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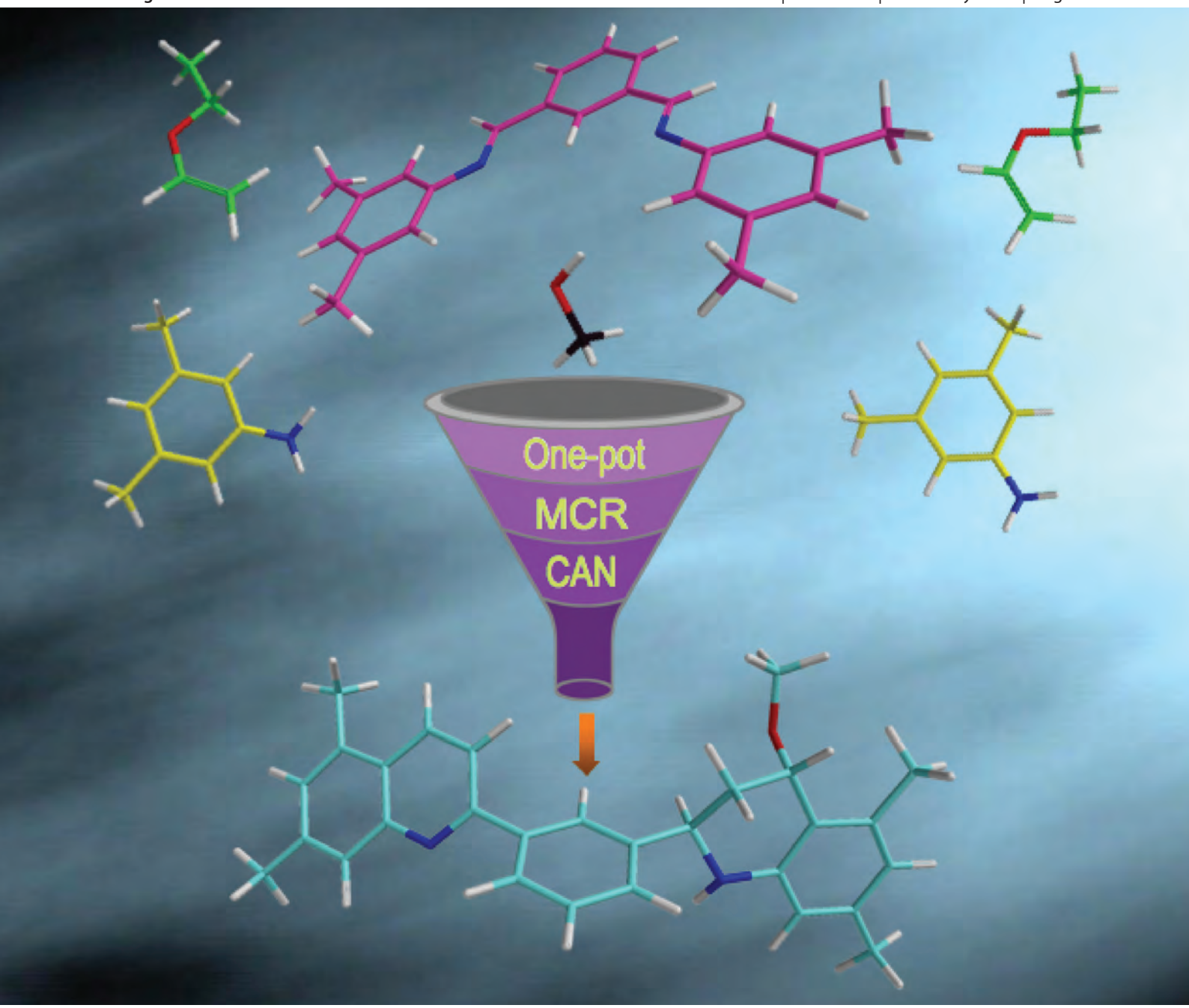


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J. Carlos Menéndez *et al.*

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# Diastereoselective, multicomponent access to *trans*-2-aryl-4-arylamino-1,2,3,4-tetrahydroquinolines *via* an AA'BC sequential four-component reaction and their application to 2-arylquinoline synthesis†

Pascual Ribelles, Vellaisamy Sridharan, Mercedes Villacampa, Mª Teresa Ramos and J. Carlos Menéndez*

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The CAN-catalyzed reaction between 3,5-disubstituted anilines, vinyl ethers and aromatic aldehydes leads to *trans*-2-aryl-4-arylaminotetrahydroquinolines, in an AA'BC sequential multicomponent transformation related to the Povarov reaction that was also extended to the use of a second aniline as the C-4 substituent. The unusual *trans* stereochemistry was explained by stabilization of the corresponding intermediate by intramolecular hydrogen bonding. The presence of the 4-anilino substituent allowed adapting the method to the synthesis of 4-unsubstituted 2-arylquinolines, by treatment of the crude product from the MCR with $FeCl_3$ in methanol.



