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Aurélien Brion, Vittoria Martini, Marine Lombard, Pascal Retailleau, Nicola Della Ca', et al.. Phenolic Dienes as Highly Selective Dienophiles in Asymmetric Organocatalyzed Three-Component Vinylogous Povarov Reaction. *Journal of Organic Chemistry*, 2024, 89 (17), pp.12298-12306. 10.1021/acs.joc.4c01239 . hal-04733247

**HAL Id: hal-04733247**

**<https://hal.science/hal-04733247v1>**

Submitted on 11 Oct 2024

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# Phenolic Dienes as Highly Selective Dienophiles in Asymmetric Organocatalyzed Three-Component Vinylogous Povarov Reaction

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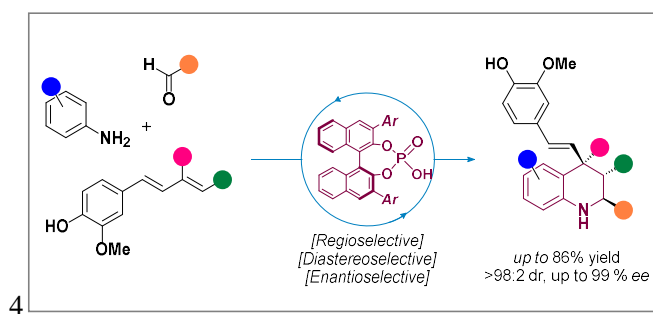
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## ABSTRACT



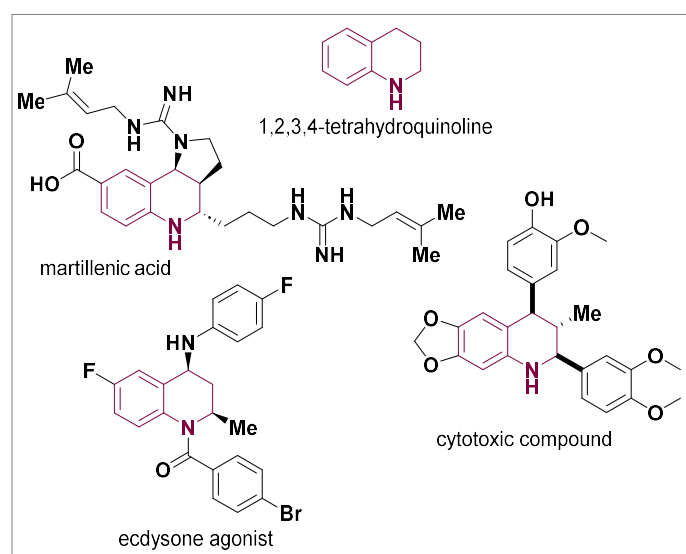
Our study presents a novel enantioselective route for 1,2,3,4-tetrahydroquinolines (THQs) synthesis via a chiral phosphoric acid-catalyzed 3-component Povarov reaction, employing phenolic dienes as dienophiles. This approach produces a diverse array of 2,3,4-trisubstituted tetrahydroquinolines, each featuring a styryl group at the 4-position, in high yields with excellent regio-, diastereo- and enantioselectivities (>95:5 dr and up to >99% ee).

## INTRODUCTION

1,2,3,4-tetrahydroquinolines (THQs) stand as significant heterocycles in medicinal chemistry, highlighted by their prevalence in a wide array of natural and synthetic compounds exhibiting biologically active properties (Figure 1).<sup>1,2</sup> Among the array of available synthetic methodologies the Povarov reaction, operating as an inverse-electron demand aza-Diels-Alder (IEDDA)<sup>3</sup> reaction between electron-rich dienophiles and *N*-arylimines, has emerged as a powerful synthetic method for constructing THQs with high structural diversity and excellent diastereoselectivity in the majority of instances.<sup>4</sup> It's therefore no surprise that numerous research groups directed their efforts toward developing asymmetric variants. Following seminal work by Kobayashi,<sup>5</sup> which introduced the first asymmetric version using a Yb/BINOL catalyst, alternative efficient methods based on chiral Lewis acids have been explored for producing enantioenriched THQs.<sup>6</sup> Moreover, a diverse array of enantioselective

organocatalytic approaches have been investigated. Notably, chiral ureas and proline derivatives have shown high efficiency.<sup>7</sup> However, chiral phosphoric acid (CPA) catalysts, particularly those based on a BINOL or SPINOL skeleton,<sup>4a</sup> have demonstrated broader applicability in asymmetric Povarov reactions, following Akiyama's pioneering work showcasing their high efficiency in achieving highly enantioselective reactions between vinyl ethers and *N*-arylimines.<sup>8</sup> For instance, our group developed a three-component (3-C) Povarov reaction catalyzed by chiral phosphoric acid, utilizing enecarbamates or enethioureas as dienophiles to access 4-amino-THQs with excellent enantioselectivities and complete diastereoselectivity (Scheme 1a).<sup>9</sup> Subsequently, other research groups have further developed this Povarov reaction by utilizing enecarbamates to synthesize significant heterocycles derived from 4-amino-THQs.<sup>4c,10</sup> Then, our group,<sup>11</sup> as well as the Shi group,<sup>12</sup> independently demonstrated that phenolic styrenes bearing either a *para*- or *ortho*-phenol were also suitable dienophiles in the CPA-catalyzed enantioselective cycloaddition, producing 4-aryl-THQs with notable stereoselectivities (Scheme 1a). Inspired by Seidel's work,<sup>7c,13</sup> we subsequently described a CPA-catalyzed enantioselective intramolecular Povarov reaction with styrenic dienophiles,<sup>14</sup> leading to the formation of various highly enantioenriched polycycles. Additionally, many others electron rich dienophiles (including indoles, enamines) were used in CPA-catalyzed Povarov reactions.<sup>15,16</sup>

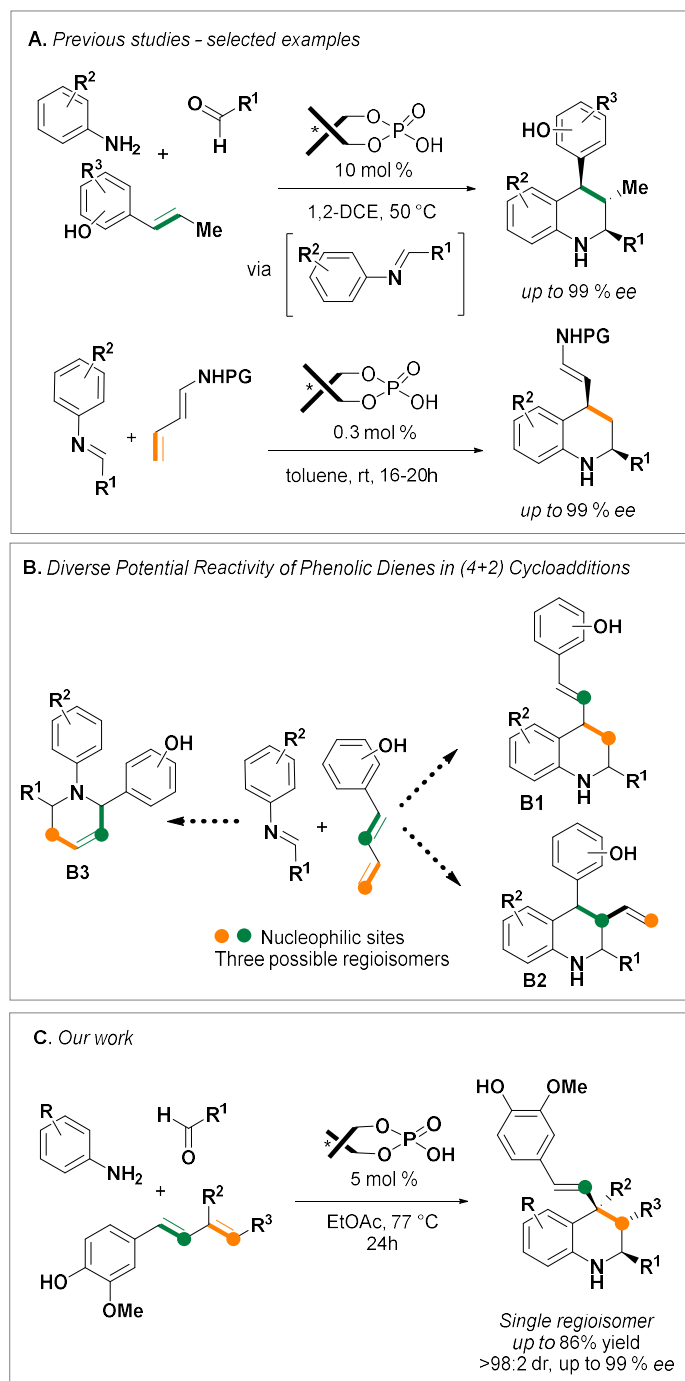
**Figure 1.** Examples of biologically active 1,2,3,4-tetrahydroquinolines.



