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RESEARCH ARTICLE

Enantioselective synthesis of complex fused heterocycles *via* chiral phosphoric-acid catalyzed intramolecular inverse-electron demand aza-Diels-Alder reaction

Lucie Jarrige,[a] Vincent Gandon,*[b] Géraldine Masson*[a]

Abstract: *A stable asymmetric intramolecular Povarov reaction has been established to provide an efficient method to access structurally diverse trans,trans-trisubstituted tetrahydrochromeno[4,3-b]quinolines in high stereoselectivities of up to >99:1 dr and 99% ee, without any purification step. Additionally, in order to facilitate large-scale application of this method, a low catalyst loading protocol was employed, using 0.2 mol % of chiral phosphoric acid, providing the cycloadducts without any loss in yield and enantioselectivity. The theoretical studies revealed that the reaction occurred through a sequential Mannich reaction and an intramolecular Friedel–Crafts reaction, wherein the phosphoric acid acted as bifunctional catalyst to activate para-phenolic dienophile and N-2-hydroxy-2-azadienes, simultaneously.*

Introduction

Chiral tetracyclic tetrahydroquinolines are privileged heterocyclic scaffolds found in various bioactive natural products and pharmaceuticals. For instance, tetrahydrochromeno[4,3-*b*]quinolines (THCQs) exhibit significant biological activities such as progesterone receptor modulators,[1] anticancer,[2] antibacterial,[3] ulcerogenic, and anti-inflammatory.[4] Consequently, much effort has been made to develop effective methods for the synthesis of enantioenriched tetrahydrochromeno[4,3-*b*]quinolines. As such, intramolecular inverse electron-demand aza-Diels-Alder reaction (IEDADA), also called Povarov reaction, represents one of the most efficient, straightforward, and atom-economic approaches allowing the construction of two fused rings in a single transformation.[5] Up to the present time, in contrast to intermolecular Povarov reaction (A, Scheme 1),[5b,5g,6] for which there are several methods identified, successful examples of enantioselective intramolecular Povarov reaction remain elusive (B, Scheme 1).[7] Meanwhile, in 2015, Seidel and co-workers pioneered the asymmetric intramolecular Povarov reaction using a chiral catalyst with two Brønsted acid sites, which achieved excellent diastereo- and enantioselectivity when indolines were employed to generate *in situ* the reactive 2-azadienes (C, eq 1, Scheme 1).[8] Subsequently, the same group reported chiral phosphoric acid catalyzed kinetic asymmetric intramolecular Povarov reaction of racemic 2-substituted indolines (C, eq 2, Scheme 1).[9] Although the cycloadducts were generally isolated with excellent diastereo- and enantiomeric excesses, the necessity of using indolines as reaction partners limited the structural diversity of THCQs that can be accessed by these protocols. To address this limitation, the first example of asymmetric intramolecular Povarov using primary anilines as reaction partners was reported by our group in 2017 (D, Scheme 1).[10] Under mild conditions, a series of trisubstituted tetrahydrochromeno[4,3-*b*]quinolin-6-ones and their nitrogen analogues tetrahydrodibenzo[1,6]naphthyridin-6-ones were obtained in good to excellent yields with high diastereo- and enantioselectivities by using a chiral phosphoric acid catalyst. Remarkably, no purification was required to isolate each cycloadduct in excellent purity. Our previous studies showed that the presence of OH groups on both the aniline and dienophile were crucial to reach excellent enantioselectivity. Moreover, *para*-phenol on the dienophile was found to be critical for the success of the intramolecular IEDADA reaction, since *ortho*- and *meta*-analogs were completely unreactive in this cycloaddition.

We would now like to report advances in the scope and limitations of our methodology providing access to more diverse enantioenriched tetrahydrochromeno[4,3-*b*]quinolin-6-ones. In particular, we extended this special protocol to the synthesis of other fused tetraheterocycles such as tetrahydrothiochromeno[4,3-*b*]quinolin-6-ones, tetrahydrochromeno[4,3-*b*]quinolines, and hexahydrodibenzo[*b*,*h*][1,6]naphthyridines and excellent diastereo- and enantioselectivities were achieved. Furthermore, a computational study based on DFT calculations was performed to elucidate the reaction mechanism, and rationalize the stereochemical course of the reaction. Finally, the key role of the *para*-phenol on the dienophile to the success of this transformation was also explained by theoretical studies.