## Introduction

Heterocycles are the most important single class of compounds in the pharmaceutical and agrochemical industries, and comprise around 60% of all drug substances in therapeutic use. The tetrahydroquinoline ring system, in particular, is a very common structural motif and is found in a large number of bioactive natural products and pharmacologically relevant compounds. Owing to the significance of these scaffolds in drug discovery and medicinal chemistry, the development of new methodologies for the synthesis of tetrahydroquinoline derivatives continues to be a very active field of research.[1,2]

Among the many bioactive 1,2,3,4-tetrahydroquinolines, compounds bearing a nitrogen substituent at C-4 are particularly important. Fig. 1 summarizes the structures of a few representative examples, including torcetrapib **1**,[3] a potent inhibitor of cholesteryl ester transfer protein (CETP) that was studied clinically for the treatment of hypercholesterolemia, although it was later withdrawn due to an unexpected high mortality in Phase III clinical studies, and has served as the stimulus to the preparation of other families of analogues.[4] Other pharmacologically relevant compounds belonging to this group include *cis*-2-methyl-4-aminotetrahydroquinolines **2**, which have been characterized as antagonists of the CRTH2 receptor, a chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes.[5] As exemplified by compounds in Fig. 1, most available biological data for 2,4-disubstituted-1,2,3,4-tetrahydroquinolines correspond to those with a *cis* relative configuration, probably due to difficulties in preparing their *trans* analogues. Furthermore, in spite of advances in synthetic methodology, some types of substitution in

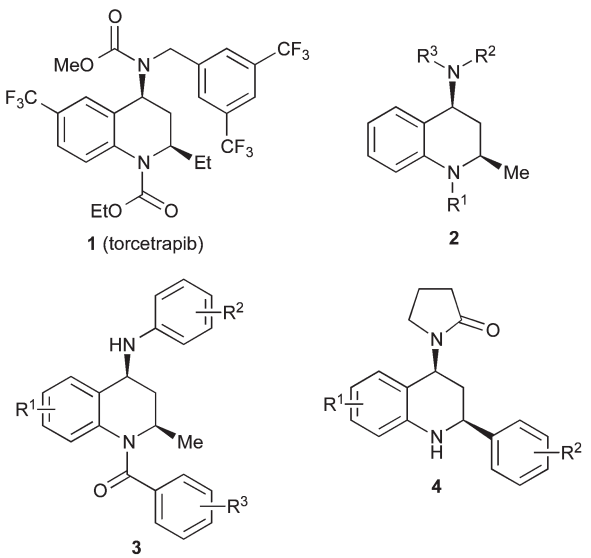


**Fig. 1** Some bioactive tetrahydroquinolines with a C-4 nitrogen substituent.

*Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain. E-mail: josecm@farm.ucm.es; Fax: +34 91 3941822; Tel: +34 91 3941840*

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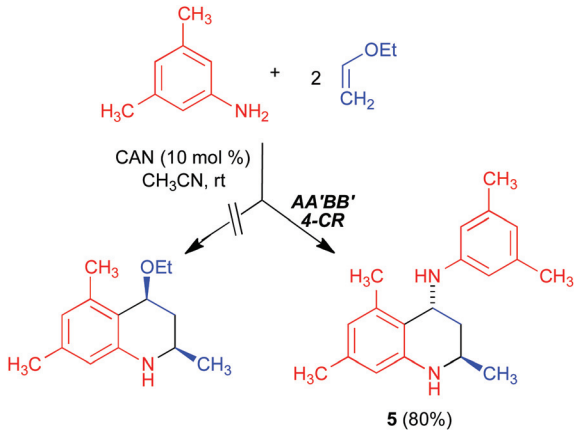
tetrahydroquinolines (*e.g.* at C-5) remain relatively unaccessible. In this context, we describe here a Povarov-type reaction that leads to *trans*-2-aryl-4-arylamino-1,2,3,4-tetrahydroquinolines with additional substitution at the C-5 and other positions of the benzene ring, together with two synthetic applications of these compounds.

