolones. Thus, a first pyrroloquinoline bearing a pending naphthyl substituent boded well and afforded **3a** with an excellent yield. The resulting crystalline solid was suitable for X-Ray diffraction and confirmed the absolute *R*-configuration of the major isomer. Then, *ortho*-substituted cinnamaldehyde compounds **3b–3d**, decorated with aryl or alkyl groups, were synthesized in moderate to excellent yields and a good level of enantioselectivity. Halogen atoms were incorporated into this position, giving rise to compounds **3e–3h** with enantiomeric excesses ranging from 87 to 91%. Alkyl ethers of different sizes with increasing steric hindrance were included and compounds **3i–3l** were generated with the same effectiveness. Finally, pyrroloquinolines **3m–3s** embedding 5- or 6-membered heteroaromatic scaffolds were obtained with fair yields and enantioselectivities.

We then carefully studied the reaction leading to the formation of axially chiral 2-(hetero)aryl quinolones **4** (Scheme 3).<sup>18</sup> Two challenges have to be met to achieve this transformation: fine-tuning the oxidative conditions to enable an efficient oxygenation reaction while ensuring a total central-to-axial chirality conversion. MnO<sub>2</sub> proved to

## Scheme 2. Enantioselective formation of pyrroloquinolines.<sup>a–c</sup>



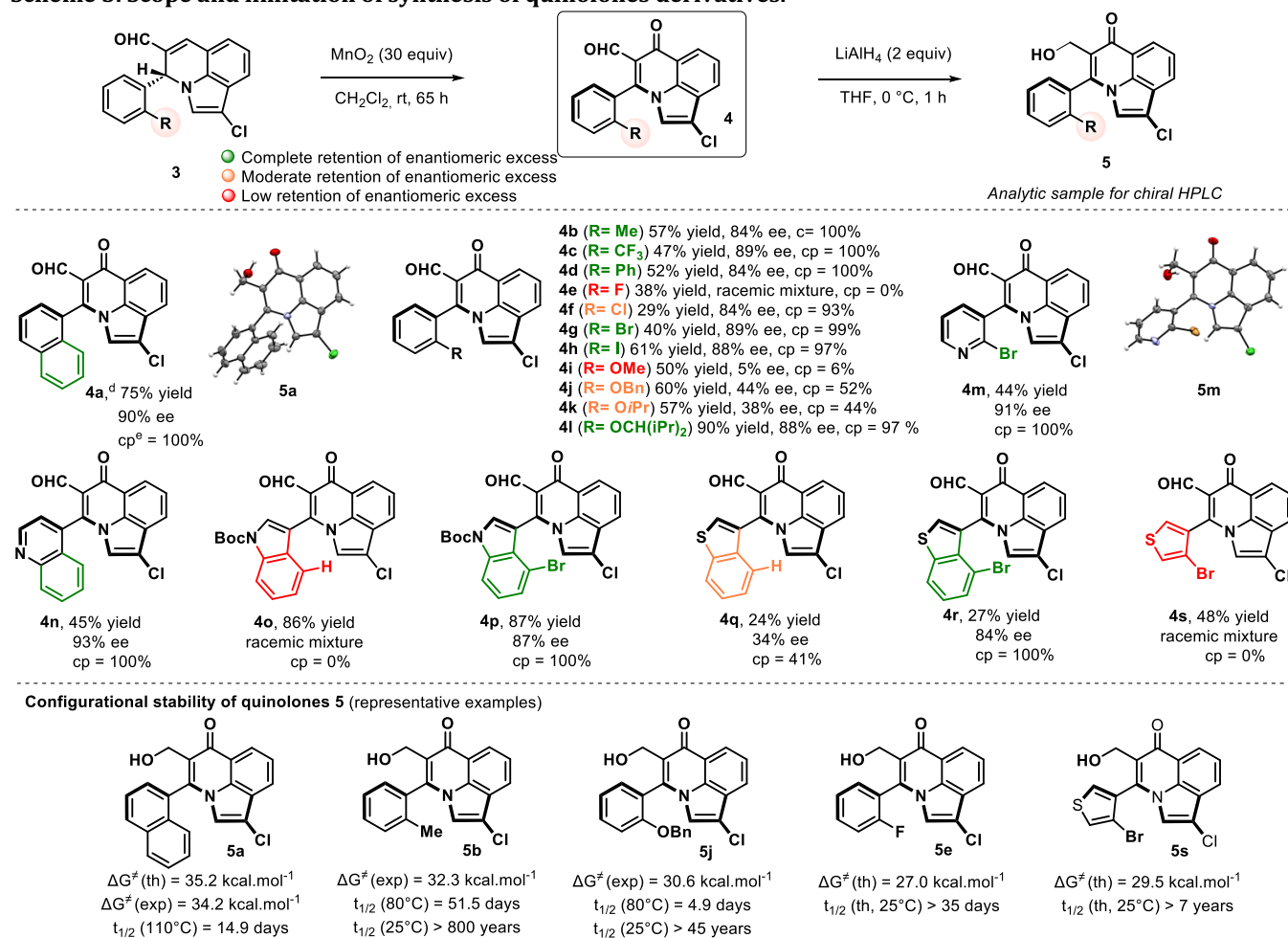
<sup>a</sup> General condition: **1** (0.28 mmol), **2** (0.19 mmol), AcONa (0.20 mmol) and Hayashi-Jørgensen catalyst (20 mol%) in CHCl<sub>3</sub> (0.9 mL) at 55 °C for 40 h. <sup>b</sup> Yield of isolated pure product after column chromatography. <sup>c</sup> ee determined by HPLC analysis on a chiral stationary phase.