However, their asymmetric vinylogous counterparts using activated polyenes as dienophiles are rare in the literature. In 2013, Bernardi and co-workers demonstrated the ability of  $\delta$ -unsubstituted dienecarbamates to act as efficient dienophiles in such cycloaddition with high regio-, diastereo-, and enantioselectivities in presence of CPA catalysts.<sup>17,18</sup> Later on, the group of Shi showed that 2- and 3-vinylindoles were also successful substrates in CPA-catalyzed enantioselective Povarov reaction.<sup>16c,16e,17-19</sup> Despite notable achievements, research has predominantly focused on nitrogen-containing polyenes as dienophiles in vinylogous asymmetric Povarov reactions. Surprisingly, while aryl dienes have been widely used as dienes in asymmetric Diels-Alder reactions,<sup>20</sup> there is currently no reported example of an enantioselective Povarov reaction using aryl dienes as dienophiles. Our research seeks to address this gap by developing an enantioselective variant of the Povarov reaction employing aryl dienes as dienophiles. Drawing upon our previous work, we hypothesized that phenolic dienes could serve as suitable partners for an enantioselective Povarov reaction, leveraging chiral phosphoric acid catalysts.<sup>11</sup> Indeed, we anticipated that the simultaneous dual activation through hydrogen bonding of the bifunctional chiral phosphoric acid with both the *N*-arylimine and the free hydroxyl group of the phenolic diene could ensure high reactivity and stereoselectivity. Investigating such an enantioselective Povarov reaction raises the question of regioselectivity, possibly resulting in two distinct regioisomers depending on the double bond involved in the cycloaddition. While the terminal double bond is expected to be the most reactive, examples in

the literature have shown that 1,2-disubstituted alkenes can also be engaged as dienophiles in cycloadditions with various imines under Brønsted acid catalysis (Scheme 1b, products **B1** vs **B2**).<sup>11</sup> Furthermore, phenolic dienes could potentially react with *N*-aryl imines in a conventional Diels-Alder reaction, as we previously observed in a CPA-catalyzed Diels-Alder reaction between diene-carbamates and *N*-heteroaryl imines, to generate enantioenriched tetrahydropyridines (Scheme 1b, product **B3**).<sup>21</sup>

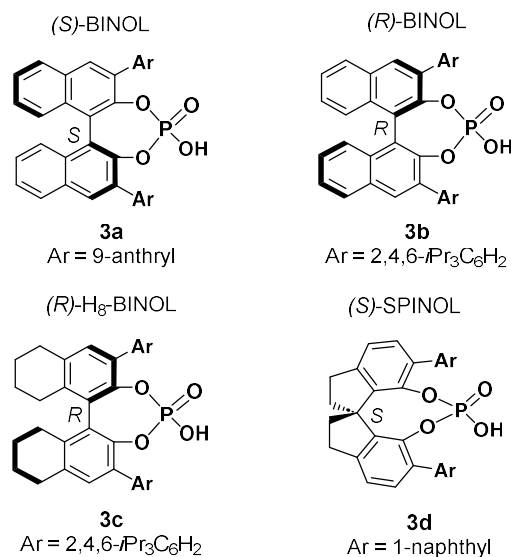
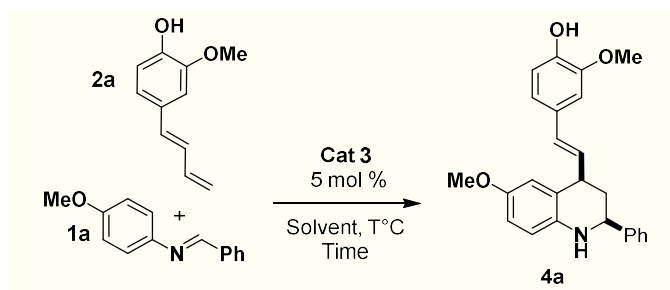
**Scheme 1.** (A) Enantioselective organocatalytic Povarov reactions (B) Different potential outcomes in (4+2) cycloaddition with phenolic dienes (C) Our present work with phenolic dienes as dienophiles



## RESULTS AND DISCUSSION

In this context, our aim was to develop an enantioselective and regioselective vinylogous Povarov reaction utilizing phenolic dienes as dienophiles (Scheme 1c). We began our investigation by evaluating diene **2a**, using 3.0 equivalents, with imine **1a** in presence of catalytic amounts of various CPAs (Table 1). Encouragingly, in our initial trials, after 72 hours of reaction at room temperature, we observed the formation of THQ **4a** as a single regioisomer and *cis*-diastereomer with 5 mol % of **3a**, exhibiting encouraging enantiocontrol (82% ee, entry 1). Moving to bulkier catalysts, the 2,4,6-*i*-Pr<sub>3</sub>-C<sub>6</sub>H<sub>2</sub> substituted CPA (**3b**) led to an increased yield (54%) and enantiomeric excess (87%, entry 2). In order to enhance both enantioselectivity and yield, we further refined the condition. However, other catalysts derived from H<sub>8</sub>-BINOL and SPINOL, namely **3c** and **3d**, did not yield better results than **3b** (entries 3 and 4). The solvent screening identified toluene as a better solvent for the reaction, resulting in an 86% yield of compound **4a** with a 97% enantiomeric excess and a reduced reaction time from 72 to 48 h (entries 5 and 6). Unexpectedly, the use of a green solvent like ethyl acetate (EtOAc) resulted in comparable yields and enantiomeric excess (ee) to those obtained with toluene (entry 7). Generally, non-coordinating solvents like toluene and CH<sub>2</sub>Cl<sub>2</sub> are preferred in this type of reaction to prevent competitive secondary hydrogen bonding interactions between the solvent, the catalyst, and/or the substrates, which can disrupt a well-organized transition state required for high enantio-induction. Although polar solvents have been used in CPA catalysis,<sup>22</sup> this reaction represents one of the rare examples of the successful use of EtOAc in enantioselective IEDDA reactions.<sup>22g</sup> To enhance the efficiency of the process, we decided to investigate the 3-C version of the reaction. Initially, we conducted the reaction of anisidine (**5a**), benzaldehyde (**6a**) and diene **2a** (3 eq.) in the presence of 5 mol% of **3b** for 48 h at room temperature in EtOAc. We were delighted to achieve **4a** with the same level of enantioselectivity as in the 2-component process, despite observing a decrease in yield (entry 8). However, by extending the reaction time to 72 h, we successfully improved the yield without compromising enantioselectivity (entry 9). In an effort to reduce reaction times, we investigated the effect of temperature. To our satisfaction, at 50°C, we isolated the product with a good yield in just 24 h while maintaining excellent enantioselectivity (entry 10). Furthermore, upon refluxing the solvent, the product was obtained with 85% yield and 97% ee within 24 hours (entry 11). Additionally, *i*-PrOAc was also tested as an alternative green solvent yielding the desired product **4a** in similar efficiency (79% yield, 97% ee, entry 12). Finally, we observed that exposing a 1:1 Z:E mixture of diene **2a** led to the formation of a single product, the Z isomer being unreactive in these conditions (entry 13).