The formal [4 + 2] cycloaddition reaction between aromatic imines and electron-rich alkenes to give 1,2,3,4-tetrahydroquinolines was developed in the 1960s and is known as the Povarov reaction.[6] It can also be performed in a three-component fashion and received relatively little attention until the discovery of its efficient catalysis by lanthanide triflates,[7] which prompted its widespread use in the synthesis of tetrahydroquinolines and related fused systems.[8] While alkyl ethers are the most commonly employed dienophiles, reactions with *N*-vinylamides are also quite common, and allow the synthesis of compounds bearing nitrogen substituents at C-4. The reactions using acyclic dienophiles, which provide access to non-fused 1,2,3,4-tetrahydroquinoline systems, have received relatively little attention in the literature, probably because of the lower reactivity of these compounds when compared with their cyclic counterparts. Regarding the stereochemical outcome of the Povarov reaction, the use of cyclic dienophiles tends to give mixtures of the two diastereomers arising from the *exo*- and *endo*-approaches.[9] Reactions starting from acyclic dienophiles are normally accepted to give *cis*-2,4-disubstituted tetrahydroquinolines as the major or only products,[10] although one example of the opposite diastereoselection has been described for an organocatalyzed version of the reaction carried out under reaction conditions rather different than the usual ones and involving the presence of a chiral thiourea catalyst able to interact with the reactants *via* hydrogen bonding.[11]

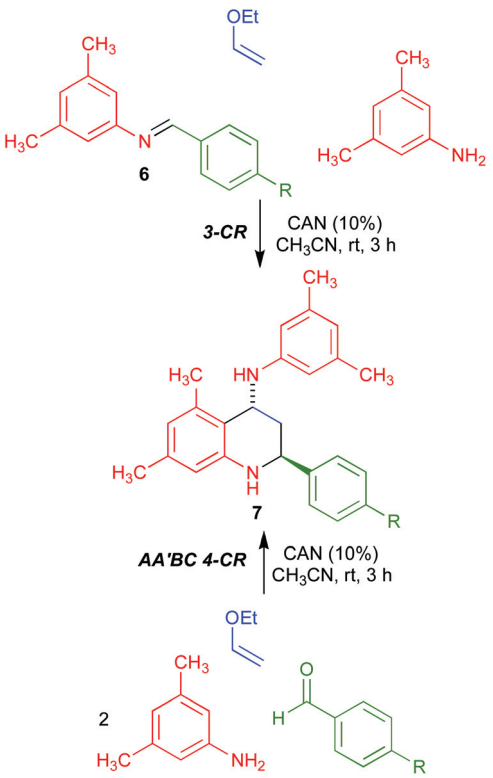
## Results and discussion

The reaction between anilines and vinyl ethers in the presence of cerium(IV) ammonium nitrate provides ready access to *cis*-2-methyl-4-alkoxy-1,2,3,4-tetrahydroquinolines.[12] While striving to extend the scope of this transformation, we have discovered that the use of 3,5-dimethylaniline as the starting material caused the reaction to deviate to a different course, affording the *trans*-2-methyl-4-arylamino-1,2,3,4-tetrahydroquinoline derivative **5** in a fully diastereoselective fashion (Scheme 1). This transformation can be considered as one of the few examples of reactions taking place *via* an AA′BB′ multicomponent mechanism, since the final product contains two units of each of two components, all of which have different chemical roles in the process and hence react in a chemodifferentiated fashion. The ABB′-type multicomponent reactions and related transformations have attracted much attention because of their ability to generate molecular diversity and complexity from a very reduced number of starting materials.[13]

In view of the interest in this unexpected transformation, we sought to broaden its scope. We first decided to explore the possibility of introducing an aromatic substituent at C-2, and




**Scheme 1** AA′BB′ multicomponent reaction leading to *trans*-4-arylamino-2-methyl-1,2,3,4-tetrahydroquinolines.




**Scheme 2** Three- and four-component access to *trans*-2-aryl-4-(3,5-dimethylphenylamino)-1,2,3,4-tetrahydroquinolines.

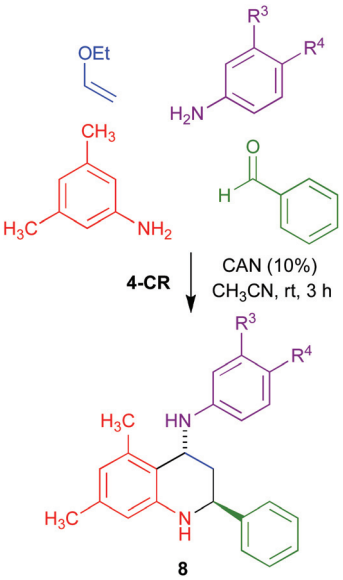
to this end we examined the three-component reaction between isolated aromatic imines **6**, 3,5-dimethylaniline and ethyl vinyl ether, which afforded compounds **7** in excellent yields. An AA′BC four-component sequential protocol with no isolation of the imine was then examined, involving mixing equimolecular amounts of 3,5-dimethylaniline and the aldehyde, together with the catalyst, for about 1 min, followed by addition of ethyl vinyl ether and a second molecule of the aniline. This modified method gave very similar results to the three-component one (Scheme 2 and Table 1).