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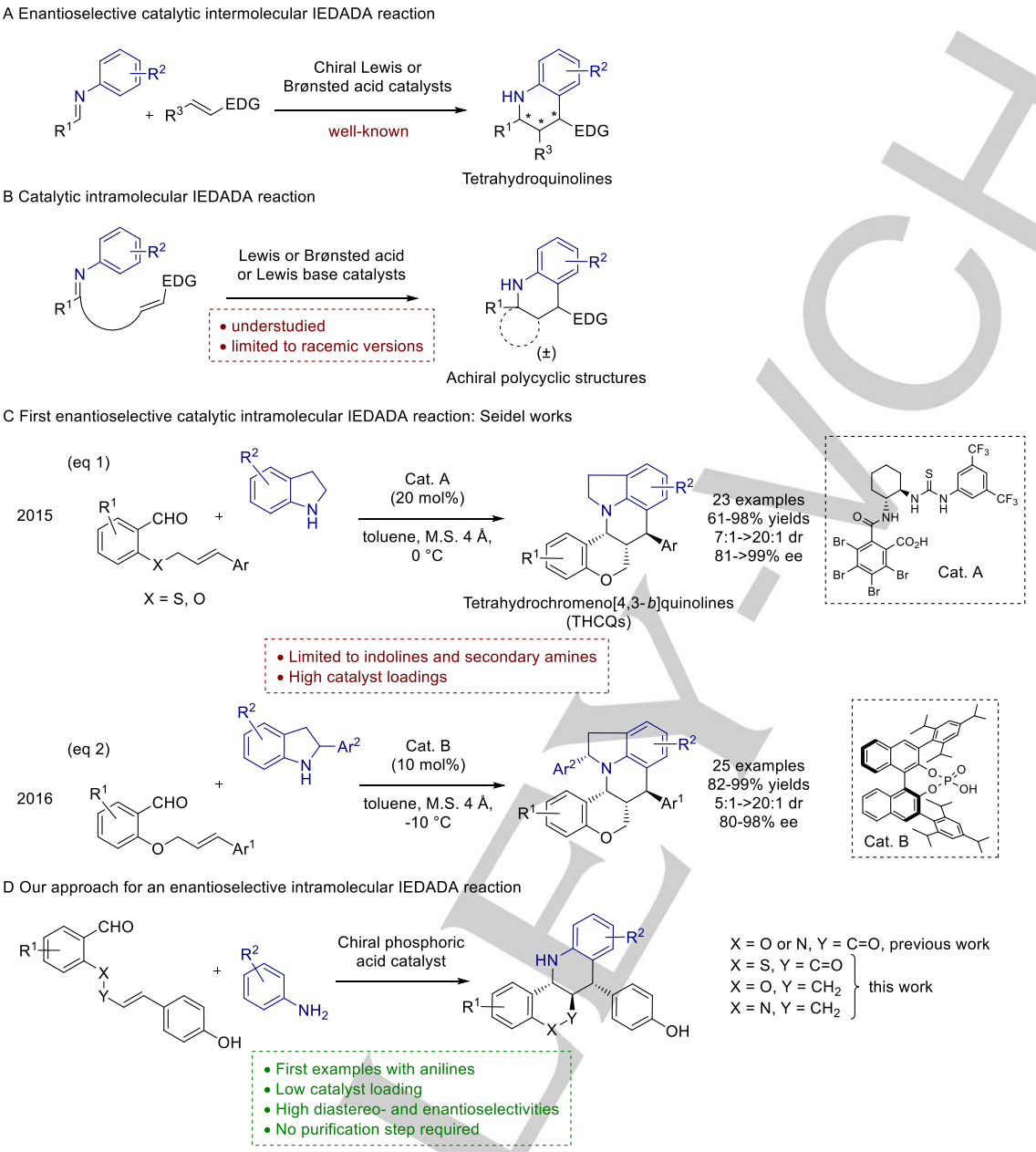


Scheme 1. Catalytic asymmetric IEDADA reactions: background and our strategy

Results and Discussion

We have previously demonstrated that bulky (*S*)–2,4,6-triisopropylphenyl BINOL phosphoric acid **1** was able to efficiently promote the enantioselective intramolecular Povarov reaction between 2-formylphenyl 3-(4-hydroxyphenyl)acrylate derivatives **2** and 2-aminophenols **3**. A wide range of 2-aminophenols electron-donating and electron-withdrawing groups were appropriate substrates affording *trans-trans* tetrahydrochromeno[4,3-*b*]quinolin-6-ones **4** with both high enantioselectivities (98->99% ee) and diastereoselectivities (>99:1 dr).[10] Various substituents on the aromatic ring of phenolic dienophile partners were also well-tolerated. At the same time, few substituents on aromatic aldehydes were evaluated in our previous studies and mainly limited to bromide, methyl and methoxy groups. In this context, we turned our attention to investigate further other substituted salicylaldehydes, possessing synthetic handles for further synthetic elaboration. We began our novel studies with the preparation of various formylaryl 3-(4-hydroxyphenyl)acrylates **2** containing a wide range of electronically diverse salicylaldehydes (see the Supporting Information) to examine the effect these would have on the outcome and selectivity of the proposed reaction. Thus,

