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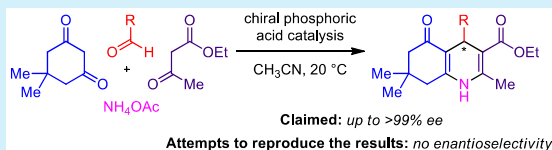


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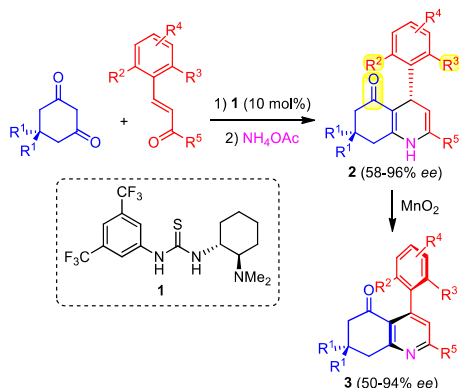
Ophélie Quinonero, Clément Lemaitre, Marion Jean, Nicolas Vanthuyne, Christian Roussel, Damien Bonne, Thierry Constantieux, Cyril Bressy,* Xavier Bugaut,* and Jean Rodriguez*

ABSTRACT: A reinvestigation of a chiral phosphoric-acid-catalyzed four-component Hantzsch enantioselective synthesis of polyhydroquinolines reported in 2009 is presented. In our hands, when the reaction was performed with fidelity to the original report using a chiral enantiopure phosphoric acid catalyst, no enantioselectivity was observed. Unlike in the original report, enantioselectivity results are backed by baseline separation of the enantiomers by HPLC analyses on chiral stationary phase with UV and chiroptical detection.

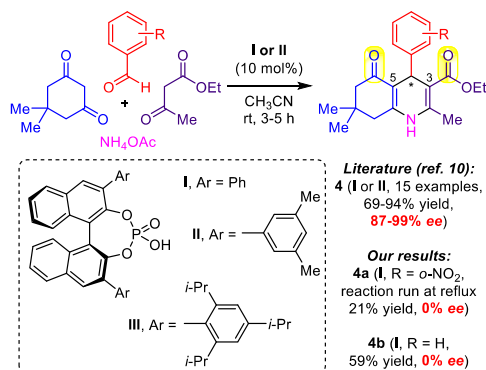


Recently, our group¹ has developed an atroposelective version of the Hantzsch pyridine synthesis (Scheme 1).² Our strategy was to achieve the enantioselective organocatalytic preparation of suitably substituted 4-aryl-1,4-dihydropyridines (DHPs) **2**³ and then oxidize them into the corresponding 4-arylpyridines **3**, with a central-to-axial conversion of chirality.⁴ The first challenge was to prepare enantioenriched 4-aryl-1,4-DHPs that bear at least three substituents around the stereogenic axis⁵ providing the required steric hindrance to ensure high enough barriers to rotation in the final products. Our studies began by a survey of the literature methods to synthesize enantioenriched 4-aryl-1,4-DHPs to define which ones tolerate additional steric hindrance. Generally, these transformations rely on a 1,4-addition to a Michael acceptor followed by an annulation process. Singh's stepwise synthesis combining 2-enoylpyridines and cyclic 1,3-diketones in the

Scheme 1. Atroposelective Hantzsch Pyridine Synthesis



Scheme 2. Enantioselective Organocatalytic Hantzsch Synthesis of Polyhydroquinolines: Literature Report and Our Early Results



presence of Takemoto catalyst **1** allowed the preparation of a series of targeted compounds **2**.⁶ However, the other methodologies that were evaluated, including those of Renaud,⁷ Gong,⁸ and Rueping,⁹ furnished no expected product. Either the substrates remained unreacted, even in more forcing reaction conditions than in the original reports, or competing pathways including 1,2-addition became predominant over the desired 1,4-addition.