**Table 1** Structures and yields of compounds **7a–e**[a]

| Entry | Compound | R | Yield (%) (3-CR) | Yield (%) (4-CR) |
|---|---|---|---|---|
| 1 | **7a** | H | 85 | 83 |
| 2 | **7b** | Me | 86 | 86 |
| 3 | **7c** | OMe | 89 | 87 |
| 4 | **7d** | Cl | 88 | 87 |
| 5 | **7e** | Br | 87 | 87 |

[a] Isolated yields after chromatography.




**Scheme 3** Four-component reaction leading to *trans*-2-aryl-4-(arylamino)-1,2,3,4-tetrahydroquinolines containing two different aniline fragments.

**Table 2** Synthesis of *trans*-2-aryl-4-(arylamino)-1,2,3,4-tetrahydroquinolines **8a–c**

| Entry | Compound | $R^3$ | $R^4$ | Yield[a] (%) |
|---|---|---|---|---|
| 1 | **8a** | H | Cl | 87 |
| 2 | **8b** | H | Br | 88 |
| 3 | **8c** | Cl | Cl | 72 |

[a] Isolated yields after chromatography.

In view of the almost instantaneous formation of the intermediate imine, we reasoned that it should be feasible to broaden the scope of our method by devising a modified four-component reaction involving two different anilines. Thus, *in situ* generation of the imine derived from 3,5-dimethylaniline as described above, followed by immediate addition of a second aniline and ethyl vinyl ether, afforded compounds **8** in good to excellent yields, without any trace of products derived from a transimination reaction (Scheme 3 and Table 2).

As previously mentioned, the generation of a *trans*-2,4-disubstituted 1,2,3,4-tetrahydroquinoline is unusual in Povarov chemistry, which almost always gives *cis* derivatives. For this reason, it was important to establish unambiguously the relative configuration of compounds **5**, **7**, and **8**. Our initial

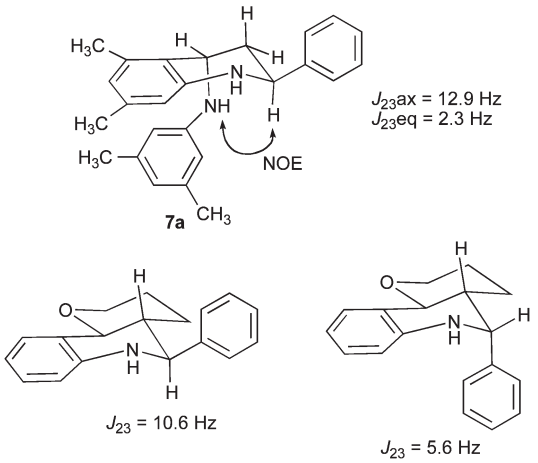


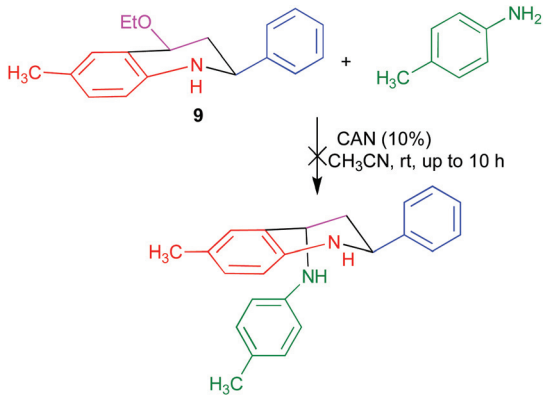

**Fig. 2** NMR evidence for the assignment of a *trans* stereochemistry to compounds **7** and **8**.

**Fig. 3** X-Ray diffraction structure of compound **7b**.

assignment of the *trans* structure with an axial 4-arylamino group was based on the coupling constants of the H-2 proton; for instance, in compound **7a** this signal is observed as a doublet of doublets with *J* values of 12.9 and 2.3 Hz, which are compatible only with an axial arrangement for H-2. For comparison purposes, the $J_{23}$ values of two previously reported related compounds are given in Fig. 2. Furthermore, a NOESY experiment proved the spatial proximity of the H-2 and Ar–NH protons, which can only be explained by a *trans* structure with an axial anilino substituent. Finally, the structure of compounds **7** was definitively confirmed by an X-ray diffraction study of **7b**, which is shown in Fig. 3.[14]