substituents other than bromine on the 5 position of salicylaldehyde were examined under our standard conditions (Table 1). Pleasingly, the 5-fluoro and 5-chloro derivatives **2b** and **2c** were successfully engaged in the process affording the corresponding *trans-trans* tetrahydrochromeno[4,3-*b*]quinolin-6-ones **4b** and **4c**, respectively as single diastereomers in high yields and with excellent enantioselectivities.[11] Furthermore, substrates having a bulky substituent, such as a *tert*-butyl group, at the 5-position **2d** did not affect the cycloaddition reaction, and tetraheterocycle **4d** was isolated in 95% yield with 97% ee. Notably, substrate **2e** with an ester group on the salicyladehyde moiety was proven to be a suitable reaction partner, accessing the corresponding product **4e** as a sole diastereomer in 91% yield and 94% ee. Moreover, methyl substituents at 4-position of the arene ring of salicyladehyde **2f** was also tolerated, albeit with slightly lower enantioselectivity (89% ee). Surprisingly, the doubly-substituted on the salicylaldehyde moiety showed different reactivity towards the intramolecular Povarov reaction. For instance, the 3-bromo-5-chlorosalicylaldehyde derivative **2g** reacted smoothly to give the corresponding cycloadduct **4g** as a single diastereomer, in good yield and with high enantioselectivity (98% ee). However, the 4,6-dimethoxysalicylaldehyde which is more congested gave no product **4h** under the same conditions. Presumably steric hindrance is responsible for this effect, some further work is required to clarify this point.

In our previous work, we observed that presence of the 2-hydroxy group on the 2-azadiene played an important role for the asymmetric induction.[10] In this context, we were then interested in investigating the influence of using other hydrogen-bond donors on the enantioselectivity. 2-Aminothiophenol (**3b**) and Boc-monosubstituted-1,2-diaminobenzene (**3c**) were tested in the intramolecular IEDADA with **2a** and **5a**. Surprisingly, the 2-aminothiophenol (**3b**) appeared unreactive whatever linear partner used, no desired product was isolated (**4i** or **6a**), even at higher temperature (50 °C). However, while no reaction was seen with the linear precursor bearing an ester linker **2a**, the bulky diaminobenzene **3c** reacted efficiently with **5a** having an amide linker. Indeed, the hexahydrobenzo[1,6]naphthyridinone **6b** was produced in nearly quantitative yield (99% yield) as a single diastereomer but in lower enantioselectivity (76% ee). Unfortunately, no improvement in enantioselectivity was observed at lower temperature (79% ee, at 0 °C). This result suggests that the enantioselectivity is sensitive to both steric and pka properties of H-bond donor of 2-azadiene.

The chiral phosphoric acid-catalyzed intramolecular Povarov reaction was then extended to thioester linear precursor **7** for the synthesis of medicinally important thiochromanes (Table 1). Indeed, they hold a special interest in medicinal chemistry due to their presence in a number of bioactive compounds showing anti-HIV and antibacterial activities.[12] However, to the best of our knowledge, such intramolecular cycloaddition remained unknown even in racemic form. The reactions between 2-aminophenol **3a** and thioester derivatives **7** were performed under the optimized reaction conditions. Even though excellent diastereo- and enantioselectivity were observed as well, some difficulties in achieving complete conversions were encountered. Pleasingly, a slight increase of catalyst loading to 2 mol % furnished the corresponding cycloadducts **8a** and **8b** in satisfying yields.