be the most efficient reagent achieving both the oxidation reaction<sup>19</sup> and a complete central-to-axial chirality conversion (See SI for details). The reaction proceeded smoothly when 30 equivalents of MnO<sub>2</sub> were added in dichloromethane for 65 hours at room temperature delivering the quinolone **4a** in 70% isolated yield (Scheme 3, top). In addition, the reaction can be scaled up to 2.5 mmol, giving **4a** in 75% isolated yield and 90% ee (conversion percentage (cp) = (ee<sub>product</sub>/ee<sub>substrate</sub>)×100 = 100%).<sup>15c</sup> With these conditions in hands, we explored the scope and limitation of the oxygenation reaction on the prepared pyrroloquinolines. Noteworthy, in order to obtain an optimal separation of both enantiomers by HPLC, the aldehyde moiety was reduced to the corresponding primary alcohol. Gratifyingly, compound **5a**, resulting from the reduction of **4a**, was also suitable for X-ray diffraction and unambiguously unveiled the *aR* configuration of the major atropisomer. When the R group was an alkyl (-CH<sub>3</sub>, -CF<sub>3</sub>) or an aryl (-Ph) and regardless of the steric contribution, the corresponding compounds **4b–4d** were obtained in good yield with a complete retention of the enantiomeric excess. Unfortunately, an entire erosion of the ee was observed for the *ortho*-fluorinated derivative **3e** and compound **4e** was isolated in 38% yield as a racemic mixture. Interchanging a fluorine atom with a chlorine atom considerably improved the conversion percentage (93% in this case). As

anticipated, replacing the chlorine atom for a larger halogen atom such as bromine or iodine further improved the stereoselectivity of the reaction in both cases. Another interesting case study was observed when R was chosen as an alkoxide group. The presence of a methoxy group in the *ortho* position allowed the formation of quinolone **4i** in 50% isolated yield but with a disappointing enantiomeric excess (5% ee). Gradually increasing the size of the alkyl substituent in the ether-oxide moiety (-OBn, -OiPr) enhanced the retention of the enantiomeric excess and gave quinolones with better selectivities (44% ee and 38% ee for **4j** and **4k** respectively). Finally, an almost complete retention of the enantiomeric excess (cp = 97%) was reached for R=OCH(iPr)<sub>2</sub> and compound **4l** was obtained in 90% yield and 88% ee. The behavior of pyrroloquinolines whose stereogenic center is substituted by a heteroaromatic moiety was then surveyed. Nitrogen-containing six-membered ring such as 2-bromopyridyl (**3m**) or unsubstituted quinolyl (**3n**) groups were amenable to the oxidative process and the corresponding quinolones **4m** and **4n** were obtained with 44% and 45% yield respectively (cp = 100% in each case). With **5m** in hands, obtained upon reduction of its analogue **4m**, we concluded on the generalization of the absolute *aR* configuration of 2-