**Table 1.** Optimization of the tandem processes.<sup>a</sup>

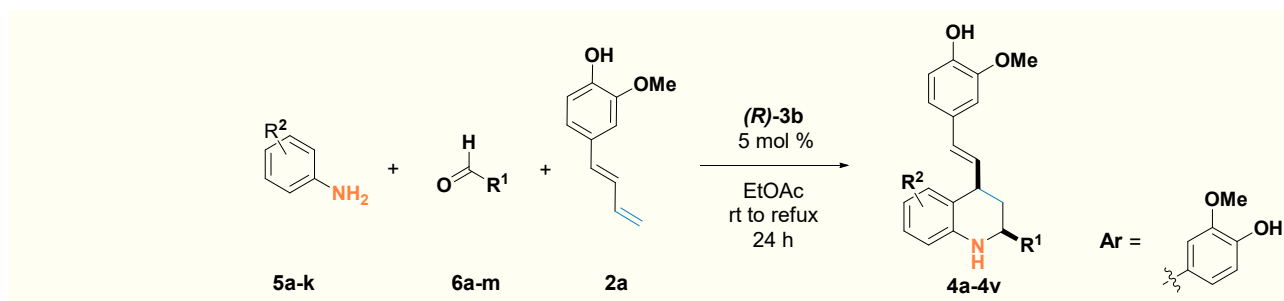


entry	Cat	solvent	yield (%) <sup>b,c</sup>	ee (%) <sup>d</sup>
1	<b>3a</b>	CH <sub>2</sub> Cl <sub>2</sub>	14	-82 <sup>e</sup>
2	<b>3b</b>	CH <sub>2</sub> Cl <sub>2</sub>	54	87 <sup>f</sup>
3	<b>3c</b>	CH <sub>2</sub> Cl <sub>2</sub>	20	69
4	<b>3d</b>	CH <sub>2</sub> Cl <sub>2</sub>	30	-60 <sup>g</sup>
5	<b>3b</b>	(CH <sub>2</sub> Cl) <sub>2</sub>	51	87
6	<b>3b<sup>h</sup></b>	toluene	86	97
7	<b>3b<sup>h</sup></b>	EtOAc	84	97
8	<b>3b<sup>i</sup></b>	EtOAc	64	96
9	<b>3b<sup>ij</sup></b>	EtOAc	76	96
10	<b>3b<sup>ik,l</sup></b>	EtOAc	72	96
11	<b>3b<sup>ik,m</sup></b>	EtOAc	85	97
12	<b>3b<sup>ik,n</sup></b>	<i>i</i> -PrOAc	79	97
13	<b>3a<sup>ik,m,o</sup></b>	EtOAc	21	94

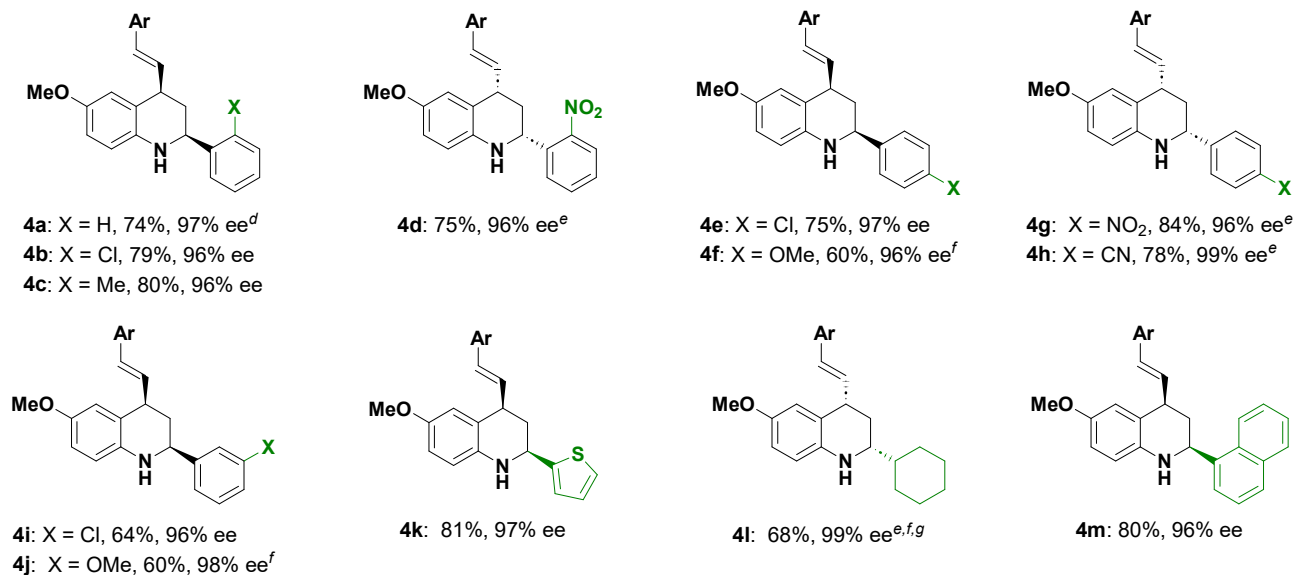
<sup>a</sup> General condition: imine **1a** (0.10 mmol), diene **2a** (0.30 mmol), and **3** (0.005 mmol), in solvent (1.0 mL) at rt under Ar atmosphere for 72 h. <sup>b</sup> Yields refer to chromatographically pure *cis*-isomer. <sup>c</sup> *dr* was determined to be higher than 95:5 by <sup>1</sup>H NMR analysis of the crude reaction mixture. The *cis*-diastereoselectivity of **4a** was assumed by analogy of **4e** determined by X-ray analysis (cf Supporting information). <sup>d</sup> Enantiomeric excess was determined by HPLC analysis on chiral stationary phase. <sup>e</sup> Catalyst derived from (S)-BINOL. <sup>f</sup> Catalyst derived from (R)-BINOL. <sup>g</sup> Catalyst derived from (S)-SPINOL. <sup>h</sup> Reaction conducted for 48 h. <sup>i</sup> Reaction performed through a 3-C condition: anisidine (**5a**, 0.10 mmol), benzaldehyde (**6a**, 0.10 mmol), diene **2a** (0.30 mmol), and **3b** (0.005 mmol), in solvent (1.0 mL) at rt under Ar atmosphere. <sup>j</sup> Reaction conducted for 72 h. <sup>k</sup> Reaction conducted for 24 h. <sup>l</sup> Reaction at 50°C. <sup>m</sup> Reaction at 77°C. <sup>n</sup> Reaction at 90 °C. <sup>o</sup> A E:Z mixture (1:1) of diene **2a** was used (0.30 mmol of E isomer).

With the optimized reaction conditions in hand, we next investigated the scope of this 3-C reaction. Various *ortho*-, *meta*- and *para*- substituted benzaldehydes were found to be suitable for this reaction, yielding a wide range of 2-aryl-THQ derivatives with excellent diastereo- and enantioselectivities (**4b-4j** and **4m**, Scheme 2). Notably, 2-azadienes **1** derived from benzaldehydes carrying electron-withdrawing group (EWG) substituents such as halogens, NO<sub>2</sub>, and CN exhibited heightened reactivity compared to their counterparts derived from electron-rich aldehydes, attributed to the enhanced electrophilicity of the imine. The latter necessitated prolonged reaction times of 48 hours, resulting in diminished yields observed in selected examples (**4f** and **4j**). The 3-C-Povarov reaction efficiently produced compound **4k** from heteroaromatic aldehyde, achieving high yields and enantiomeric excess (**4k**, Scheme 2). We were also delighted to observe the formation of aliphatic derivative **4l** in 68% yield and 98% ee demonstrating that contrary to unsubstituted aliphatic aldehydes that did not prove to be suitable substrates, hindered aliphatic aldehyde were fully compatible with the transformation. Next, the reaction scope of THQs was investigated relative to the aniline partner (**5**). The electronic nature of substituents at the *para*-position on the anilines minimally affected the reaction outcome (**4n-4o** and **4q-4r**) except for strong electron-withdrawing groups such as NO<sub>2</sub>, which led to a lower yield of **4p** while the enantioselectivity remained consistently high. Then, the 3C-protocol was tested with *ortho*-substituted aniline derivative, giving the THQ **4s** in moderate yield and nearly racemic ee. This observation suggests that the presence of the *ortho* substituent could disrupt or even prevent hydrogen bonding between the catalyst and the imines due to steric clash. Consequently, the bifunctional activation of proposed intermediate **I-TS** in Scheme 4 no longer occurs, and only the dienophilic phenol could interact with the chiral catalyst, resulting in a complete loss of enantioselectivity during the attack of the dienophile on the diene, as well as a decrease in reactivity. Interestingly, the *meta*-substituted anilines exclusively yielded one regioisomer out of the two possible options (compound **4t-4v**, scheme 2). However, while the 5-amino-1,3-benzodioxole produced the less congested isomer **4t** with high enantioselectivity, *m*-chloroaniline as well as 2-naphthylamine formed the most congested isomer **4u** and **4v** with a lower enantiomeric excess of 70%. These results suggest that at electronic properties not only dictate regioselectivity but also impact the transition state stability in the Friedel-Crafts reaction. Specifically, electron-neutral or electron-poor substituents like chlorine or aryl groups seem to favor *ortho* substitution, aligning with their observed propensity to form the less hindered product. In contrast, the presence of oxygen at position 1 in 5-amino-1,3-benzodioxole might hypothetically enhance *para* substitution due to specific electronic effects, thereby contributing to the formation of the less hindered product. Additionally, it appears that there is a delicate balance between electronic and steric effects to govern enantioselectivity. It is hypothesized that unfavorable interactions may occur between the catalyst with azadiene and dienophile disrupting the transition state and thereby reducing selectivity.