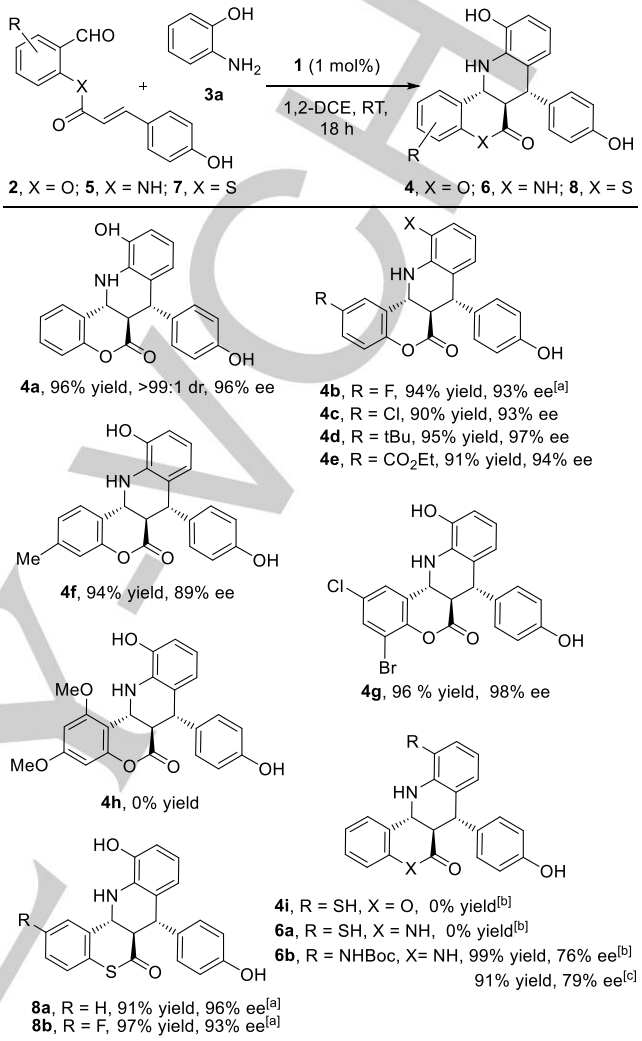


Table 1. Scope of the enantioselective intramolecular Povarov reaction with ester-, amide-, and thioester-based substrates **2**, **5** and **7**. General reaction conditions: **2**, **5** or **7** (0.10 mmol), **3a** (0.10 mmol), **1** (0.001 mmol, 1 mol%), 1,2-DCE (1.0 mL), RT, 18 h. Yields after isolation of the product by filtration. The dr values were determined by ^{1}H NMR spectroscopic analysis to be higher than 99:1. The ee values were determined by HPLC analysis using a chiral stationary phase. [a] The reaction was carried out with 0.002 mmol of **1** (2 mol%). [b] The reaction was carried out with 0.005 mmol of **1** (5 mol%). [c]The reaction was carried out at 0 °C.

To further demonstrate the efficiency and scope of the present method, we next applied linear precursors **9** and **11** bearing an ether or amine group as a linker between the aromatic aldehyde ring and the styrene group to the chiral phosphoric acid-catalyzed intramolecular Povarov reaction (Table 2). Precursors with an ether group as linker, were smoothly converted to the corresponding tetrahydrochromeno[4,3-*b*]quinolines **10a-e** in excellent yields, enantioselectivities and *trans,trans*-diastereoselectivities.[11] Both electron-withdrawing and electron-donating substituents at the 5-position of the salicylaldehydes were tolerated well under the standard catalytic conditions. In

addition, 2-amino-5-methylphenol (**3d**) participated in the reaction to form the corresponding cycloadduct **10f** in 98% ee. Then, we explored the cycloaddition to linear precursors with an amine linker **11** to provide access to hexahydrodibenzo[*b*,*h*][1,6]naphthyridines **12**. With 2 mol % catalyst loading, various cycloadducts **12a-g** were synthetized in excellent yields, enantio- and diastereoselectivities.[11] Diversely substituted 2-aminophenols **3** were suitable partners to afford the corresponding cycloadducts **12b** and **12c** in high yields and excellent enantioselectivities (98% ee). Modification of the protecting group on N afforded the desired products **12f** and **12g** with similar yields, although with slightly lower enantioselectivity (87 and 89% ee). It is also worth noting that all formed cycloadducts precipitated in the reaction vessel and were isolated by filtration under pure form, thus demonstrating the smart procedure's simplicity.