arylquinolones substituted with both monocyclic and fused aromatic systems. The trend was different for 5-membered heterocycles such as *N*-protected indolyl and thiophenyl scaffolds. It turns out that the substitution of the C4 position by a bromine atom was mandatory to ensure a central-to-axial chirality conversion with excellent enantiomeric purities (**4o** vs **4p** and **4q** vs **4r**). Finally, even though pyrroloquinoline **3s** was accommodated with a substituted thiophenyl group, the resulting quinolone **4s** was obtained as a racemic mixture in 48% yield. The latter was predictable since the bromine atom is no longer in close proximity with the tricyclic core due to bond angles in 5-membered aromatic systems (119° in **4m** vs 114° in **4s**). We then examined the configurational stability of quinolone **5a** by determining experimentally<sup>20</sup> and theoretically<sup>21</sup> the enantiomerization Gibbs free energy barrier ( $\Delta G^\ddagger$ ) and the racemization half-time (Scheme 3, bottom). We found that the racemization half-time of **5a** was higher than 14 days at 110°C which ranks this compound in Class 3 atropisomer and corresponds to configurationally robust molecules.<sup>22</sup> The computed value was close to the experimental one, validating the choice of the calculation method used. In all cases except for compound **5o**, the obtained results rule out

**Scheme 3. Scope and limitation of synthesis of quinolones derivatives.**<sup>a-c</sup>

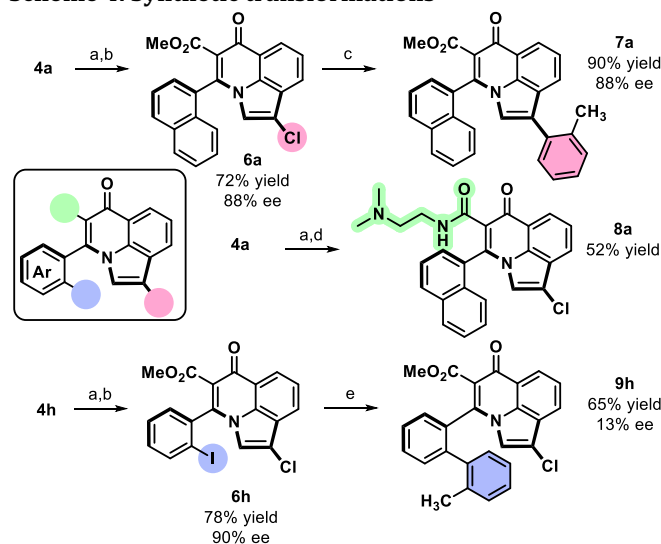


<sup>a</sup> General condition: **3** (0.084 mmol), MnO<sub>2</sub> (30 equiv) in CH<sub>2</sub>Cl<sub>2</sub> at rt for 65 h. <sup>b</sup> Yield of isolated pure product after chromatography. <sup>c</sup> ee determined on the corresponding primary alcohol by HPLC analysis on a chiral stationary phase. <sup>d</sup> On 2.5 mmol scale. <sup>e</sup> Conversion percentage (cp) = (ee<sub>product</sub>/ee<sub>substrate</sub>) × 100

the possibility of racemization during the process (reactions or purifications) as the racemization half-times are higher than 35 days at 25°C (assuming that  $\Delta G^\ddagger$  is independent of the temperature).<sup>20</sup> Therefore, we can conclude that the stereoselectivity during the chirality conversion step is inefficient in these cases and that the absence of a bulky group in the *ortho* position of the aromatic ring is detrimental to the formation of enantioenriched quinolones **4**. To better assess the synthetic utility of 2-arylquinolones **4**, several transformations were implemented on the 3 anchoring points of the molecule. Conversion of the aldehyde moiety of compound **4a** to carboxylic acid was achieved through a Pinnick-Lindgren oxidation followed by an amide coupling in the presence of EDCI/HOBt to afford **8a**. Then C-Cl and C-I bonds were harnessed to functionalize the quinolones **4**. Products **4a** and **4h** were engaged in a two-step sequence comprising an oxidation step of the aldehyde moiety to the corresponding carboxylic acid followed by an esterification reaction. Methyl esters **6a** and **6h** were obtained in good overall yields without racemization. Compound **6a** was engaged in a Suzuki-Miyaura coupling with (2-methyl)phenylboronic acid and gave rise to **7a** in 90% yield and 88% ee. Finally, compound **6h** was amenable a site selective Pd-catalyzed cross-coupling reaction leading to **9h** in 65% yield but racemization occurred.