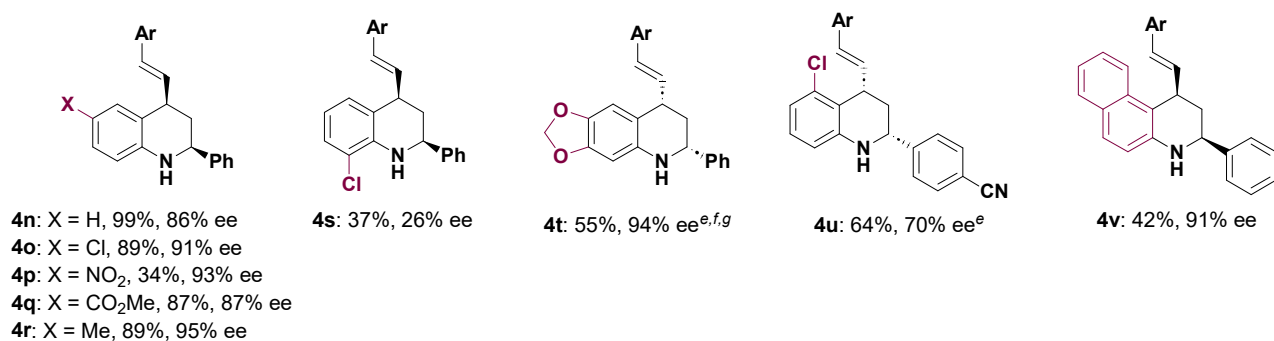
**Scheme 2.** Substrate scope of the enantioselective 3-CR synthesis of THQs.<sup>a-d</sup>



#### Aldehydes:



#### Anilines:



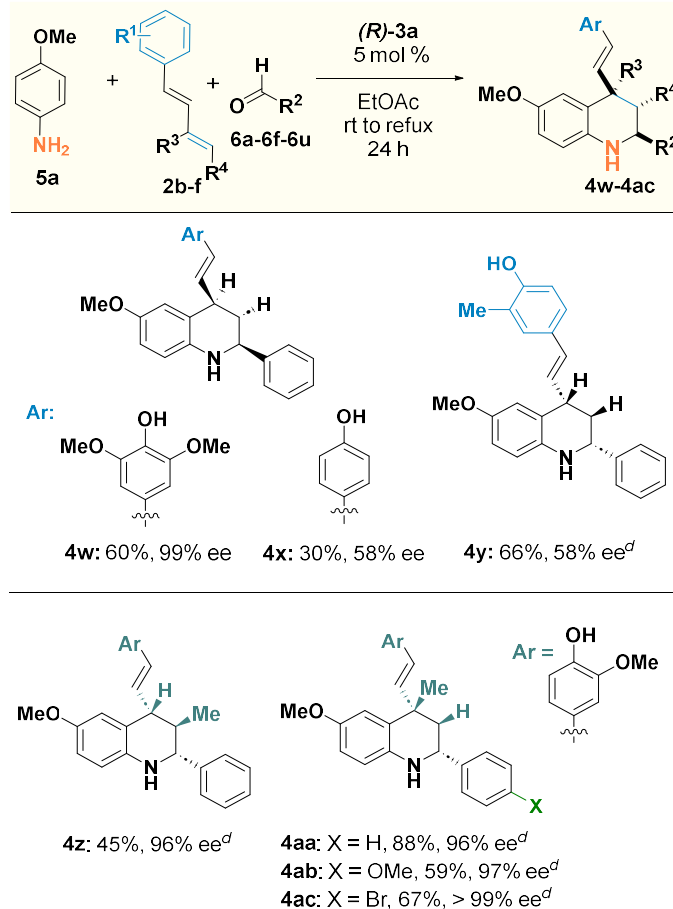
<sup>a</sup> General conditions: aniline **5** (0.10 mmol), aldehyde **6** (0.10 mmol), diene **2a** (0.30 mmol), and **(R)-3b** (0.005 mmol), in ethyl acetate (1.0 mL) at reflux under Ar atmosphere for 24 h. <sup>b</sup> Yields refer to chromatographically pure *cis*-isomer. <sup>c</sup> *dr* was determined to be higher than 95:5 by <sup>1</sup>H NMR analysis of the crude reaction mixture. The *cis*-diastereoselectivity was assumed by analogy of **4e** determined by X-ray analysis (cf Supporting information). Enantiomeric excesses were determined by HPLC analysis on chiral stationary phase. <sup>d</sup> Performed on 1 mmol scale. <sup>e</sup> Reaction conducted with **(S)-3b** instead of **(R)-3b**. <sup>f</sup> Reaction conducted for 48 h. <sup>g</sup> 0.15 mmol of **2a** were used.

The scope of the enantioselective vinylogous Povarov reaction was expanded to include dienes with diverse substitution patterns on the aryl ring and alkene substituents. The phenolic dienes were employed exclusively in their (*E*) isomer form, following an *E/Z* isomerization performed in refluxing toluene in the final step of their synthesis. The di-*ortho*-methoxy phenolic diene **2b** led to cycloadduct **4w** with a 60% yield and an excellent enantiomeric excess of 99%. When less electron-rich phenolic dienes **2c** and **2d** were employed, the resulting THQs **4x** and **4y** were obtained with moderate yields and enantiomeric excess. To our satisfaction, the terminally substituted diene **2e**, used as a mixture of *E* and *Z* isomers (4:1), successfully underwent the reaction with



benzaldehyde and anisidine to yield THQ **4z** with three contiguous stereocenters as a single *trans-trans* diastereomer<sup>23</sup> maintaining a high enantiomeric excess, albeit with a reduced yield compared to the unsubstituted diene **2a**. Unfortunately, substituting the terminal methyl group of **2e** with an isobutyl or phenyl group did not yield the desired cycloadduct product; only starting materials were recovered, underscoring the reaction's sensitivity to both steric and electronic properties of dienophiles. Efforts to synthesize 1,2,3,4-tetrahydroquinolines featuring a quaternary center at position 4 through catalytic enantioselective Povarov reactions have encountered limitations in previous studies.<sup>6c,12</sup> However, our investigation produced promising results with the internally substituted diene **2f**, which displayed reactivity as a dienophile in the asymmetric 3-C Povarov reaction under established conditions. Interestingly, when reacted with various aromatic aldehydes, the target THQs **4aa**, **4ab** and **4ac** were obtained with moderate to high yields and high enantioselectivities (96 to >99% ee).