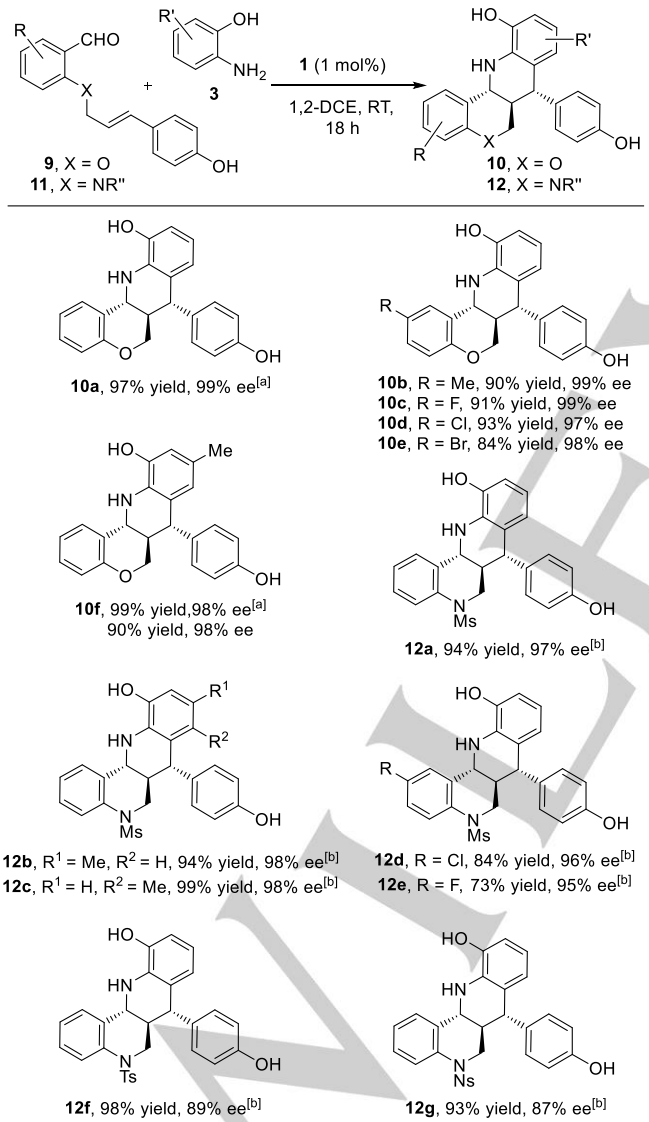
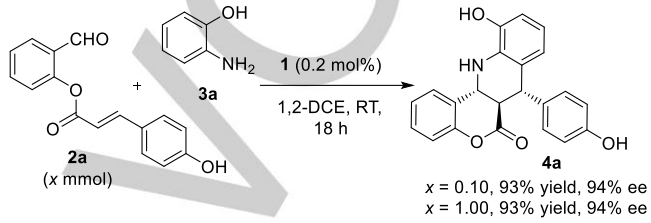


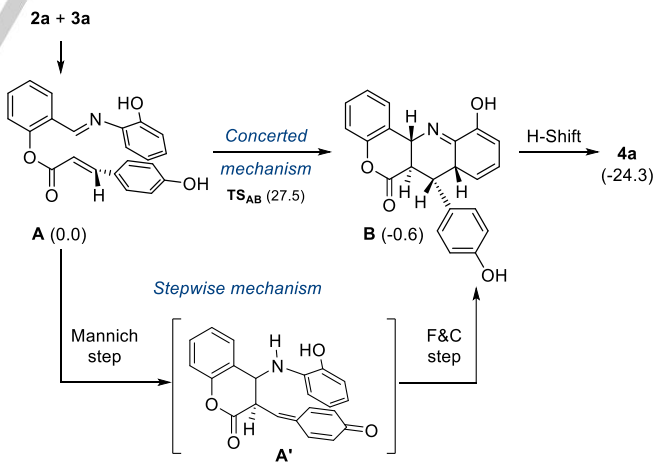
Table 2. Scope of the enantioselective intramolecular Povarov reaction from ether- and amine-based substrates **9** and **11**. General reaction conditions: **9** or **11** (0.10 mmol), **3** (0.10 mmol), **1** (0.001 mmol, 1 mol%), 1,2-DCE (1.0 mL), RT, 18 h. Yields after isolation of the product by filtration. The dr values were determined by ^{1}H NMR spectroscopic analysis to be higher than 99:1. The ee values were determined by HPLC analysis using a chiral stationary phase. [a] The reaction was carried out with 0.005 mmol of **1** (5 mol%). [b] The reaction was carried out with 0.002 mmol of **1** (2 mol%).

In order to demonstrate the synthetic utility of our process, a representative cycloaddition was carried out on gram-scale (Scheme 2). Before this, we attempted to lower the catalyst loading. It was found that the reaction could still proceed smoothly at a 0.2 mol % catalyst loading with 0.1 mmol of **2a** to give **4a** in 93% yield and 94% ee. To our delight, the reaction on 10-fold bigger scale of the linear precursor **2a** (1.00 mmol) with 2-aminophenol **3a** furnished cycloadduct **4a** in the same yield and enantioselectivity for this reaction.