To conclude, we have developed an efficient two-step procedure for the synthesis of enantioenriched 2-aryl quinolones from simple and readily available substrates. The sequence includes an organocatalytic asymmetric annulation of 3-chloro-7-formyl indole followed by a to axial chirality conversion strategy and leads to the formation of original axially chiral compounds. The configurational stability of the obtained products has been confirmed both theoretically and experimentally. Finally,

#### Scheme 4. Synthetic transformations



Conditions: a)  $\text{H}_2\text{O}_2$ ,  $\text{KH}_2\text{PO}_4$ ,  $\text{NaClO}_2$ ,  $\text{CH}_3\text{CN}/\text{MeOH}/\text{H}_2\text{O}$ , rt, 2 h; b)  $\text{TMSCHN}_2$ ,  $\text{MeOH}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C, 3 h. c)  $\text{Pd}(\text{OAc})_2$  (10 mol%), XPhos (20 mol%), (2-methyl)phenylboronic acid,  $\text{K}_3\text{PO}_4$ , dioxane/  $\text{H}_2\text{O}$ , 80 °C, 16 h; d) EDCI-HCl, HOBt, *N,N*-dimethylethane-1,2-diamine,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 12 h, ee of **8a** could not be determined; e)  $\text{Pd}(\text{PPh}_3)_4$  (10 mol%), (2-methyl)phenylboronic acid,  $\text{K}_2\text{CO}_3$ , toluene, 90 °C, 20 h.

post modification reactions were developed on the 3 anchors of our building blocks to highlight the synthetic potential of this strategy.

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its supporting information.

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/>. Experimental procedures, compound characterization data,  $^1\text{H}$ ,  $^{13}\text{C}$ , spectra and HPLC traces for all new compounds reported, and X-ray data for compounds **3a**, **5a** and **5m** (PDF).

### Accession Codes

CCDC 2361619, 2361620 and 2361621 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

## AUTHOR INFORMATION

### Corresponding Author

**Vincent Coeffard**, Nantes Université CNRS, CEISAM, UMR 6230, 44000 Nantes, France. <https://orcid.org/0000-0003-2982-7880>; Email: [vincent.coeffard@univ-nantes.fr](mailto:vincent.coeffard@univ-nantes.fr)

**Xavier Moreau**, Université Paris-Saclay, UVSQ, CNRS, UMR 8180 Institut Lavoisier de Versailles, 78035 Versailles Cedex, France. <http://orcid.org/0000-0002-6737-9671>; Email: [xavier.moreau@uvsq.fr](mailto:xavier.moreau@uvsq.fr)

### Author Contributions

**Tourya Khelifi**, Université Paris-Saclay, UVSQ, CNRS, UMR 8180 Institut Lavoisier de Versailles, 78035 Versailles Cedex, France.  
**Chaïmae Jbilou**, Nantes Université CNRS, CEISAM, UMR 6230, 44000 Nantes, France.

**Alexis Leblais**, Université Paris-Saclay, UVSQ, CNRS, UMR 8180 Institut Lavoisier de Versailles, 78035 Versailles Cedex, France.

**Jérôme Marrot**, Université Paris-Saclay, UVSQ, CNRS, UMR 8180 Institut Lavoisier de Versailles, 78035 Versailles Cedex, France.

**Isabelle Chataigner**, Université Rouen Normandie, INSA Rouen Normandie, CNRS, Normandie Univ, COBRA, 76000 Rouen, France; Sorbonne Université, CNRS, Laboratoire de Chimie Théorique, LCT UMR7616, 75005 Paris, France. <https://orcid.org/0000-0001-6302-7831>

**Clément Ghiazza**, Université Paris-Saclay, UVSQ, CNRS, UMR 8180 Institut Lavoisier de Versailles, 78035 Versailles Cedex, France. <https://orcid.org/0000-0002-1264-2559>

### Notes

The authors declare no competing financial interest.

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