**Scheme 3.** Phenolic diene scope for enantioselective 3-CR Povarov reaction.<sup>a-c</sup>

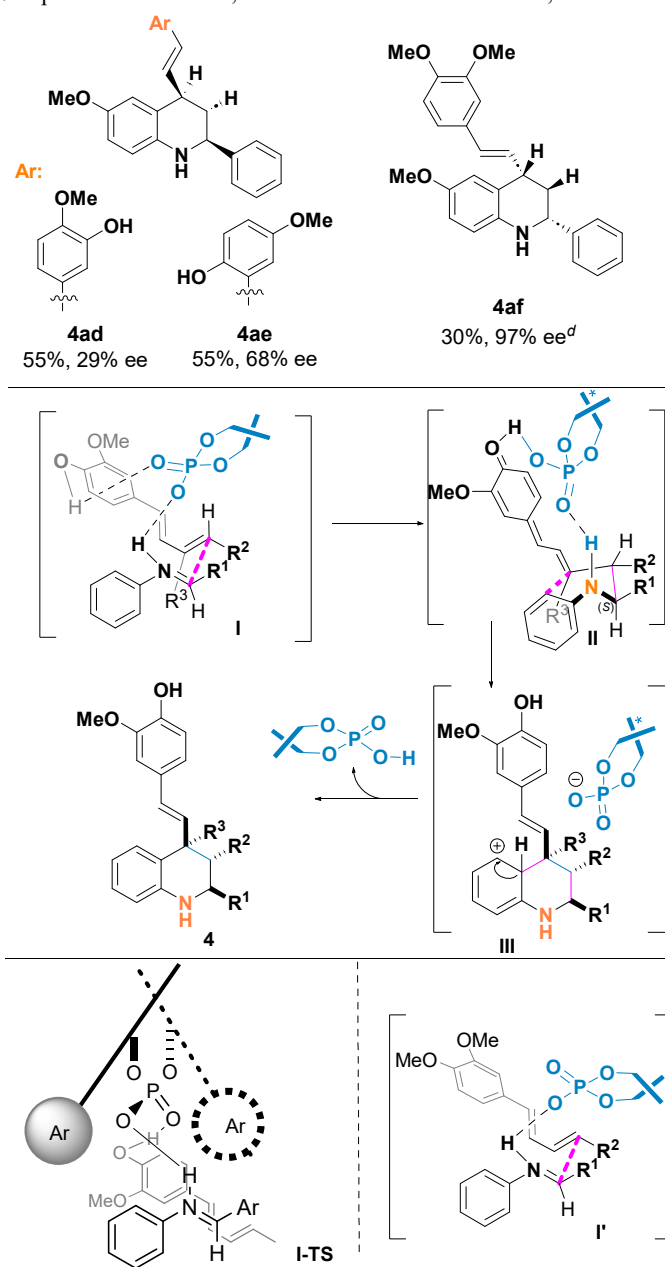


<sup>a</sup> General condition: aniline **5** (0.10 mmol), aldehyde **6** (0.10 mmol), diene **2** (0.30 mmol), and (**R**)-**3a** (0.005 mmol), in ethyl acetate (1.0 mL) at reflux under Ar atmosphere for 24 h. <sup>b</sup> Yields refer to chromatographically pure *cis*-isomer. <sup>c</sup> *dr* was determined to be higher than 95:5 by <sup>1</sup>H NMR analysis of the crude reaction mixture. The *cis*-diastereoselectivity of **4a** was assumed by analogy of **4e** determined by X-ray analysis (cf Supporting information). Enantiomeric excesses were determined by HPLC analysis on chiral stationary phase vs racemic. <sup>d</sup> Reaction conducted with (**S**)-**3a** instead of (**R**)-**3a**.

Building on previous research and precedent mechanistic studies,<sup>4c,9b,11,12</sup> we propose a plausible stepwise process involving a Mannich reaction followed by Friedel-Crafts alkylation (Scheme 4). To elucidate the observed enantioselectivity, several control experiments were conducted. Under standard conditions, the reaction involving dienes containing *meta*- and *ortho*-phenolic groups **2g** and **2h** resulted in the formation of THQs **4ad** and **4ae** with low yields and enantiomeric excess values of 29% and 68%, respectively (**4ad** was obtained in 55% yield along with an inseparable impurity). Additionally, the di-methoxy diene **2i** produced the corresponding cycloadduct **4af** with high enantioselectivity (96% ee) albeit with a low yield.

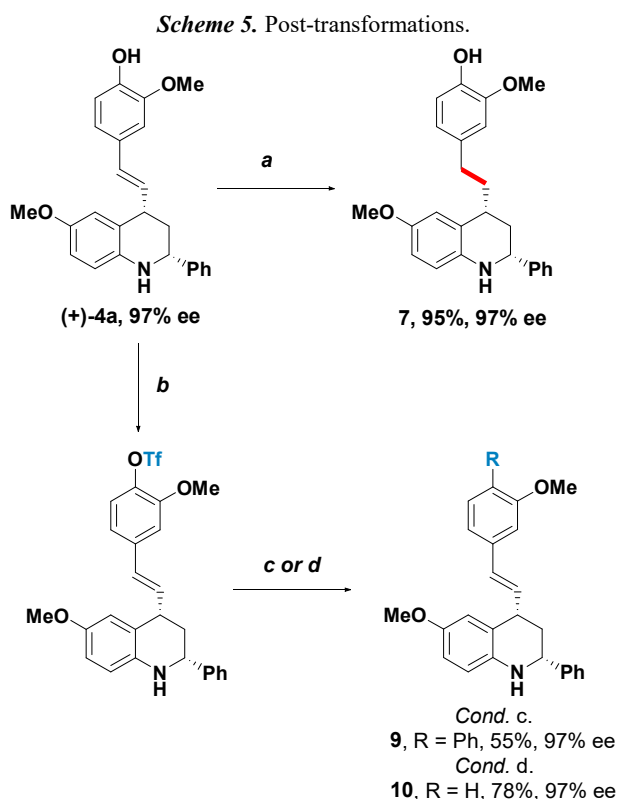
Based on these experimental findings, we proposed that activation of the imine occurs through interaction with the chiral phosphoric acid (*R*)-**3b**. Subsequently, hydrogen bonding takes place between the phenol and the Lewis basic phosphoryl oxygen. Following this and according to the Simón and Goodman model,<sup>24,25</sup> a pseudo-intramolecular Si-face attack of the dienophile **2** onto the imine *via* transition state **I-TS** is expected to form (*S*)-amine **II**. Finally, an intramolecular aza-Friedel-Crafts reaction *via* the less sterically congested conformer **II** would result in the observed *trans, trans* trisubstituted tetrahydroquinoline **4z** with a defined absolute configuration, as depicted in Scheme 3. It is difficult to rely on a bifunctional activation mode when considering the use of di-methoxy diene **2i** which leads to compound **4af** with high enantioselectivity (96% ee). In this case, a simple mono activation of imine (possibly an ion pair if full protonation of the imine is taking place) allows for facial discrimination when reacting with the rich dimethoxy diene **2i** (**I'**). Presence of two hydroxy unit (OH and OMe or 2 OMe) on the arene, seems crucial for achieving reactivity. We believe that, when possible, establishment of a hydrogen bond between Lewis basic phosphoryl oxygen and the phenol group is the rule thereby increasing reactivity and enhancing yield. However,, position of the hydroxy unit is of critical importance for high enantioselectivity, where contrary to *meta*- and *ortho*- position (phenolic groups **2g** and **2h**) only the *para* position allows for a geometrically well-defined transition state and high induction.

**Scheme 4.** Experimental Control<sup>a</sup>, Potential Reaction Mechanisms, and Activation Modes



<sup>a</sup> For condition and outcomes, see footnotes *a-d* of scheme 3.

To demonstrate the synthetic applicability of this transformation and to further modify the enantioenriched THQ products, we conducted several post-transformations (Scheme 5). The hydrogenation of THQ **4a** using a flow hydrogenation apparatus (H-Cube) proceeded smoothly, affording **7** in 97% yield in high purity without purification and with no erosion of enantioselectivity. Chemoselective modification of the phenol residue could also be demonstrated. The phenol group was protected as a triflate group, followed by a Pd-mediated reduction using formic acid, resulting in compound **9** in 78% yield over 2 steps without compromising enantioselectivity. Additionally, the Suzuki coupling of THQ **8** with phenylboronic acid afforded compound **10** in 55% yield with no erosion of enantioselectivity.



**a.** H<sub>2</sub>, Pd/C, H-cube, Full H<sub>2</sub> mode, 1 mL/min, 20 °C, MeOH; **b.** Tf<sub>2</sub>NPh, DMAP (cat.), Et<sub>3</sub>N, DCM, rt, 1h; **c.** Pd(dppf)Cl<sub>2</sub>.DCM (10 mol %), PhB(OH)<sub>2</sub>, Cs<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, toluene, THF, 65 °C, 90 °C, 5h; **d.** Pd(OAc)<sub>2</sub> (10 mol %), dppf (10 mol %), Et<sub>3</sub>N, HCOOH, THF, reflux, 2h.

## CONCLUSION

In summary, we have developed an enantioselective 3-C Povarov reaction employing phenolic dienes as dienophiles. This innovative method enables the synthesis of 1,2,3,4-tetrahydroquinolines containing a styryl group at the 4-position with excellent levels of enantioselectivity, regioselectivity, and diastereoselectivity. We propose a plausible mechanism, supported by experimental evidence, to account for the stereochemical outcomes. Furthermore, the pivotal role of the *para*-positioned free phenol group combined with a *meta*-positioned methoxy group on the phenolic dienes in facilitating this transformation was demonstrated.

## EXPERIMENTAL SECTION

**Materials and General methods.** All reactions requiring anhydrous conditions and inert atmosphere were carried out under argon atmosphere in dried glassware. EtOAc was distilled over CaCl<sub>2</sub>. Immersion coolers IMC-40 and TC100E fitted with a temperature probe and a flexible cooling tube were used to perform reactions at low temperature. The heat source employed for the synthesis of catalyst and substrates was an oil bath. Solvents were distilled by standard methods using the appropriate drying agent and stored over molecular sieves under argon.