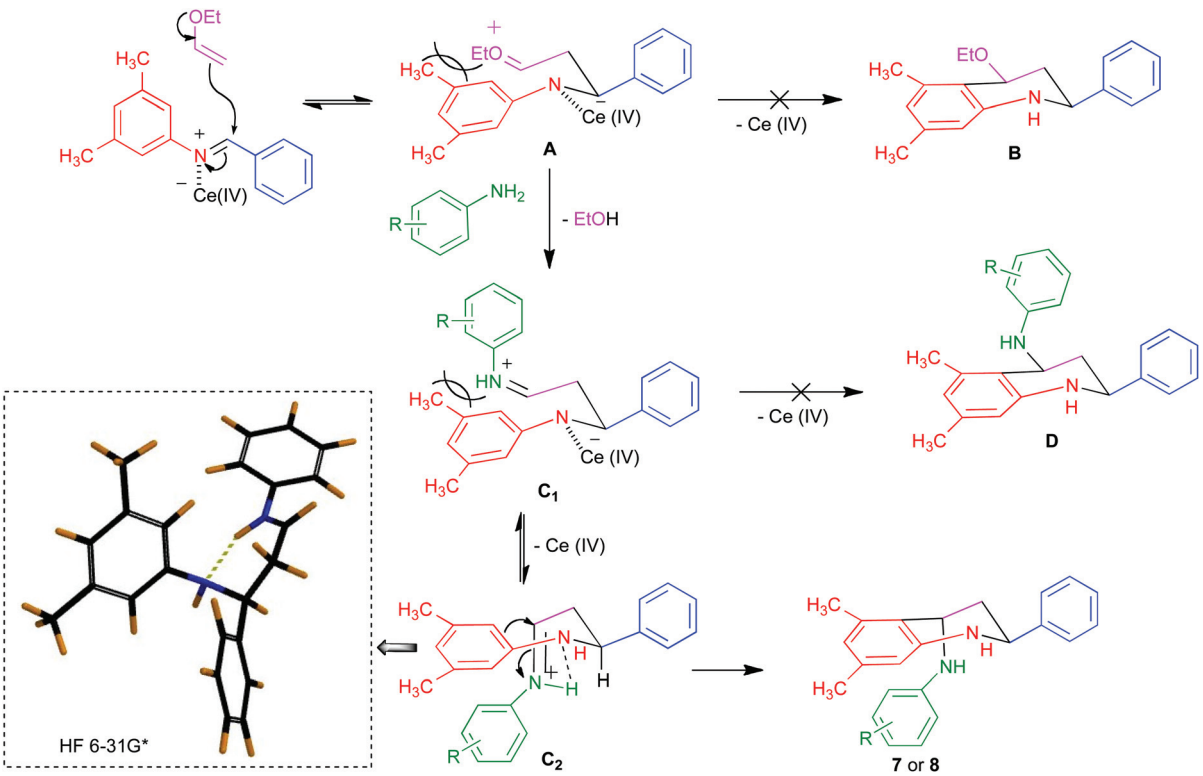
Regarding the mechanism of the reaction, there were several points that needed to be established. In the first place, due to the fact that Ce(IV) species normally act as one-electron oxidants,[15] our transformation might be expected to take place *via* a radical mechanism. However, this possibility was discarded by a control experiment carried out in the presence of a large amount of 1,1-diphenylethylene, a well-known radical

trap, which showed no decrease in yield for the reaction leading to **7a**. This suggests that in this case CAN is acting as a Lewis acid catalyst, a behaviour that has been established in recent years on a firm basis.[16] Secondly, the unusual preference for the *trans* stereochemistry had to be explained. A first mechanistic possibility that could account for this result would be a pathway comprising a normal Povarov reaction leading to a *trans*-4-ethoxy-2-aryl-1,2,3,4-tetrahydroquinoline and a subsequent nucleophilic displacement of the alkoxy group by a second molecule of aniline, with inversion of the configuration at C-4. While we were unable to prepare an example of this type of intermediate from 3,5-dimethylaniline because **7** or **8** were obtained instead, compound **9** was available to us from our previous work on CAN-catalyzed Povarov reactions,[17] and we found that its treatment with *p*-toluidine under our usual conditions did not lead to a 4-anilino derivative, but only to recovered starting materials (Scheme 4).




**Scheme 4** Experiment that discarded a normal Povarov mechanism followed by displacement of the 4-alkoxy group by a molecule of toluidine.

With this result in mind, we propose the mechanism summarized in Scheme 5 to explain our results. Oxonium intermediate **A**, from addition of vinyl ether to the imine generated from the starting aniline and aldehyde, cannot undergo the usual Friedel–Crafts-like cyclization leading to the normal Povarov product **B** owing to steric compression between the alkoxy substituent and the C-3 methyl. This allows the attack of a second molecule of aniline to **A**, giving iminium species $\mathbf{C_1}$, which has the same problems as **A** to cyclize to a *cis*-tetrahydroquinoline **D**. However, in this case a conformational change to $\mathbf{C_2}$ is possible, in spite of an unfavorable interaction with the "axial" C-2 proton, owing to its stabilization by formation of an intramolecular hydrogen bond, which was confirmed by an *ab initio* study of $\mathbf{C_2}$ at the HF 6-31G* level. Furthermore, the *trans* final products are more stable according to computational studies; for instance, **7a** was found to be 5.25 kcal $mol^{-1}$ more stable than its *cis* isomer at the B3LYP/6-31G* level. While this is not the usual behaviour for Povarov reactions, which normally have similar stabilities for the two possible diastereomeric final products,[10f] in our case the unstabilizing effect of the interaction between the C-5 methyl and the equatorial C-4 substituent in the *cis* compound has to

