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Chiral Phosphoric Acid-Catalyzed Enantioselective Three-Component Povarov Reaction Using Enecarbamates as Dienophiles: Highly Diastereo- and Enantioselective Synthesis of Substituted 4-Amino- tetrahydroquinolines

Guillaume Dagousset,[†] Jieping Zhu^{‡}, and Géraldine Masson,^{*†}*

[†] Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles (ICSN), CNRS, 91198 Gif-sur-Yvette Cedex, France.

[‡] Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), EPFL-SB-ISIC-LSPN, CH-1015 Lausanne, Switzerland.

AUTHOR EMAIL ADDRESS: jieping.zhu@epfl.ch and masson@icsn.cnrs-gif.fr

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CORRESPONDING AUTHOR FOOTNOTE

¹ Centre de Recherche de Gif, ICSN

² Institute of Chemical Sciences and Engineering, EPFL

ABSTRACT

Chiral phosphoric acid (**5**)-catalyzed three-component Povarov reaction of aldehydes **2**, anilines **3**, and enecarbamates **4** afforded *cis*-4-amino-2-aryl (alkyl)-1,2,3,4-tetrahydroquinolines **1** in high yields with excellent diastereoselectivities (>95%) and almost complete enantioselectivities (up to >99%). The reaction was applicable to a wide range of anilines bearing electron-donating (OMe) and electron-withdrawing groups (e.g. Cl, CF₃, NO₂) and allowed for the first time, the aliphatic aldehydes to be employed in the enantioselective Povarov reaction. With β -substituted acyclic enecarbamates, 2,3,4-trisubstituted 1,2,3,4-tetrahydroquinolines with three contiguous stereogenic centers were produced in excellent diastereo- and enantioselectivities (87->99% *ee*). A detailed study about the active catalytic species allowed us to reduce the catalyst loading from 10% to 0.5% with no deterioration of enantiomeric excess. In addition, mechanistic studies allowed us to conclude unequivocally that the Povarov reaction involving enecarbamate as dienophile proceeded via a stepwise mechanism. The key role of the free NH function of the enecarbamate to the success of this transformation was demonstrated. NMR experiments indicating the catalyst-substrate interaction as well as a linear correlation between catalyst and product *ees* were also documented.

KEYWORDS

Organocatalysis, Povarov reaction, tetrahydroquinoline, enantioselective multicomponent reaction, heterocycle, chiral Brønsted acid, phosphoric acid

Introduction

Tetrahydroquinoline is a key structural unit found in many biologically active natural products¹ and synthetic pharmaceutical agents.^{1a,2} In particular, 4-amino-1,2,3,4-tetrahydroquinolines³ represent an important sub-class of this family which has been found in natural products such as martinelliacid,⁴ a potent bradykinin antagonist. It displayed also an excellent track record in medicinal chemistry, the

notable examples being torcetrapib[®],⁵ a potent and first cholesteryl ester transfer protein (CETP) inhibitor and (-)-L-689,560,⁶ a potent antagonist at the *N*-methyl-D-aspartate (NMDA) receptor glycine site (Figure 1).

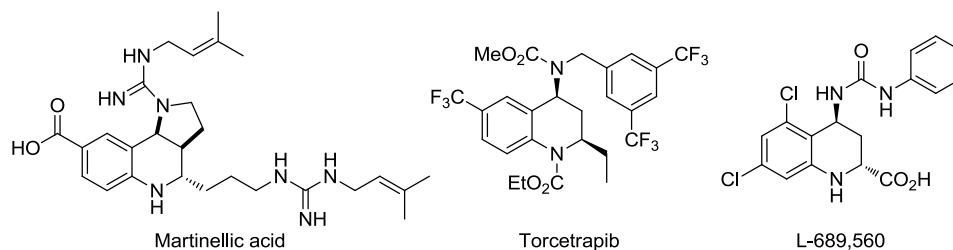
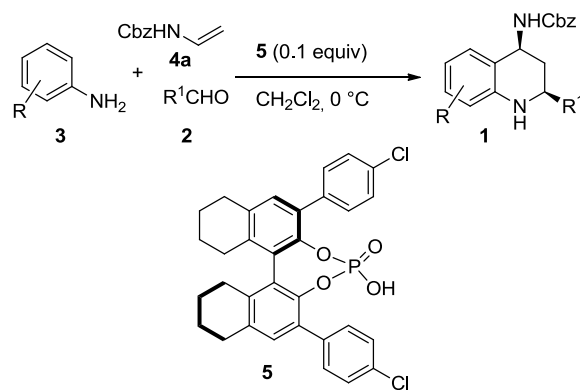