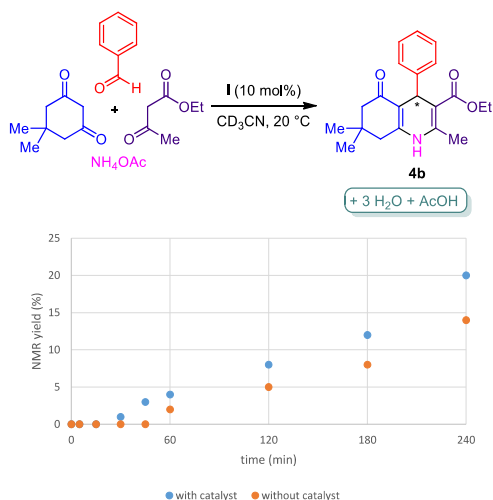
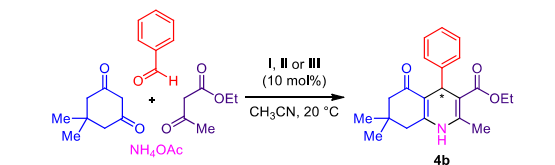


Figure 1. Conversion over time in the presence or absence of catalyst.

Table 1. Influence of NH₄OAc and the Catalyst^a



entry	reaction conditions	results
1	catalyst I and no NH ₄ OAc	no conversion
2	catalyst I, AcOH instead of NH ₄ OAc	no conversion
3	catalyst II	38%, 0% ee
4	catalyst III	47%, 0% ee
5	catalyst III, 0 °C	77%, 0% ee
6	catalyst III, -20 °C	no conversion

^aYield of analytically pure product after purification by flash chromatography and ee determined by HPLC on chiral stationary phase after identification of the enantiomers by baseline separation on the racemic mixture.

Alternatively, one of the most appealing methods in the literature was the report by Evans and Gestwicki consisting of the four-component reaction between ethyl acetoacetate, dimedone, aldehydes, and ammonium acetate in the presence of enantiopure BINOL-derived phosphoric acids I and II (Scheme 2).¹⁰ Indeed, the expected polyhydroquinolines **4** were assembled in a single synthetic operation from commercially available starting materials in impressive yields and enantioselectivities for such a complex transformation. Even more interesting for us, the 4-aryl-1,4-DHP ring of **4** was flanked by two different carbonyl substituents on positions 3 and 5, opening a possibility to attain sufficient steric hindrance even using aromatic aldehydes substituted only at one of the two *ortho* positions. *o*-Nitrobenzaldehyde was selected to start investigating this transformation in the presence of enantiopure catalyst I. The reaction mixture had to be refluxed to observe the formation of product **4a**. It was isolated in 21% yield, but its analysis by HPLC on chiral stationary phase (Chiralpak IC, Hept/EtOH 70:30, 1 mL min⁻¹, UV and circular dichroism CD detectors, ~3 min interval between the signals of the two

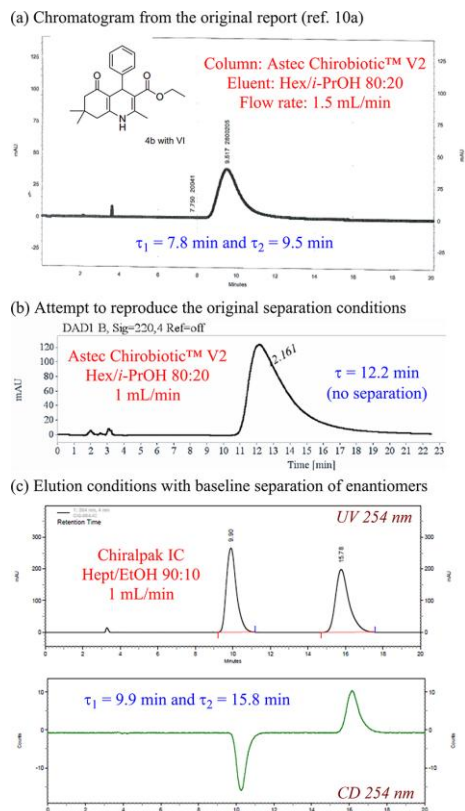


Figure 2. Selected HPLC data for compound **4b**.