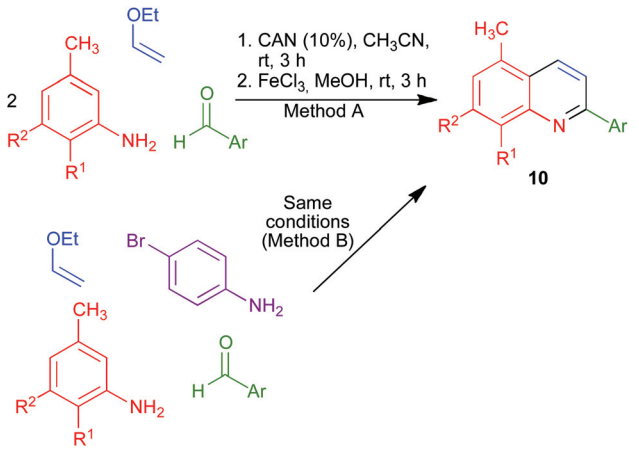



**Scheme 5** Mechanistic proposal explaining the formation and *trans* stereochemistry of compounds **7** and **8**.

be considered. As a precedent, we will cite the reaction of *N*-vinylpyrrolidone with a 3,5-disubstituted aromatic imine to give a 1 : 1 mixture of the *cis* and *trans* Povarov products and this mixture could be epimerized to the *trans* product, showing that the latter is thermodynamically more stable.[18]

While the preparation of compounds **7** and **8** was interesting in itself, we also planned to investigate their application as synthetic intermediates, prompted by the presence of a good leaving group at C-4. Due to the pharmacological importance of 2-arylquinolines,[19] we started this study by examining their aromatization with concomitant elimination of the 4-anilino group, using the crude of the reaction leading to compound **7a** as the model substrate (Scheme 6 and Table 3). We compared several methods, the first of which was based on the treatment of the crude **7a** with hydrochloric acid, which gave 65% of **10a** in our first experiment but turned out to be not general (entry 1). The traditional dehydrogenation with Pd–C in refluxing toluene gave **10a** in 89% yield (entry 2), but we selected as our method of choice the reaction with iron trichloride in methanol, which gave virtually the same yield and was experimentally more convenient while having the additional advantage of involving the use of milder conditions and a much cheaper reagent (entry 3). We then set out to extend the scope of the method by completing the examples summarized in entries 4–10 of Table 3, which show that the reaction consistently proceeded in good to excellent yields. It will be noted that the step leading to the intermediate tetrahydroquinoline could be carried out either by the three-component or the four-component protocols previously described. Interestingly, our method allows the preparation of quinolines bearing a substituent at C-5, which cannot be easily done with many of the known methods. It can be regarded as complementary to Povarov reactions involving alkynes as dienophiles, which cannot be readily adapted to the preparation of quinolines bearing only a C-2 substituent at the heterocyclic ring.[20] Furthermore, our protocol provides compounds with substitution patterns (*e.g.* 2,5-disubstitution) that are not readily accessible by other methods.




**Scheme 6** Synthesis of 2-arylquinolines from anilines, aromatic aldehydes and vinyl ethers.

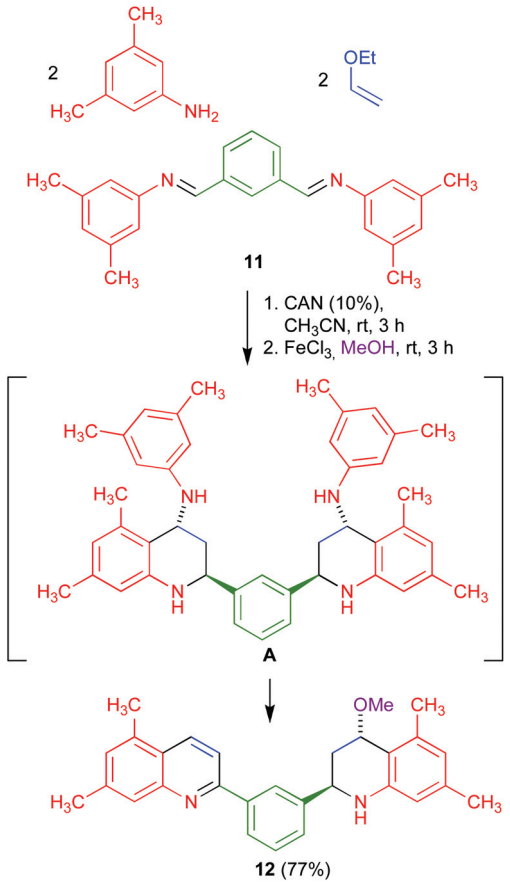
**Table 3** Scope and yields of the synthesis of 2-arylquinolines **10**