Figure 1. Selected examples of bioactive 4-aminotetrahydroquinolines

Consequently, the development of new synthetic routes to tetrahydroquinolines has been actively investigated in recent years.⁷ Among many reported methods for the construction of polysubstituted tetrahydroquinolines, the Povarov reaction,⁸ an inverse electron-demand aza-Diels-Alder (IEDDA) reaction between 2-azadienes and electron-rich olefins catalyzed by either protic or Lewis acids, stood out as one of the most attractive ones. Since most of the tetrahydroquinoline-containing natural products and drug candidates contain stereogenic center(s), the ability to render the Povarov reaction enantioselective is of significant importance. However, despite of efforts dedicated to this field, the development of enantioselective Povarov reaction met with only limited success. Kobayashi⁹ and Sundararajan¹⁰ disclosed the first examples of enantioselective two-component Povarov reaction using chiral BINOL-ytterbium and aminodiol-titanium (IV) complexes, respectively, as catalysts. The enantioselectivities and application scope of these two catalytic processes were nevertheless moderate. A major breakthrough came from Akiyama's group who documented a phosphoric acid-catalyzed enantioselective Povarov reaction of vinyl ethers and *N*-arylimines derived from *ortho*-hydroxyanilines. Although the Povarov adducts were generally obtained with excellent diastereo- and enantiomeric excesses under Akiyama's conditions, the necessity of using *ortho*-hydroxyaniline as one of the reaction partner limited the access only to 8-hydroxytetrahydroquinoline derivatives.¹¹ In addition, only imines derived aromatic aldehydes were accepted as substrates in all these catalytic enantioselective

processes.^{9,11}

In 2009, we reported the first example of three-component enantioselective Povarov reaction for the synthesis of 4-amino-1,2,3,4-tetrahydroquinolines (**1**, Scheme 1). Thus, the reaction of aldehydes **2**, anilines **3**, and enecarbamates **4** in the presence of a catalytic amount of chiral phosphoric acid (**5**) furnished 4-amino-1,2,3,4-tetrahydroquinolines **1** in good to high yields with excellent diastereo- (up to >99:1) and enantioselectivities (up to >99% ee).¹² Importantly, the aliphatic *N*-arylimines generated *in situ* have been successfully employed in the enantioselective Povarov reaction for the first time. The use of benzyl-*N*-vinylcarbamate (**4a**) possessing the free NH function as dienophile^{13,14} allowed us to use simple anilines, instead of *o*-hydroxyanilines, giving therefore access to structurally diverse tetrahydroquinolines **1**.

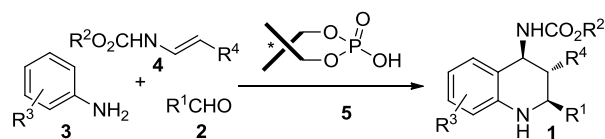


Scheme 1. Catalytic enantioselective Povarov three-component synthesis of 2,4-disubstituted-1,2,3,4-tetrahydroquinolines

Subsequent to our initial disclosure, Gong reported a three-component synthesis of tricyclic ring system of julolidine by combining the enantioselective Povarov reaction with the intramolecular hydroamination reaction.¹⁵ Ricci et al.¹⁶ and Feng et al.¹⁷ described two catalytic asymmetric IEDDA reactions employing vinylindoles and cyclopentadiene, respectively, as dienophiles. Jacobsen et al. developed an efficient asymmetric two-component Povarov reaction using 2,3-dihydrofuran, vinyl-lactam and *N*-Cbz-2,3-dihydropyrrole as dienophiles, in the presence of a dual chiral-achiral acid

catalytic system.¹⁸

Despite of this significant progress, enantioselective accesses to 2,3,4-trisubstituted tetrahydroquinolines via the Povarov reaction were restricted to cyclic dienophiles.^{9,17 and 18} To the best of our knowledge, there is no convenient method for the preparation of 4-amino-1,2,3,4-tetrahydroquinolines **1** with various substitution patterns at C-2, C-3 and C-4. In this paper, we shortly summarize our previous studies on the Brønsted acid-catalyzed enantioselective three-component Povarov reaction for the synthesis of highly substituted 4-aminotetrahydroquinolines. The use of β -substituted acyclic enecarbamates as a key reaction partner allowed us to access for the first time the enantiomerically enriched 2,3,-disubstituted 4-amino-1,2,3,4-tetrahydroquinolines **1** (Scheme 2). We detail also control experiments, NMR titration experiment, linear correlation between catalyst and product *ees*, the mechanistic studies as well as a rationale for the stereochemical outcome of this transformation.



Scheme 2. Enantioselective synthesis of 2,3,4-trisubstituted-1,2,3,4-tetrahydroquinolines.

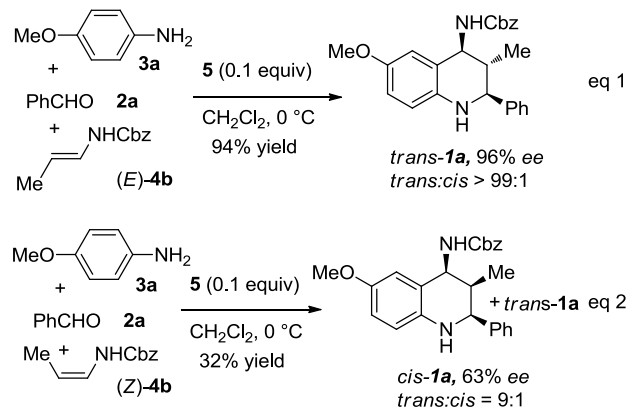
Results and Discussion

In our preliminary communication, we have demonstrated that chiral phosphoric acid derived from octahydro-(R)-BINOL **5** (*cf* Supp info for details) was able to efficiently promote the enantioselective three-component Povarov reaction between aldehydes **2**, anilines **3** and benzyl *N*-vinylcarbamate (**4a**).^{8,19,20} A wide range of electron-neutral, -rich and -poor aromatic aldehydes were appropriate substrate affording *cis* 2,4-disubstituted 4-aminotetrahydroquinolines **1**²¹ with both high enantioselectivities [98->99% ee] and diastereoselectivities (>95:5 dr).¹² Remarkably, the optimized reaction conditions were also applicable to aliphatic aldehydes. Both α - and β -branched aldehydes