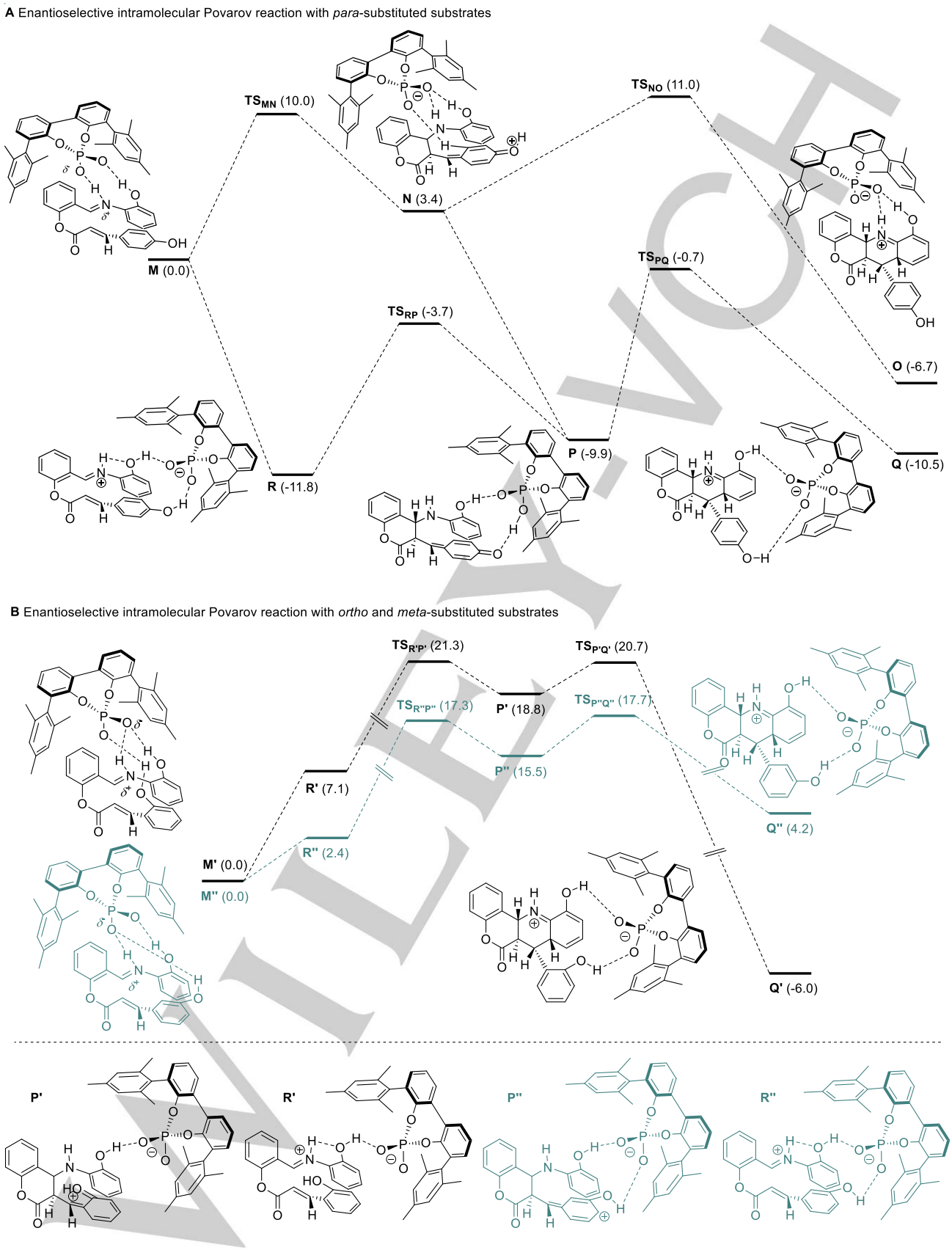


Scheme 2. Scale-up reaction employing 0.2 mol% of catalyst **1**.

We were then intrigued by the mechanism of this reaction for which two different mechanisms remain possible: a concerted Diels–Alder reaction or a stepwise Mannich/Friedel-Crafts alkylation process (Scheme 3). In order to validate which pathway is the most likely, we carried out a control experiment. First, we reacted **2a**, **3a** and **1** in presence of alcohol in order to trap intermediate **A'** generated after the Mannich reaction. Since there was no trapped intermediate observed in the reaction, we could not conclude at this stage. We therefore conducted a computational study based on Density-Functional Theory (DFT)



Scheme 3. Plausible reaction mechanisms and calculated energy of the enantioselective intramolecular Povarov reaction without catalyst (ΔG_{298}, kcal/mol).



Scheme 4. Calculated energy profiles of the enantioselective intramolecular Povarov reaction in presence of a bulky chiral phosphoric acid catalyst (ΔG_{298}, kcal/mol).