All other reagents were obtained from commercial suppliers and directly used unless otherwise noted. Flash column chromatography was carried out using 40-63  $\mu\text{m}$  particle sized silica gel with air pressure. Analytical thin layer chromatography (TLC) plates (silica gel 60 F254) were visualized either with a UV lamp (254 nm), or by submersion in potassium permanganate, ninhydrine or iodine. Melting points were recorded using a melting point apparatus (Büchi B-540) and are uncorrected. Specific rotations for chiral compounds were recorded on a Perkin Elmer 141 using sodium D ray (589 nm) at room temperature in a 700- $\mu\text{L}$  cell with a path length of 1 dm in  $\text{CH}_2\text{Cl}_2$ . Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and the characteristic IR absorption frequencies are reported in  $\text{cm}^{-1}$ . Proton NMR ( $^1\text{H}$ ) spectra were recorded on a Bruker Avance 500 MHz or 300 MHz and proton-decoupled carbon 13 NMR ( $^{13}\text{C}\{^1\text{H}\}$ ) spectra were recorded at 75 MHz. NMR experiments were carried out in deuteriochloroform ( $\text{CDCl}_3$ ) or in trideuteroacetonitrile ( $\text{CD}_3\text{CN}$ ). Proton-decoupled fluorine  $^{19}\text{F}$  NMR ( $^{19}\text{F}\{^1\text{H}\}$ ) spectra were recorded at 282 MHz. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) relative to residual solvent as an internal reference ( $^1\text{H}$ : 7.26,  $^{13}\text{C}$ : 77.16 ppm for  $\text{CHCl}_3/\text{CDCl}_3$  and  $^1\text{H}$ : 1.94,  $^{13}\text{C}$ : 1.32 ppm for  $\text{CHD}_2\text{CN}/\text{CD}_3\text{CN}$ ). The following abbreviations are used for the multiplicities: s: singlet; d: doublet; t: triplet; q: quadruplet; quint: quintuplet; m: multiplet or overlap of non-equivalent resonances; br s: broad singlet; app: apparent; rot: rotamer. Coupling constants ( $J$ ) are reported in Hertz (Hz). Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. High resolution mass spectra were determined on an AEI MS-9 using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer. Enantiomeric excesses were determined by high performance liquid chromatography (HPLC) equipped with diode array UV detectors, using Chiralpak<sup>®</sup> AD-H, OD-H, AS-H, OJ-H, IA and IB columns.

#### General procedure for the enantioselective construction of 4-substituted tetrahydroquinolines:

A vial equipped with a Teflon stir bar was flame-dried under vacuum and backfilled with argon three times. Then, aniline (1.0 eq, 0.1 mmol), aldehyde (1.0 eq, 0.1 mmol) and (*R*)- or (*S*)-TRIP (0.05 eq, 0.005 mmol, 3.7 mg) were added to the vessel and dissolved in EtOAc (1 mL). The resulting solution was stirred at rt for 1h, followed by the addition of phenolic diene **2** (1.0-3.0 eq, 0.1-0.3 mmol). The reaction was stirred at reflux in an oil bath for 24h-72h depending on the substrates. When the reaction was deemed complete by TLC analysis, the mixture was concentrated under reduced pressure. The crude was then purified by flash column chromatography on silica gel using PET/EtOAc (8:2) as the eluent to yield the desired tetrahydroquinoline.

The racemic versions were synthesized using the same procedure, on a 0.05 mmol scale regarding the aldehyde, in 500  $\mu\text{L}$  of EtOAc, using *rac*-BINOL CPA as the catalyst (5 mol%).

#### 2-methoxy-4-((*E*)-2-((2*S*,4*R*)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)vinyl)phenol (**4a**):

Synthesized according to general procedure using *p*-anisidine (1.0 eq, 0.1 mmol, 12 mg), benzaldehyde (1.0 eq, 0.1 mmol, 10  $\mu\text{L}$ ), diene **2a** (3.0 eq, 0.3 mmol, 53 mg) and (*R*)-TRIP. After 24h of reaction, the crude was purified to yield product **4a** as brown powder (33 mg, >95:5 *dr*, 96% *ee*) in 85% yield.  $[\alpha]_{\text{D}}^{22} = -52$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ). **Rf**: 0.28 (PET/EA 8:2, UV & vanillin). **Mp**: 125-127  $^{\circ}\text{C}$ . **IR** (neat)  $\nu$  ( $\text{cm}^{-1}$ ): 3472, 3365, 2943, 2830, 1733, 1601, 1509, 1463, 1449, 1429, 1350, 1258, 1211, 1152, 1119, 1034.  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.47 – 7.28 (m, 5H), 6.93 – 6.84 (m, 3H), 6.78 (dd,  $J = 2.8, 1.1$  Hz, 1H), 6.68 (ddd,  $J = 8.7, 2.9, 0.8$  Hz, 1H), 6.55 (d,  $J = 4.9$  Hz, 1H), 6.51 (d,  $J = 12.0$  Hz, 1H), 6.00 (dd,  $J = 15.6, 9.1$  Hz, 1H), 4.47 (dd,  $J = 11.2, 2.5$  Hz, 1H), 3.89 (s, 3H), 3.88 – 3.80 (m, 1H), 3.72 (s, 3H), 2.19 (ddd,  $J = 13.0, 5.8, 2.5$  Hz, 1H), 2.01 (dt,  $J = 13.1, 11.5$  Hz, 1H).  **$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )**  $\delta$  152.3, 146.8, 145.4, 144.3, 139.2, 131.6, 130.9, 130.1, 128.8, 127.8, 126.8, 124.8, 120.2, 115.6, 115.1, 114.5, 113.5, 108.1, 56.9, 56.1, 56.0, 42.6, 39.8. **HRMS** (ESI/Q-TOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calc. for  $\text{C}_{25}\text{H}_{26}\text{NO}_3$ : 388.1892, Found: 388.1892; **HPLC** Daicel Chiralpak IA, Hept/EtOH 90:10, flow rate = 1 mL/min, 254 nm): minor isomer  $t_{\text{R}} = 33.9$  min, major isomer:  $t_{\text{R}} = 42.1$  min.

#### ASSOCIATED CONTENT

## Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

## Accession Code

CCDC 2345645 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223336033

## NOTE

The authors declare no competing financial interest.

## AUTHOR CONTRIBUTIONS

All authors have given approval to the final version of the manuscript.

## ACKNOWLEDGMENT

Financial supports from ICSN and CNRS. A.B. and M. L. thank Paris-Saclay University for the doctoral fellowship. V.M. was supported by National Programs (PON “Ricerca e Innovazione” 2014-2020 Azione IV.4 and Azione IV.5) of the Italian Ministry of University and Research (MUR).