participated effectively in the three component reaction (*cf* Supp info for details). On the other hand, linear aldehydes gave lower yields due to the competitive isomerization of the *in situ* formed aliphatic N-arylimines to the corresponding enamines.^{4,22,24} However, we were pleased to find that when the reaction was carried out at $-30\text{ }^{\circ}\text{C}$, the expected cycladducts were isolated in good yields with high ees (*cf* Supp info for details).¹² A wide range of anilines were also suitable partners to afford the corresponding cycloadducts in good to high yields and excellent enantioselectivities (up to 99% ee). However, in our previous report, when anilines with strong electro-withdrawing substituents such as 4-trifluoromethyl were subjected to the same conditions, moderate yields were observed. Thus, we decided to reinvestigate the reaction with 4-trifluoromethylaniline. Fortunately, by simply increasing the reaction time from 1 h to 12 h, the yield of tetrahydroquinoline was significantly enhanced (*cf* Supp info for details). This modification increased the overall yield of our original synthesis of the torcetrapib[®], a potent and first cholesteryl ester transfer protein (CETP), from 32% to 40%.¹²

Having succeeded in the elaboration of optically enriched *cis*-2,4-disubstituted-1,2,3,4-tetrahydroquinolines (*cf* Supp info for details), we next investigated the use of β -substituted enecarbamates as nucleophiles in order to generate three adjacent stereogenic centers in one operation. As the geometry of the dienophile can impact the stereochemical outcome of the reaction, we decided to test the benzylprop-1-enylcarbamate (*E*)-**4b** and (*Z*)-**4b** separately. Pleasingly, the three-component reaction using (*E*)-benzyl-prop-1-enylcarbamate (*E*)-**4b**, benzaldehyde (**2a**) and 4-methoxyaniline (**3a**) under our standard conditions afforded the desired tetrahydroquinoline (*trans*-**1a**, all *trans*) in 94% yield with excellent enantio- and diastereoselectivity (eq 1, Scheme 3). On the other hand, the (*Z*)-enecarbamate (*Z*)-**4b** was much less reactive than its *E* counterpart **4b**, affording **1a** in 32 % yield as a mixture of two separable diastereoisomers (*trans*:*cis* = 9:1). Surprisingly, the major product isolated from the reaction of (*Z*)-**4b** was found to be the same (all *trans*) as that derived from (*E*)-**4b** (eq 2, Scheme 4). We assumed that, in the presence of phosphoric acid, a slow *Z/E* isomerization of enecarbamate (*Z*)-**4b** to (*E*)-**4b** via the *N*-acyliminium intermediate occurred before the Mannich

reaction. The subsequent reaction of (*E*)-**4b** with **2a** and **3a** gave then *trans*-**1a** as a major product. It is also interesting to note that while the *trans* isomer **1a** was obtained in 90% *ee*, the *cis*-**1a** was isolated in a much lower *ee* (63%). The *trans* relative stereochemistry between C-2 and C-3 and between C-3 and C-4 in **1a** was established by NOESY experiments (Scheme 3).



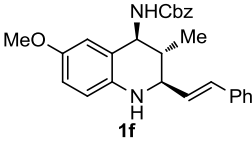
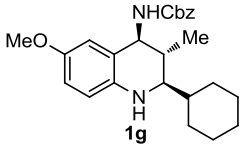
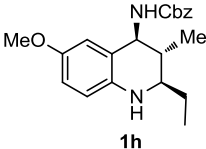
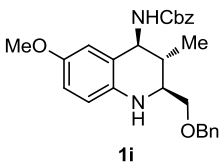
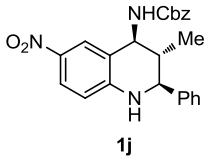
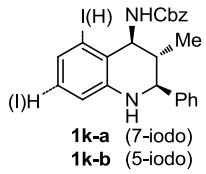
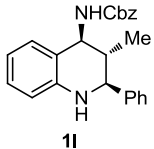
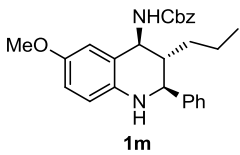
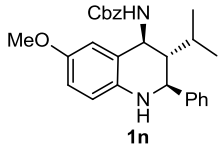
Scheme 3. Povarov reaction of β -substituted acyclic enecarbamate (*E*)-**4b** and (*Z*)-**4b**.