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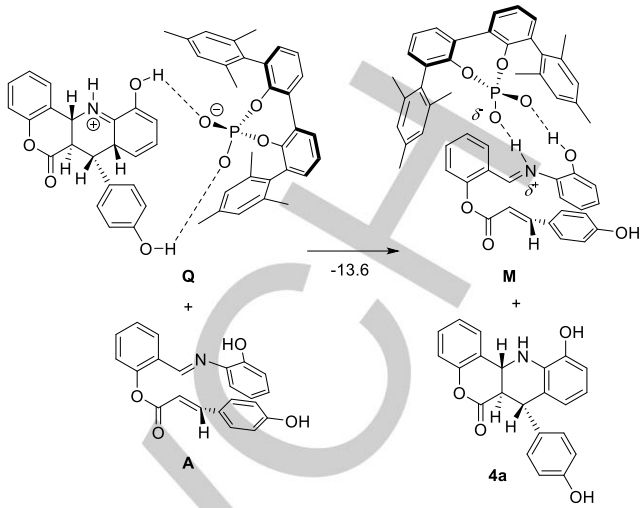
using the Gaussian 09 software package at the M06-2X/6-311+G**//M06-2X/6-31G* level[13] to distinguish between the two potential mechanisms mentioned above (see the Supporting Information for details). The uncatalyzed version of this cycloaddition was first modeled with imine **A** as model substrate, resulting from the reaction between **2a** and **3a (**Scheme 3). While the formation of cycloadduct **4a** is appreciably exergonic by 24.3 kcal/mol, its formation requires a quite high free energy of activation of 27.5 kcal/mol (**TS$_{AB}$**). These calculations support a concerted mechanism but the uncatalyzed version seems unlikely (see the Supporting Information).

Then, we studied the same reaction in presence of a chiral sterically demanding phosphoric acid catalyst (Scheme 4A, see also the Supporting Information for the effect of the steric hindrance, compounds **C**–**L**). When the imine coordinates in a bidentate fashion to the chiral phosphoric acid *via* a nine-membered cyclic transition state, the formation of the cycloadduct can then be modeled in a stepwise fashion (see the Supporting Information for more details). The activated imine reacted with the double bond. These electrons are pushed by the *para*-phenol moiety, leading to the triply H-bonded compound **N** in an endergonic way (3.4 kcal/mol) with a free energy cost of 10.0 kcal/mol (Scheme 4). The newly formed amine **N** could react with the double bond *via* an *exo* attack to provide the intermediate **O**. This step requires 7.6 kcal/mol of free energy of activation and is exergonic by 10.1 kcal/mol. It is important to note that the binding of the two phenol moieties by the chiral anionic phosphoric acid could be considered from the compound **N**. This displacement promoted the deprotonation of the phenoxonium group and led to the resulting complex **P**, more stable than **N** by 13.3 kcal/mol. The formation of the second C-C bond was then determined as kinetically favored from **P**, **TS$_{PQ}$** being 11.7 kcal/mol more stable than **TS$_{NO}$**. The newly-formed cycloadduct **Q** (-10.5 kcal/mol) was also more stable than the compound **O** (-6.7 kcal/mol). We finally computed the entire reaction sequence with a double activation of phenol groups by the catalyst. In this case, the first cyclization seemed possible from the ion pair **R**, more stable than the compound **M** by 11.8 kcal/mol, with an energetic cost of 8.1 kcal/mol. Therefore, it turns out that the favored mechanism in the reaction between the substrate **A** and the model bulky catalyst is a sequential mechanism involving the intermediates **M**, **R**, **P** and **Q** in the given order. As a result, these calculations suggested that phosphoric acids favored a stepwise reaction pathway, with ionic intermediates, rather than a concerted one. Moreover, the computed pathway involving the two phenol functions appeared thermodynamically favored, even though various computed pathways seemed viable with the model phosphoric acid used in the computations. The renewable of the catalytic cycle was also studied by calculating the energy barrier of the recycling reaction of the chiral catalyst (Scheme 5). Calculations showed us that the free energy of the reaction of **Q** with the substrate **A** to give **M** and the final product **4a** is exergonic by 13.6 kcal/mol. As a result, the disassociation/association process of the catalyst is thermodynamically favored.



Scheme 5. Calculated free energy of the recycling of the catalyst for a new turn-over (ΔG_{298}, kcal/mol).

Further, these calculations allowed us to explain the origin of the stereoselectivity observed during this process. Indeed, geometry constraints prevent the rotation of either the aminophenol or of the methylene phenoxonium moieties in ion pairs **N** or **P,** due to the presence of the phosphoric acid catalyst. The dissociation of this later would be necessary to allow this rotation movement. However, since the second cyclization barriers are low (7.6 and 9.2 kcal/ mol respectively), the reaction would remain much faster than any dissociation/rotation/cyclization sequence. Therefore, the high level of stereocontrol of this process was guaranteed, despite the sequential nature of the mechanism. Of note, the simplified phosphoric acid catalyst used in this computational study predicts the right enantiomer. The formation of the minor enantiomer is clearly less kinetically favored (see the Supporting Information).