## REFERENCES

- (1) For representative reviews, see: (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. Recent Progress in the Synthesis of 1,2,3,4,-Tetrahydroquinolines. *Tetrahedron* **1996**, *52* (48), 15031–15070. (b) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. Advances in the Chemistry of Tetrahydroquinolines. *Chem. Rev.* **2011**, *111* (11), 7157–7259. (c) Muthukrishnan, I.; Sridharan, V.; Menéndez, J. C. Progress in the Chemistry of Tetrahydroquinolines. *Chem. Rev.* **2019**, *119* (8), 5057–5191. (d) Clerigué, J.; Ramos, M. T.; Menéndez, J. C. Enantioselective catalytic Povarov reactions. *Org. Biomol. Chem.* **2022**, *20*, 1550-1581.
- (2) For selected examples, see: (a) Kumar, A.; Srivastava, S.; Gupta, G.; Chaturvedi, V.; Sinha, S.; Srivastava, R. Natural Product Inspired Diversity Oriented Synthesis of Tetrahydroquinoline Scaffolds as Antitubercular Agent. *ACS Comb. Sci.* **2011**, *13* (1), 65–71. (b) Kouznetsov, V. V.; Merchan-Arenas, D. R.; Tangarife-Castaño, V.; Correa-Royero, J.; Betancur-Galvis, L. Synthesis and Cytotoxic Evaluation of Novel 2-Aryl-4-(4-Hydroxy-3-Methoxyphenyl)-3-Methyl-6,7-Methylenedioxy-1,2,3,4-Tetrahydroquinolines, Podophyllotoxin-like Molecules. *Med. Chem. Res.* **2016**, *25* (3), 429–437. (c) Yokoi, T.; Nakagawa, Y.; Miyagawa, H. Asymmetric Synthesis of Tetrahydroquinoline-Type Ecdysone Agonists and QSAR for Their Binding Affinity against Aedes Albopictus Ecdysone Receptors. *Pest Manag. Sci.* **2019**, *75* (1), 115–124. (d) Smith, H. C.; Cavanaugh, C. K.; Friz, J. L.; Thompson, C. S.; Sagers, J. A.; Michelotti, E. L.; Garcia, J.; Tice, C. M. Synthesis and SAR of *Cis*-1-Benzoyl-1,2,3,4-Tetrahydroquinoline Ligands for Control of Gene Expression in Ecdysone Responsive Systems. *Bioorg. Med. Chem. Lett.* **2003**, *13* (11), 1943–1946.
- (3) Jiang, X.; Wang, R. Recent Developments in Catalytic Asymmetric Inverse-Electron-Demand Diels–Alder Reaction. *Chem. Rev.* **2013**, *113* (7), 5515–5546.
- (4) For selected reviews in CPA-catalyzed cycloadditions, see: (a) Varlet, T.; Masson, G. Enamides and Dienamides in Phosphoric Acid-Catalysed Enantioselective Cycloadditions for the Synthesis of Chiral Amines. *Chem. Commun.* **2021**, *57* (34), 4089–4105. (b) Ghashghaei, O.; Masdeu, C.; Alonso, C.; Palacios, F.; Lavilla, R. Recent Advances of the Povarov Reaction in Medicinal Chemistry. *Drug Discov. Today Technol.* **2018**, *29*, 71–79. (c) Lemos, B. C.; Venturini Filho, E.; Fiorot, R. G.; Medici, F.; Greco, S. J.; Benaglia, M. Enantioselective Povarov Reactions: An Update of a Powerful Catalytic Synthetic Methodology. *Eur. J. Org. Chem.* **2022**, *2022* (2), e202101171.

- (5) Ishitani, H.; Kobayashi, S. Catalytic Asymmetric Aza Diels-Alder Reactions Using a Chiral Lanthanide Lewis Acid. Enantioselective Synthesis of Tetrahydroquinoline Derivatives Using a Catalytic Amount of a Chiral Source. *Tetrahedron Lett.* **1996**, *37* (41), 7357–7360.
- (6) For selected examples in Lewis-acid asymmetric Povarov reaction, see: (a) Sundararajan, G.; Narayanasamy, P.; Varghese, B. First Asymmetric Synthesis of Quinoline Derivatives by Inverse Electron Demand (IED) Diels–Alder Reaction Using Chiral Ti(IV) Complex. *Org. Lett.* **2001**, *3* (13), 1973–1976. (b) Xie, M.; Chen, X.; Zhu, Y.; Gao, B.; Lin, L.; Liu, X.; Feng, X. Asymmetric Three-Component Inverse Electron-Demand Aza-Diels–Alder Reaction: Efficient Synthesis of Ring-Fused Tetrahydroquinolines. *Angew. Chem. Int. Ed.* **2010**, *49* (22), 3799–3802. (c) Xie, M.; Liu, X.; Zhu, Y.; Zhao, X.; Xia, Y.; Lin, L.; Feng, X. Asymmetric Synthesis of Tetrahydroquinolines with Quaternary Stereocenters through the Povarov Reaction. *Chem. – Eur. J.* **2011**, *17* (49), 13800–13805.
- (7) For representative examples of organocatalyzed Povarov transformations, see: (a) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. Asymmetric Cooperative Catalysis of Strong Brønsted Acid–Promoted Reactions Using Chiral Ureas. *Science* **2010**, *327* (5968), 986–990. (b) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. Conjugate-Base-Stabilized Brønsted Acids as Asymmetric Catalysts: Enantioselective Povarov Reactions with Secondary Aromatic Amines. *Angew. Chem. Int. Ed.* **2013**, *52* (52), 14084–14088. (c) Min, C.; Lin, C.-T.; Seidel, D. Catalytic Enantioselective Intramolecular Aza-Diels–Alder Reactions. *Angew. Chem. Int. Ed.* **2015**, *54* (22), 6608–6612. (d) Wu, H.; Wang, Y.-M. One-Pot Organocatalytic Enantioselective Michael/Povarov Domino Strategy for the Construction of Spirooctahydroacridine-3,3'-Oxindole Scaffolds. *Chem. – Eur. J.* **2014**, *20* (20), 5899–5904.
- (8) Akiyama, T.; Morita, H.; Fuchibe, K. Chiral Brønsted Acid-Catalyzed Inverse Electron-Demand Aza Diels–Alder Reaction. *J. Am. Chem. Soc.* **2006**, *128* (40), 13070–13071.
- (9) For representative examples from our group, see: (a) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. Chiral Brønsted Acid-Catalyzed Enantioselective Three-Component Povarov Reaction. *J. Am. Chem. Soc.* **2009**, *131* (13), 4598–4599. (b) Dagousset, G.; Zhu, J.; Masson, G. Chiral Phosphoric Acid-Catalyzed Enantioselective Three-Component Povarov Reaction Using Encarbamates as Dienophiles: Highly Diastereo- and Enantioselective Synthesis of Substituted 4-Aminotetrahydroquinolines. *J. Am. Chem. Soc.* **2011**, *133* (37), 14804–14813. (c) Dagousset, G.; Retailleau, P.; Masson, G.; Zhu, J. Chiral Phosphoric Acid-Catalyzed Enantioselective Three-Component Povarov Reaction Using Cyclic Enethioureas as Dienophiles: Stereocontrolled Access to Enantioenriched Hexahydropyrroloquinolines. *Chem. – Eur. J.* **2012**, *18* (19), 5869–5873. (d) Brioché, J.; Courant, T.; Alcaraz, L.; Stocks, M.; Furber, M.; Zhu, J.; Masson, G. Chiral Phosphoric Acid-Catalyzed Enantioselective Three-Component Aza-Diels–Alder Reactions of Aminopyrroles and Aminopyrazoles. *Adv. Synth. Catal.* **2014**, *356* (8), 1719–1724. (e) He, L.; Laurent, G.; Retailleau, P.; Folléas, B.; Brayer, J.-L.; Masson, G. Highly Enantioselective Aza-Diels–Alder Reaction of 1-Azadienes with Encarbamates Catalyzed by Chiral Phosphoric Acids. *Angew. Chem. Int. Ed.* **2013**, *52* (42), 11088–11091.
- (10) For other examples of CPA-catalyzed Povarov reaction, see: (a) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. Highly Enantioselective Relay Catalysis in the Three-Component Reaction for Direct Construction of Structurally Complex Heterocycles. *Org. Lett.* **2010**, *12* (10), 2266–2269. (b) Lin, J.-H.; Zong, G.; Du, R.-B.; Xiao, J.-C.; Liu, S. The Asymmetric Synthesis of CF<sub>3</sub>- or -CF<sub>2</sub>-Substituted Tetrahydroquinolines by Employing a Chiral Phosphoric Acid as Catalyst. *Chem. Commun.* **2012**, *48* (62), 7738–7740. (c) Richmond, E.; Khan, I. U.; Moran, J. Enantioselective and Regiodivergent Functionalization of N-Allylcarbamates by Mechanistically Divergent Multicatalysis. *Chem. – Eur. J.* **2016**, *22* (35), 12274–12277. (d) Kazancioglu, M. Z.; Kalay, E.; Kazancioglu, E. A.; Peshkov, V. A. Enantioselective Assembly of Tricyclic Tetrahydroquinoline Derivatives. *ChemistrySelect* **2019**, *4* (30), 8797–8799. (e) Zhou, Z.; Ye, L.; Yang, L.; Li, X.; Zhao, Z.; Li, X. Enantioselective Synthesis of Pyrroloquinolines via a Three-Component Povarov Reaction with Aminoindoles. *Org. Chem. Front.* **2023**, *10* (24), 6219–6224.