Encouraged by the high levels of diastereo- and enantioselectivity observed in the reaction of (*E*)-**4b**, we next examined the scope of this reaction by varying the structure of aldehydes (Table 1). A variety of aromatic aldehydes, ranging from electron-rich substrates [3-methoxybenzaldehyde (**2b**), furaldehyde (**2e**)], to electron-poor aromatic aldehydes [4-nitrobenzaldehyde (**2c**)], underwent reaction with (*E*)-**4b** and 4-methoxyaniline (**3a**) without event to afford the corresponding tetrahydroquinolines in good yields with excellent enantioselectivities (entries 1, 2 and 4). *Ortho*-substituted aromatic aldehydes such as 2-bromobenzaldehyde (**2d**) and cinnamaldehyde (**2f**) required longer reaction times (12 h) to derive the reaction to completion (entries 2 and 5). α -Substituted aliphatic aldehydes (entry 6) also performed well under the standard reaction conditions, although reaction with linear aldehydes (entries 7 and 8) had to be carried out at $-30\text{ }^\circ\text{C}$ to avoid undesired isomerization of the imine intermediate and enecarbamate.^{4,22,24} Anilines having electron-donating (4-methoxy), -neutral (H, entry 11, Table 1), and -withdrawing groups (4-nitro, entry 9, Table 1) were suitable reaction partners to afford the corresponding adducts in high yields and excellent enantioselectivities. As previously described,¹² when

a *meta*-substituted aniline, such as 3-iodo aniline (**3c**, entry 10), was used, two regioisomers, 7-iodo-**1k** and 5-iodo-**1k** were isolated with the sterically more congested isomer 5-iodo-**1k** being the major one. To evaluate the influence of the substituent at the C-2 position of the double bond, a series of enecarbamates, bearing propyl (**4c**), isopropyl (**4d**) and *tert*-butyldiphenylsilyloxypropyl (**4e**) substituents, were prepared and were subjected to react with benzaldehyde (**2a**) and 4-methoxyaniline (**3a**) under our optimized conditions. With **4c** and **4e**, yields and selectivities were high and were comparable to those obtained with (*E*)-**4b**. A lower yield, but still good enantioselectivity, was obtained with the bulkier (*E*)-benzyl 3-methylbut-1-enylcarbamate **4d** (entry 11, Table 3).

Table 1. Scope of the enantioselective Brønsted acid-catalyzed three-component Povarov Reaction with β -substituted (*E*)-enecarbamates.^a

| entry | R ¹ | Ar | (<i>E</i>)- 4 | 1 | yield (%) ^b | ee (%) ^c |
|-------|---|-----------|------------------------|----------|------------------------|---------------------|
| 1 | <i>m</i> -MeOC ₆ H ₄ (2b) | 3a | 4b | | 87 | 97 |
| 2 | <i>p</i> -NO ₂ C ₆ H ₄ (2c) | 3a | 4b | | 78 | 92 |
| 3 | <i>o</i> -BrC ₆ H ₄ (2d) | 3a | 4b | | 78 ^d | 98 |
| 4 | 2-Furyl (2e) | 3a | 4b | | 69 | 97 |

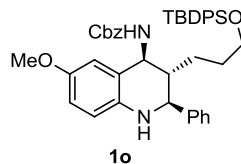
| | | | | | | |
|----|---|---|-----------|--|----------------------------|----------|
| 5 | <i>E</i> -PhCH=CH ₂ (2f) | 3a | 4b |  1f | 71 ^d | 95 |
| 6 | <i>c</i> C ₆ H ₁₁ (2g) | 3a | 4b |  1g | 89 | 91 |
| 7 | Et (2h) | 3a | 4b |  1h | 82 ^{d,e} | 96 |
| 8 | BnOCH ₂ (2i) | 3a | 4b |  1i | 72 ^{d,e} | 96 |
| 9 | 2a | <i>p</i> -NO ₂ C ₆ H ₄ (3b) | 4b |  1j | 78 | 92 |
| 10 | 2a | <i>m</i> -IC ₆ H ₄ (3c) | 4b |  1k-a (7-iodo) 1k-b (5-iodo) | 15 (7-iodo) 66 (5-iodo) | 98 92 |
| 11 | 2a | C ₆ H ₅ (3d) | 4b |  1l | 85 | 96 |
| 12 | 2a | 3a | 4c |  1m | 84 | 96 |
| 13 | 2a | 3a | 4d |  1n | 48 | 87 |

14

2a

3a

4e

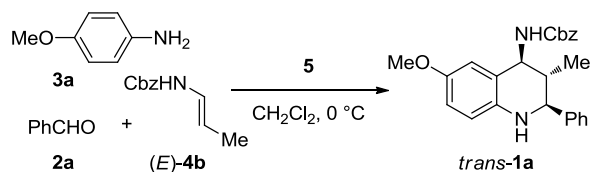


97

93

^a General conditions: aldehyde (0.10 mmol), amine (0,10 mmol), β -substituted enecarbamate (0.11 mmol) and **5** (0.01 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C during 1 h. ^b Yields refer to chromatographically pure product. ^c Enantiomeric excess was determined by enantiodiscriminating HPLC analysis. ^d 12 h reaction time. ^e Reaction performed at -30 °C.