enantiomers¹²) revealed no enantioselectivity. Suspecting that the nitro substituent and/or the increase in the reaction temperature might have a deleterious influence on the enantioselection process, we repeated the preparation of product **4b**, which was present in the original report.^{10a} Surprisingly, this second product was also isolated as a racemate. Puzzled by these results, we conducted an in-depth evaluation of our operating conditions including the reperification of catalyst I¹¹ and all starting materials, the use of a brand-new batch of ammonium acetate, and the purification of the product by several techniques (recrystallization or flash chromatography), without any influence on the stereochemical outcome of the reaction.¹² Moreover, home-prepared catalyst I evaluation in another protocol described in the literature attested to its integrity.^{12,13}

At this point of the study, a close analysis of the original publication raised the following questions:^{10a}

- The reaction is said not to proceed in the absence of the catalyst, but product **4b** was obtained with good yields (75–90%) in comparable reaction times (3–5 h) with catalysts as different as Yb(OTf)₃, a proline derivative, chiral diphosphines, and chiral phosphoric acids. It appeared unclear how such diversified chemical entities that are likely to proceed by different modes of activation could result in very similar results. Moreover, all chiral catalysts but the phosphoric acids resulted in negligible enantioinduction.

Table 2. Test of Various Aldehydes^a

Entry	R	Catalyst	Product number	Lit. yield (%) ^[10a,17]	Lit. ee (%) ^[10a,17]	Yield (%) ^[b]	ee (%) ^[c]
1	4-[(CH ₃) ₂ N]C ₆ H ₄	II	4c	75-78	93	92	0
2	2-CF ₃ C ₆ H ₄	I	4d	79-85	>99	38	0
3	PhCH ₂ CH ₂	II	4e	92-94	94	28	0
4		III	4f	25.92	>90	35	7

^aReaction conditions: mixture of dimedone (1.5 equiv), ethyl acetoacetate (1.0 equiv), catalyst (0.1 equiv), aldehyde (1.0 equiv), and NH₄OAc (1.0 equiv) in CH₃CN stirred at room temperature for the appropriate time. ^bYield of analytically pure product after purification by flash chromatography. ^cDetermined by HPLC on chiral stationary phase after identification of the enantiomers by baseline separation on the racemic mixture.

- (ii) In the literature, catalysts **I** and **II** scarcely allow the reaching of high enantiomeric excesses, and bulkier congeners such as **III** are often preferred.¹⁴
- (iii) An enantiomeric excess determination for product **4b** (98% ee) was performed by HPLC on chiral stationary phase using an Astec Chirobiotic V2 column (Figure 2a).^{10a} However, no chromatogram of the racemic mixture was provided to ascertain the identification of the two enantiomers but only the chromatogram of the “racemic mixture spiked with product from reaction with catalyst”, which shows no baseline separation between the enantiomers in the HPLC conditions employed. Moreover, the former chromatogram disappeared from the Supporting Information in a correction of the original article that was published in 2014.¹⁵
- (iv) For all other products, experimental proof for the identification of the two enantiomers (that is to say, the HPLC chromatogram of the racemic mixture with baseline separation) was not provided. Sometimes, the retention time for the minor enantiomer was even missing.^{10a} The correction added chromatograms of coelution of the racemic mixture and the supposedly enantioenriched product for six compounds of the reaction scope.¹⁵ However, there was once again no baseline separation. Individual elution conditions were not given and were likely to be different from the ones used for the determination of the enantiomeric excesses since retention times were utterly different (shift up to 14 min).¹²

Intrigued by these observations, we embarked on an in-depth evaluation of the results presented in the original report leading to **4b** with the model substrates shown in Figure 1. At first, product formation over time was monitored by ¹H NMR. In the presence of catalyst **I**, product started to appear after half an hour of reaction. This induction period is probably necessary to attain concentrations of the intermediates of the multicomponent reaction that are high enough to allow the formation of the target polyhydroquinoline **4b**. More interestingly, the curve of product formation over time seems to present an inflection point around 3 h, when the reaction actually accelerates. When catalyst **I** was omitted, the exact same curve was obtained with just a slightly extended induction period.