- (11) He, L.; Bekkaye, M.; Retaillieu, P.; Masson, G. Chiral Phosphoric Acid Catalyzed Inverse-Electron-Demand Aza-Diels–Alder Reaction of Isoeugenol Derivatives. *Org. Lett.* **2012**, *14* (12), 3158–3161.
- (12) Shi, F.; Xing, G.-J.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. An Asymmetric Organocatalytic Povarov Reaction with 2-Hydroxystyrenes. *J. Org. Chem.* **2012**, *77* (16), 6970–6979.
- (13) Min, C.; Seidel, D. Stereochemically Rich Polycyclic Amines from the Kinetic Resolution of Indolines through Intramolecular Povarov Reactions. *Chem. – Eur. J.* **2016**, *22* (31), 10817–10820.
- (14) For a selected example of asymmetric intramolecular IEDDA reaction, see: Jarrige, L.; Blanchard, F.; Masson, G. Enantioselective Organocatalytic Intramolecular Aza-Diels–Alder Reaction. *Angew. Chem. Int. Ed.* **2017**, *56* (35), 10573–10576.
- (15) Calleja, J.; B. González-Pérez, A.; Lera, Á. R. de; Álvarez, R.; J. Fañanás, F.; Rodríguez, F. Enantioselective Synthesis of Hexahydrofuro[3,2-c] Quinolines through a Multicatalytic and Multicomponent Process. A New “Aromatic Sandwich” Model for BINOL-Phosphoric Acid Catalyzed Reactions. *Chem. Sci.* **2014**, *5* (3), 996–1007.
- (16) For other examples, see: (a) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. Organocatalytic Asymmetric Povarov Reactions with 2- and 3-Vinylindoles. *Chem. Commun.* **2010**, *46* (2), 327–329. (b) Zhang, H.-H.; Sun, X.-X.; Liang, J.; Wang, Y.-M.; Zhao, C.-C.; Shi, F. Catalytic Asymmetric Povarov Reaction of Isatin-Derived 2-Azadienes with 3-Vinylindoles. *Org. Biomol. Chem.* **2014**, *12* (47), 9539–9546. (c) Dai, W.; Jiang, X.-L.; Tao, J.-Y.; Shi, F. Application of 3-Methyl-2-Vinylindoles in Catalytic Asymmetric Povarov Reaction: Diastereo- and Enantioselective Synthesis of Indole-Derived Tetrahydroquinolines. *J. Org. Chem.* **2016**, *81* (1), 185–192. (d) Li, J.; Gu, Z.; Zhao, X.; Qiao, B.; Jiang, Z. Asymmetric Aerobic Decarboxylative Povarov Reactions of N-Aryl  $\alpha$ -Amino Acids with Methylene-phthalimidines via Cooperative Photoredox and Chiral Brønsted Acid Catalysis. *Chem. Commun.* **2019**, *55* (86), 12916–12919. (e) Bisag, G. D.; Pecorari, D.; Mazzanti, A.; Bernardi, L.; Fochi, M.; Bencivenni, G.; Bertuzzi, G.; Corti, V. Central-to-Axial Chirality Conversion Approach Designed on Organocatalytic Enantioselective Povarov Cycloadditions: First Access to Configurationally Stable Indole–Quinoline Atropisomers. *Chem. – Eur. J.* **2019**, *25* (68), 15694–15701. (f) Wang, S.-J.; Wang, Z.; Tang, Y.; Chen, J.; Zhou, L. Asymmetric Synthesis of Quinoline-Naphthalene Atropisomers by Central-to-Axial Chirality Conversion. *Org. Lett.* **2020**, *22* (22), 8894–8898.
- (17) (a) Caruana, L.; Fochi, M.; Ranieri, S.; Mazzanti, A.; Bernardi, L. Catalytic Highly Enantioselective Vinylogous Povarov Reaction. *Chem. Commun.* **2013**, *49* (9), 880–882. See also (b) Hermitage, S.; Howard, J. A. K.; Jay, D.; Pritchard, R. G.; Probert, M. R.; Whiting, A. Mechanistic studies on the formal aza-Diels–Alder reactions of N-aryl imines: evidence for the non-concertedness under Lewis-acid catalysed conditions. *Org. Biomol. Chem.* **2004**, *2*, 2451–2460. (c) Alves, M. J.; Azoia, N. G.; Fortes, A. G. Regio- and stereo-selective aza-Diels–Alder reaction of ethyl glyoxylate 4-methoxyphenylimine with 1,3-dienes in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . Evidence for a non-concerted mechanism. *Tetrahedron* **2007**, *63* (3), 727–734.
- (18) Bernardi, L.; Bolzoni, G.; Fochi, M.; Mancinelli, M.; Mazzanti, A. An Atropisomerically Enforced Phosphoric Acid for Organocatalytic Asymmetric Reactions. *Eur. J. Org. Chem.* **2016**, *2016* (19), 3208–3216.
- (19) Retich, C.; Bräse, S. Asymmetric Organocatalytic Synthesis of Bisindoles – Scope and Derivatizations. *Eur. J. Org. Chem.* **2018**, *2018* (1), 60–77.
- (20) For selected examples in total synthesis, see: (a) Smith, M. J.; Reichl, K. D.; Escobar, R. A.; Heavey, T. J.; Coker, D. F.; Schaus, S. E.; Porco, J. A. Jr. Asymmetric Synthesis of Griffipavixanthone Employing a Chiral Phosphoric Acid-Catalyzed Cycloaddition. *J. Am. Chem. Soc.* **2019**, *141* (1), 148–153. (b) Han, J.; Li, X.; Guan, Y.; Zhao, W.; Wulff, W. D.; Lei, X. Enantioselective Biomimetic Total Syntheses of Kuwanons I and J and Brosimones A and B. *Angew. Chem. Int. Ed.* **2014**, *53* (35), 9257–9261.
- (21) Ma, W.-Y.; Montinho-Inacio, E.; Iorga, B. I.; Retaillieu, P.; Moreau, X.; Neuville, L.; Masson, G. Chiral Phosphoric Acid-Catalyzed Enantioselective Formal [4+2] Cycloaddition Between Dienecarbamates and 2-Benzothioazolimines. *Adv. Synth. Catal.* **2022**, *364* (10), 1708–1715.

- (22) For representative examples of CPA-catalyzed transformations in polar solvents, see: (a) Liu, Y.; Zhang, H.-H.; Zhang, Y.-C.; Jiang, Y.; Shi, F.; Tu, S.-J. Organocatalytic Enantioselective and (Z)-Selective Allylation of 3-Indolylmethanol via Hydrogen-Bond Activation. *Chem Commun* **2014**, 50 (81), 12054–12057. (b) Martelli, L. S. R.; Machado, I. V.; dos Santos, J. R. N.; Corrêa, A. G. Recent Advances in Greener Asymmetric Organocatalysis Using Bio-Based Solvents. *Catalysts* **2023**, 13 (3), 553. (c) Jiang, F.; Zhao, D.; Yang, X.; Yuan, F.-R.; Mei, G.-J.; Shi, F. Catalyst-Controlled Chemoselective and Enantioselective Reactions of Tryptophols with Isatin-Derived Imines. *ACS Catal.* **2017**, 7 (10), 6984–6989. (d) Reddy, K. N.; Rao, M. V. K.; Sridhar, B.; Subba Reddy, B. V. BINOL Phosphoric Acid-Catalyzed Asymmetric Mannich Reaction of Cyclic N-Acyl Ketimines with Cyclic Enones. *Chem. – Asian J.* **2019**, 14 (17), 2958–2965. (e) Qian, C.; Liu, M.; Sun, J.; Li, P. Chiral Phosphoric Acid-Catalyzed Regio- and Enantioselective Reactions of Functionalized Propargylic Alcohols. *Org. Chem. Front.* **2022**, 9 (5), 1234–1240. (f) Zheng, W.; Wojtas, L.; Antilla, J. C. Chiral Phosphoric Acid Catalyzed Peroxidation of Imines. *Angew. Chem. Int. Ed.* **2010**, 49 (37), 6589–6591. (g) Li, C.; Shao, Y.-B.; Gao, X.; Ren, Z.; Guo, C.; Li, M.; Li, X. Enantioselective Synthesis of Chiral Quinohelicenes through Sequential Organocatalyzed Povarov Reaction and Oxidative Aromatization. *Nat. Commun.* **2023**, 14 (1), 3380.
- (23) The relative *trans-trans* configuration was determined by nOESY experiments, see SI for further details.
- (24) Simón, L.; Goodman, J. M. A Model for the Enantioselectivity of Imine Reactions Catalyzed by BINOL–Phosphoric Acid Catalysts. *J. Org. Chem.* **2011**, 76 (6), 1775–1788
- (25) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. Quantum Mechanical Investigations of Organocatalysis: Mechanisms, Reactivities, and Selectivities. *Chem. Rev.* **2011**, 111 (8), 5042–5137.