Although the enantiomeric excess and yield were reliable, we found that time needed to complete the reaction varied (ranging from 1 h to 12 h) depending on the batch of chiral phosphoric acid **5** used, as it was observed earlier by Ding *et al.*²⁵ Recently Ishihara *et al.* and List *et al.* have demonstrated that purification of chiral phosphoric acids by silica gel chromatography can result in the formation of a variable amount of alkali or alkaline earth metal-phosphoric acid complexes.²⁶ The formation of these phosphate salts could explain the variation of reaction rate in these chemical reactions. Indeed when **5** washed with HCl was used, the 4-aminotetrahydroquinolines **1** were systematically obtained after one hour.²⁷ As metal phosphate salts were known to create a well-defined chiral environment and could even in certain cases reverse the enantiofacial selectivities relative to the free phosphoric acids,²⁸ we decided to evaluate its catalytic power in the enantioselective Povarov reaction. Surprisingly, no reaction occurred when calcium bis(phosphate) complex $\text{Ca}(\mathbf{5})_2$, instead of **5**, was used as catalyst under otherwise identical conditions. This demonstrated that only metal-free chiral phosphoric acid was an effective catalyst for the present Povarov reaction. Based on this observation, we reasoned that it might be possible to reduce the catalyst loadings without significantly affecting the catalytic activity and the enantioselectivity by using acid-washed phosphoric acid. The results are summarized in Table 2. It was found that with 0.5 mol% of **5**, reaction of **2a**, **3a** and (*E*)-**4b** afforded **1a** in 80% yield with 96% *ee*, albeit with a longer reaction time (12 h). In terms of operational convenience, the use of 2.5 mol% phosphoric acid **5** at 0 °C ensured high levels of reaction efficiency and enantioselectivity while maintaining the expedient reaction time.

Table 2. Optimization of catalyst loading^a

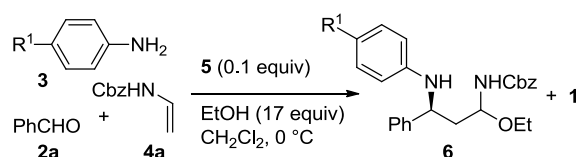
| entry | Catalyst loading (mol%) | t (h) | yield (%) ^b | ee (%) ^c |
|-------|-------------------------|-------|------------------------|---------------------|
| 1 | 10 | 1 | 94 | 96 |
| 2 | 2.50 | 3 | 78 | 96 |
| 3 | 1 | 12 | 81 | 96 |
| 4 | 0.5 | 12 | 80 | 96 |
| 5 | 0.1 | 72 | 16 | 96 |

^a General conditions: aldehyde (0.10 mmol), amine (0.10 mmol), benzyl *N*-vinylcarbamate (0.11 mmol), and **5** in CH₂Cl₂ (1.0 mL) at 0 °C. ^b Yields refer to chromatographically pure product. ^c Enantiomeric excess was determined by enantiodiscriminating HPLC analysis.

The mechanism of the Povarov reaction has long been a topic of controversy.²⁹ Several recent theoretical studies indicated that the mechanism can change from concerted to stepwise according to the dienophiles used. In our case, the polarized nature of the enecarbamate double bond led us to speculate that a stepwise mechanism initiated by the Mannich reaction might be a predominant one. If this pathway were indeed operating, it would then be possible to trap the *N*-acyliminium intermediate generated after the Mannich reaction by an external nucleophile. To verify this working hypothesis, a series of control experiments were performed. Reaction of benzaldehyde (**2a**), 4-methoxyaniline (**3a**) and enecarbamate **4a** in the presence of **5** and EtOH (17 equiv) afforded indeed the Mannich adduct **6a** in 21% yield together with the tetrahydroquinoline **1** (50%). With aniline (**3d**), and electron-poor

anilines such as 4-chloro aniline (**3e**) and 4-nitro aniline (**3b**) under otherwise identical conditions, only the Mannich adducts were isolated at the expense of the Povarov products (Table 3). These results provided not only the direct evidence of a stepwise mechanism of our catalytic enantioselective Povarov reaction, but also allowed us to develop an efficient enantioselective synthesis of 1,3-diamine via a one-pot Mannich reaction/reduction process.^{14g} The interrupted Povarov reaction has previously been elegantly exploited by Lavilla and co-workers for the synthesis of heterocycles other than tetrahydroquinolines.³⁰

Table 3. Interrupted Povarov cycloaddition.^a



| entry | R ¹ | yield (%) ^b 7 | yield (%) ^b 1 |
|-------|-------------------------------|---------------------------------|---------------------------------|
| 1 | MeO (3a) | 6a (21) | 50 |
| 2 | H (3d) | 6b (77) | 11 |
| 3 | Cl (3e) | 6c (85) | - |
| 4 | NO ₂ (3b) | 6d (72) | - |

^a General conditions: aldehyde (0.10 mmol), amine (0,10 mmol), benzyl vinylcarbamate (0.11 mmol), ethanol (1.7 mmol) and **5** (0.01 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C. ^b Yields refer to chromatographically pure product.

Dual activation of the imine and secondary enecarbamate by bifunctional chiral phosphoric acid catalysis was our working hypothesis for the development of the present transformation.^{12,14} To gain insight on this mechanistic assumption, we decided to evaluate the influence of the free NH function of carbamate on the enantioselectivity of the transformation. Tertiary enecarbamates such as benzyl *N*-methyl-*N*-vinyl carbamate (**4f**), 3-vinylloxazolidin-2-one (**4g**) and *N*-Cbz-2-pyrroline (**4h**) were synthesized and tested in the three-component reaction with **2a** and **3a** (Figure 2). With acyclic enecarbamates **4f** and **4g**, no reaction took place, while with the cyclic enecarbamate **4h**, the corresponding *endo*-cycloadduct **1p** (dr >99/1) was isolated in 30% yield with only 25% ee (Figure 2).