| Entry | Compound | $R^1$ | $R^2$ | Ar | Method | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | **10a** | H | Me | $C_6H_5$ | B | 65[b] |
| 2 | **10a** | H | Me | $C_6H_5$ | B | 89[c] |
| 3 | **10a** | H | Me | $C_6H_5$ | B | 87[d] |
| 4 | **10b** | Me | H | 4-$ClC_6H_4$ | A | 62 |
| 5 | **10c** | H | Me | 4-$MeC_6H_4$ | A | 95 |
| 6 | **10d** | H | Me | 4-$MeOC_6H_4$ | A | 92 |
| 7 | **10e** | H | Me | 4-$ClC_6H_4$ | A | 83 |
| 8 | **10f** | H | Me | 4-$BrC_6H_4$ | A | 86 |
| 9 | **10g** | H | Me |  | B | 75 |
| 10 | **10h** | H | Me |  | B | 90 |

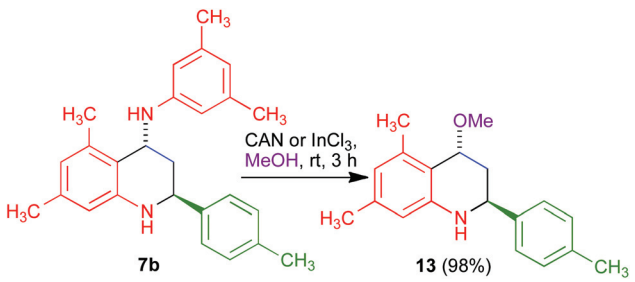
[a] Isolated yields after chromatography. [b] Conditions for the aromatization step: aqueous HCl–$CH_2Cl_2$, rt, 3 h. [c] Conditions for the aromatization step: Pd–C, toluene, reflux, 6 h. [d] Conditions for the aromatization step: $FeCl_3$, MeOH, rt, 3 h.

In an effort to extend the application of this strategy to the generation of structurally more complex quinoline systems, we also studied a reaction involving a dialdehyde. Thus, treatment of imine **11** (prepared by a standard method from 3,5-dimethylaniline and *m*-phthalaldehyde) with 2 equiv. of 3,5-dimethylaniline and 2 equiv. of ethyl vinyl ether under our usual conditions afforded a mixture of partially aromatized products that was taken directly to the $FeCl_3$ oxidation to yield compound **12** in 77% yield (Scheme 7). This reaction presumably proceeded *via* the formation of bis-tetrahydroquinoline **A** as an intermediate, followed by aromatization of one of the tetrahydroquinoline rings by elimination of the corresponding arylamino unit to give a dihydroquinoline, followed by $Fe^{3+}$-induced oxidation. In the other ring, the arylamino group is displaced by a molecule of methanol with retention of *trans* relative configuration with respect to the aryl substituent at C-2, as judged by the coupling constants between H-3 and H-4 ($J_{3(ax)-4}$ = 3.0 Hz, $J_{3(eq)-4}$ = 2.3 Hz). This indicates an $S_N1$ mechanism in which a Lewis acid-generated intermediate cation is diastereoselectively attacked by a molecule of methanol from the bottom face to avoid a repulsive interaction of the C-4 hydrogen with the $C_5$-methyl substituent in the transition state. The reason for the different behaviour of both rings can be explained by the almost planar structure of 2-phenylquinolines in comparison to biphenyls;[21] this creates a steric hindrance for the formation of a double bond in the third ring, which would bring the new vinylic proton approximately to the same plane.

In order to provide experimental support to the mechanistic proposal, we studied the reaction between compound **7b** and methanol under our reaction conditions, and found that it afforded the corresponding *trans*-4-alkoxy derivative **13** in 98% yield (Scheme 8). Again, the *trans* arrangement for the substituents was proved by the $J_{34}$ values ($J_{3(ax)-4}$ = 3.1 Hz, $J_{3(eq)-4}$ = 2.6 Hz). In contrast to its more complex analogue **12** and in line with our explanation for the stability of the latter, compound **13** showed a considerable tendency to aromatize to **10c**.




**Scheme 7** Synthesis of compound **12**.




**Scheme 8** An experiment proving the $S_N1$ displacement of the 3,5-dimethylphenylamino substituent by methanol, with retention of the C-4 configuration.