Then, we were interested to rationalize the absence of reactivity of dienophiles having a free OH group in *ortho* or *meta* positions.[10] The above computations were partially reinvestigated and the results are shown in Scheme 4B, respectively in black and green color (see the Supplementary Information for more details). Unlike *para* series, the chiral phosphoric acid could interact with the *ortho*-substituted substrates *via* the formation of three hydrogen bonds, leading to the complex **M'**. The following displacement of the phosphate provide the corresponding compound **R'** which is more unstable than the *para*-substituted analogue **R** (7.1 vs -11.8 kcal/mol), due to the lack of second hydrogen bond. Next, the formation of the first carbon-carbon occurred, leading to the resulting compound **P'** in an endergonic way (18.8 kcal/mol) with a free energy cost of 14.2 kcal/mol. Here, the presence of only one hydrogen-bond explained the great difference of energy between **P'** and its *para*-substituted analogue **P** (18.8 kcal/mol vs -9.9 kcal/mol). Ion pair **Q'** finally resulted from the formation of the second bond, in an exergonic way by 24.8 kcal/mol. In conclusion, the extra stabilization of **M'** as well as the lack of a second hydrogen bond in species **R'** and **P'**, involved very highly energetic transition

states of the cycloaddition **TS$_{R'P'}$** and **TS$_{P'Q'}$** compared to those implied in the *para* series (21.3 and 20.7 kcal/mol vs -3.7 and -0.7 kcal/mol respectively). Such important energetic differences could be the origin of the lack of the reactivity in the *ortho* series. Despite the possible formation of two hydrogen bonds between the catalyst and the phenol moieties of the intermediates **R''** and **P''**, the same issues are encountered in the *meta* series. Indeed, even though the implied transition states **TS$_{R''P''}$** and **TS$_{P''Q''}$** are more accessible than in the *ortho* series (17.3 and 17.7 vs 21.3 and 20.7 kcal/mol), the entire reaction sequence appeared endergonic in this case.

Conclusion

In summary, we have disclosed a highly efficient and stereoselective enantioselective intramolecular Povarov reaction using primary anilines as azadienes precursors. By using a bulky chiral phosphoric acid as catalyst, a wide range of diverse complex tetracyclic heterocycles were prepared with high yields and excellent diastereo- and enantioselectivities without any required purification step. Chiral hexahydrodibenzo[*b*,*h*][1,6]naphthyridines and tetrahydrothiochromeno[4,3-*b*]quinolin-6-ones, which had never been reported before, were readily synthesized in a stereoselective manner according to this process. Use of low-catalyst loading, intramolecular Povarov reaction was successfully accomplished, facilitating the synthesis of tetrahydrochromeno[4,3-*b*]quinolones on increased scale in a cost-effective manner. Finally, the theoretical studies revealed that the reaction proceeded *via* a stepwise mechanism.

Experimental Section

2-Aminophenol **3a** (0.1 mmol, 1 eq.) was added in one portion to a solution of substrate **2**, **5**, **7**, **9**, or **11** (0.1 mmol, 1 eq.) and the appropriate amount of TRIP catalyst **1** (0.001 or 0.002 mmol, 1 or 2 mol%) in 1,2-DCE (1 mL, 0.1 M). The reaction mixture was vigorously stirred overnight at room temperature, heptane (2 mL) was then added, and the resulting mixture was stirred for a further 10 min. The solution was filtered, and the resulting solid was washed three times with pentane and then solubilized with MeOH. The solvent was removed under reduced pressure to give the desired product **4**, **6**, **8**, **10**, or **12** in pure form.

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Keywords: chiral phosphoric acids • cycloaddition • tetracyclic heterocycles • hydrogen bonds • intramolecular Povarov reaction

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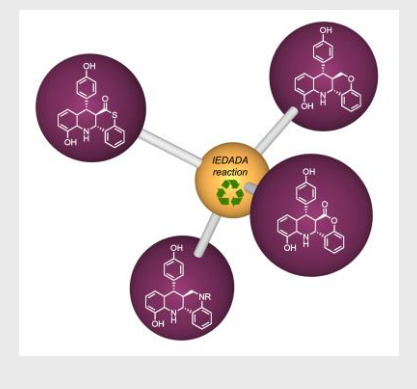

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