These results indicated clearly that the NH moiety of **4a-e** played an important role, not only for the enantioselectivity but also for the reactivity.³¹

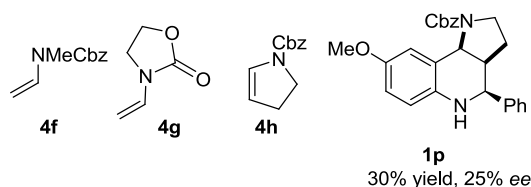


Figure 2. Povarov reaction of tertiary enecarbamates.

To probe the nature of the catalyst-substrate interaction,^{32,33} titration of imine **7** with phosphoric acid by ¹H NMR spectroscopy was performed.³⁴ When one equivalent of phosphoric acid **5** was used, a significant down field shift of aldimine proton ($\Delta\delta = 1.6$ ppm) was observed indicating the association of these two species (Figure 3).³⁵ When two equivalents of phosphoric acids **5** were used, **7** was found to exist as a single associated form **5-7**. Recent NMR studies from Gschwind, Rueping and co-workers using ¹⁵N labeled imines concluded that while ion-pairing is a predominant form in the interaction between diphenylphosphate and (*E*)-*N*-(4-methylbenzylidene)aniline, H-bonding between imines (especially those with less basic one) and phosphoric acids could also contribute to the activation of imines.³⁶ While our titration experiments could not allow us to distinguish these two activation modes, we would favor the ion-pairing activation mode in our case by the fact that imine **7** having a basic nitrogen atom. This hypothesis was also reinforced by the absence of nonlinear effect under our conditions (*cf vide infra*).

Gong and co-workers have recently demonstrated that phosphoric acids can exist as aggregates both in solution and in solid state.³⁷ They also provided evidence of asymmetric amplification of certain phosphoric acid-catalyzed reactions, especially those involving non-basic *N*-acylated imines as electrophiles. This observation prompted us to investigate the relationship between the optical purity of the phosphoric acid catalyst **5** and that of the tetrahydroquinoline *trans*-**1a** under our optimal conditions. As shown in Figure 4, the *ee* values of the tetrahydroquinolines *trans*-**1a** were nearly proportional to

those of the chiral phosphoric acid **5**, indicating the absence of a nonlinear effect.³⁸ We therefore assumed that a single catalyst molecule was involved in the activation of imine in the key Mannich addition step.