It should be noted that, during the reaction, three molecules of water and one of acetic acid are expelled. We surmised that the increasing concentration of the latter one might explain the rate acceleration in a scenario where both acidic species present in the reaction mixture (catalyst **I** and AcOH) actually promote product formation. Complementary to that, no conversion of the three organic substrates was observed when no NH₄OAc was present in the reaction mixture (Table 1, entry 1), even in the presence of AcOH (entry 2), highlighting that the nitrogen source is required early in the reaction mechanism, presumably in the initial enamine and/or iminium ion formation.¹⁶ The replacement of NH₄OAc by other ammonia sources (NH₄Cl, NH₄HCO₃, NH₃ in MeOH, or aqueous NH₃) or surrogates (HMDS) was also unsuccessful, providing either no product or the racemic product.¹² Replacing catalyst **I** by **II** also present in the original report from the group of Gestwicki or the popular TRIP catalyst **III**¹⁷ (entries 3 and 4) led to no improvement. Finally, reducing the reaction temperature does not appear as a solution to solve the enantioselectivity issue either (entries 5 and 6).

We also conducted a thorough HPLC study on racemic compound **4b** (Figure 2). When trying to reproduce the elution conditions of the original report (Figure 2a),^{10a} no separation of the enantiomers was observed (Figure 2b).¹⁸ On the opposite side, baseline separation was achieved with several other chiral columns including Chiralpak IC (Figure 2c).¹² Moreover, a sample of enantiopure polyhydroquinoline **4b** (enantiomer eluted second in the HPLC conditions presented in Figure 2c) was obtained via semipreparative HPLC. Its specific optical rotation (CHCl₃, λ = 589 nm, c = 25 mg mL⁻¹, 25 °C) is -105, to be compared with the +16 value given in the literature in the same conditions.^{10a} The strong deviation between absolute values of the optical rotations is an additional indication that the product from the original report was probably not enantiopure **4b**.

To finish our study, we evaluated the behavior of several other aldehydes presented in the initial report on the enantioselective synthesis of polyhydroquinolines **4c–4f** (Table 2).^{10a} In line with the observation on the standard substrate, no enantioinduction was observed for both products **4c** and **4d**, obtained from an electron-rich aldehyde and an electron-poor one, respectively (entries 1 and 2). In a similar fashion, 4-alkyl-

substituted polyhydroquinolines **4e** was also formed as a racemic product (entry 3). Recently, Natale and co-workers applied the title method to a few oxazole-4-carbaldehydes using TRIP catalyst **III**.¹⁹ Once again, HPLC traces presented in this publication are not fully convincing since there are discrepancies between retention times on chromatograms of the racemic product and the one obtained with the chiral phosphoric acid catalyst.¹² Moreover, the authors claim enantiomeric excesses higher than 90%, but without giving precise values. When trying to reproduce these results, we observed the formation of the expected product **4f** in moderate yield and with marginal enantioselectivity (7% ee, entry 4).

As a summary, a careful survey on the multicomponent phosphoric-acid-catalyzed synthesis of polyhydroquinolines¹⁰ was conducted. Contrary to the initial report, our study shed a new light on this transformation, where the organocatalyst actually seems to have no decisive influence either on the reaction rate or on the enantiodetermining step. As a more general conclusion, the present study along with similar ones²⁰ should be seen as a reminder for both authors working in enantioselective catalysis and reviewers that very careful attention should be placed on the evaluation of the solidity of experimental evidence proposed to determine enantiomeric excess values.

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Notes

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