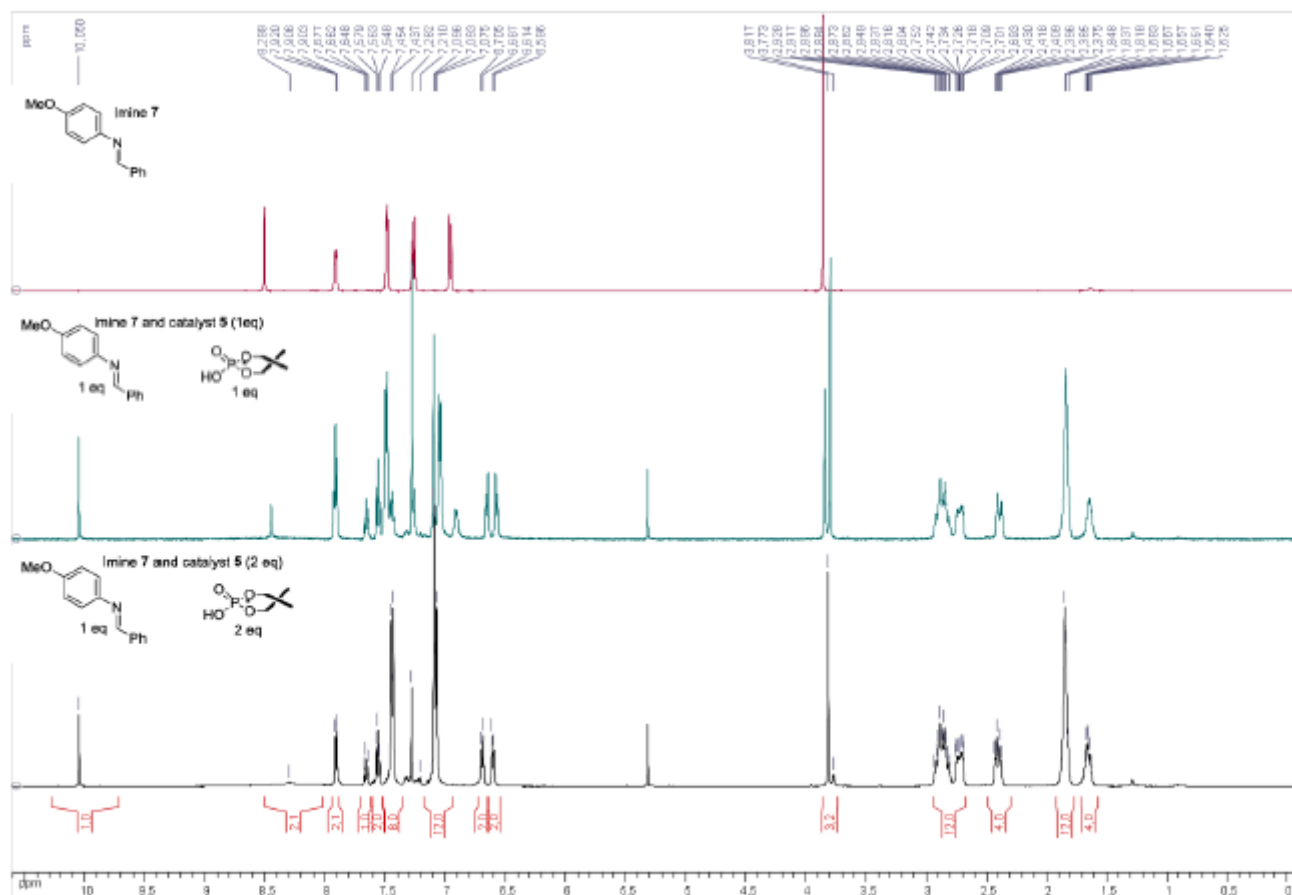


Figure 3. NMR spectra of titration experiments (500 MHz, CDCl₃).

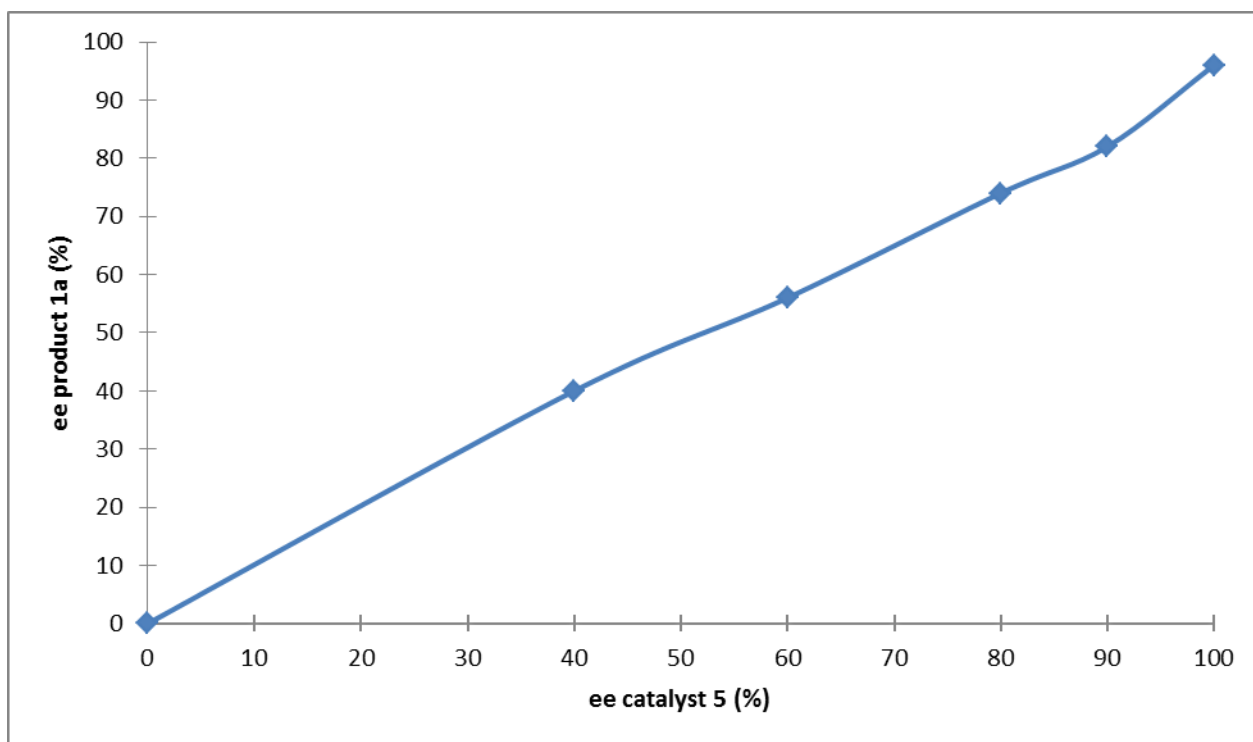
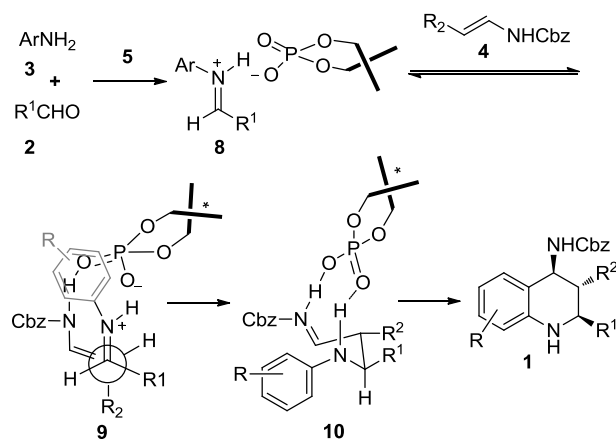
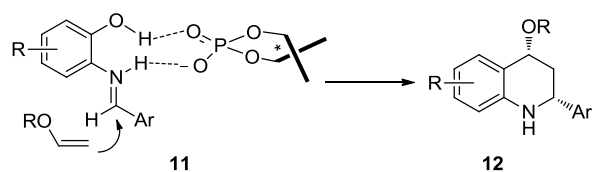


Figure 4. Correlation between the enantiomeric excess of **5** and that of product *trans*-**1a**.

On the basis of these observations, we assumed that the phosphoric acid catalyzed three-component Povarov reaction proceeded via protonation of the imine, forming chiral ion pair **8**, followed by hydrogen bonding between the enecarbamate NH and the Lewis basic phosphoryl oxygen. Then, a pseudo-intramolecular *Si*-face attack of (*E*)-enecarbamate to the iminium carbon of the chiral contact ion pairs via transition state **9** would afford iminium **10** with concurrent proton shift within the phosphoric acid sphere. Finally, an intramolecular aza-Friedel-Crafts reaction via the sterically less congested conformer **10** would furnish the observed 2,4-*cis*-substituted tetrahydroquinoline **1** with defined absolute configuration as shown in Scheme 4. It is interesting to note that the absolute configuration of tetrahydroquinoline **1** we obtained is different from that obtained by Akiyama, although chiral phosphoric acids used in both cases were derived from (*R*)-BINOL. The reversal of enantiofacial selectivity could be accounted by the difference in H-bonding models. In Akiyama's catalytic system, the phosphoric acid activated only the electrophile via the participation of the *ortho*-hydroxy group.¹¹ The *Re*-face attack of the enolether onto imine via transition state **11** would then afford the tetrahydroquinoline **12**.



Scheme 4. Proposed mechanism and stereochemical issue.



Scheme 5. Akiyama's stereochemical model.

Evidence that both activation modes via transition states **9** and **11** could be operating was obtained by engaging the *o*-hydroxyaniline (**3e**) into the Povarov reaction. Thus, reaction of **3e** with benzaldehyde (**2a**) and enecarbamate **4a** afforded the corresponding tetrahydroquinoline **1q** in 64% yield with 71% *ee*. A possible competition between our dual activation model and Akiyama's model could account for the diminished *ee* of product **1q** (Scheme 5).

Based on the results on their DFT calculation, Simón and Goodman proposed a model **13** to account for the stereochemical outcome of the Mannich reaction that we observed experimentally (Figure 5).³⁹ Although the significant difference in the reactivity observed between *Z* and *E* isomer **4b** has yet to be explained, a transition state **14** (Figure 5) displaying unfavorable interactions between the (*Z*)-enecarbamate and the ion pair complex of the imine/**5** could potentially explain the low reactivity of the (*Z*)-enecarbamate.

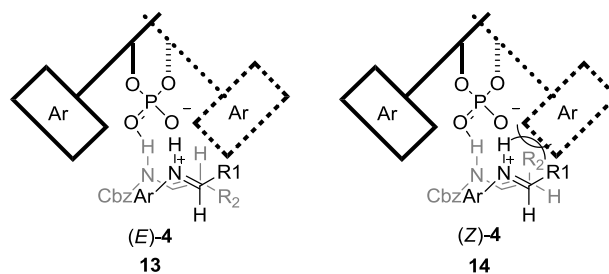


Figure 5. Simón and Goodman's model.

Conclusion

We reported the first catalytic enantioselective three-component Povarov reaction of aldehydes **2**, anilines **3** and enecarbamates **4** to furnish *cis*-1-aryl (alkyl)-4-aminotetrahydroquinolines **1** in good yields with excellent diastereo- and enantioselectivities (up to 98% *ee*). The use of acyclic β -substituted enecarbamates in this reaction allowed us to access the 2,3,4-trisubstituted 1,2,3,4-tetrahydroquinolines with three contiguous stereogenic centers, again with high diastereo- and excellent enantioselectivities. A study on active catalytic species demonstrated that only the free-phosphoric acid was catalyzing the Povarov reaction. These findings allowed us to reduce the catalyst loading by a factor of 20 to as little as 0.5 mol%. The trapping experiments provided sound evidence that the present Povarov reaction involving enecarbamate proceeded via a stepwise mechanism. Mechanistic investigations including NMR spectroscopy studies, linear effects and control experiments highlighted the crucial role played by the activation of the imine via ion-pairing and the enecarbamate via H-bonding with bifunctional phosphoric acid catalyst. The low catalyst loading, excellent yields, enantioselectivities, and operational simplicity make our catalytic system attractive for the synthesis of highly functionalized enantiomerically enriched 4-amino-tetrahydroquinolines.

Experimental Section

General Procedure for the Catalytic Enantioselective Three-Component Povarov Reaction

To a solution of aldehyde (**2**, 0.1 mmol) in dry CH_2Cl_2 (0.4 mL) at room temperature, aniline (**3**, 0.1

mmol) was added. After being stirred at room temperature for 30 minutes, the reaction mixture was cooled down to 0 °C and a solution of phosphoric acid catalyst (**5**, 0.01 mmol) in CH₂Cl₂ (0.3 mL) and enecarbamate (**4**, 0.11 mmol) in CH₂Cl₂ (0.3 mL) were added. The resulting solution was stirred under argon atmosphere at 0 °C for 1 h. Solvents were removed *in vacuo* and the residue was purified by flash chromatography on silica gel (Heptane/EtOAc) to afford the corresponding 4-amino-1,2,3,4-tetrahydroquinoline.

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Supporting information.

Experimental details, characterization of new compounds, selected NMR and HPLC spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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TOC Graphic