The preparation of **13** could be carried out with equal efficiency in the presence of indium trichloride, underscoring the fact that CAN behaves as a Lewis acid under our reaction conditions.

## Conclusions

In conclusion, we have developed an efficient method for the synthesis of *trans*-2-aryl-4-arylamino-tetrahydroquinolines from 3,5-disubstituted anilines, vinyl ethers and aromatic aldehydes. This one-pot reaction can be considered as an AA′BC chemodivergent, sequential multicomponent transformation related to the Povarov reaction, and it was also extended to the use of a second aniline as the C-4 substituent. The final products showed an unusual *trans* relative configuration for the C-2 and C-4 substituents, which was explained by stabilization of the corresponding intermediate by intramolecular hydrogen bonding. The presence of the 4-anilino substituent allowed us to develop a method for the synthesis of not readily accessible 4-unsubstituted 2-arylquinolines, by treatment of the crude product from the MCR with $FeCl_3$ in methanol.

## Experimental section

### General experimental information

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with a fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 μm) or neutral alumina (Merck S22). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as KBr pellets or as thin films on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for $^1$H and 63 MHz for $^{13}$C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer.

**(±)-(2*R**,4*R**)-4-(3,5-Dimethylphenylamino)-2,5,7-trimethyl-1,2,3,4-tetrahydroquinoline (5).** To a stirred solution of 3,5-dimethylaniline (363 mg, 3 mmol) and ethyl vinyl ether (540 mg, 7.5 mmol) in acetonitrile (15 mL) was added CAN (164.4 mg, 10 mol%). The reaction was stirred at room temperature for 2 h. After completion of the reaction, as indicated by TLC, water (20 mL) was added and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (anhydrous $Na_2SO_4$), and evaporated. The residue was purified by silica gel column chromatography eluting with a petroleum ether–ethyl acetate (96 : 4, v/v) mixture, yielding 353 mg (80%) of **5**. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.25 (d, 3H, $J$ = 6.2 Hz, $C_2$-$CH_3$), 1.49 (td, 1H, $J$ = 12.8 and 3.7 Hz, H-$3_{ax}$); 2.25 (m, 1H, H-$3_{eq}$); 2.25 (s, 3H, $CH_3$); 2.28 (s, 3H, $CH_3$); 2.32 (s, 6H, 2 $CH_3$); 3.43–3.51 (m, 1H, H-2); 3.75 (br s, 1H, NH); 3.85 (br s, 1H, NH); 4.57 (br s, 1H, H-4); 6.31 (s, 1H, H-4′); 6.33 (s, 2H, H-2′ and H-6′); 6.43 (s, 1H, H-8); 6.45 (s, 1H, H-6). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 19.1, 21.6, 22.1, 22.6, 36.0, 42.4, 46.6, 110.6, 113.3, 117.3, 119.4, 121.0, 138.6, 139.3, 139.6, 145.5, 147.1. Analysis: Calculated for $C_{20}H_{26}N_2$ (M = 294.43): C, 81.59; H, 8.90; N, 9.51. Found: C, 81.34; H, 8.75; N, 9.32.

### Synthesis of compounds 7 and 8. General procedures

**(a) Three-component method.** A mixture of 3,5-dimethylaniline (1 equiv.) and the suitable aromatic aldehyde (1 equiv.)

was stirred vigorously with a glass rod for 5 min and then it was kept at room temperature overnight in an open beaker placed in a fume cupboard to afford imines **6**, which were characterized spectroscopically and used without further purification (see below their spectral data). To a stirred solution of the suitable imine (3 mmol) and CAN (10%) in acetonitrile (10 mL) was added dropwise a solution of 3,5-dimethylaniline (1 equiv.) and ethyl vinyl ether (1 equiv.) in acetonitrile. The reaction mixture was stirred at room temperature for 3 h and upon completion, as judged by TLC, it was diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). In some cases where an emulsion was formed, the dichloromethane extracts were shaken with brine (10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and filtered, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on neutral alumina, eluting with a 98 : 2 petroleum ether–ethyl acetate mixture.

**(b) Four-component method.** To a stirred solution of 3,5-dimethylaniline (3 mmol), the suitable aromatic aldehyde (1 equiv.) and CAN (10 mol%) in acetonitrile (10 mL) was added dropwise a mixture of 1 equiv. of 3,5-dimethylaniline (preparation of **7**) or another aniline (preparation of **8**) and ethyl vinyl ether (1 equiv.) in acetonitrile (5 mL). Workup and purification were carried out as in the three-component protocol.

**3,5-Dimethyl-*N*-benzylideneaniline (6a).** Yield: 100%, as a pale brown viscous liquid. IR (NaCl) $\bar{\nu}$: 1628 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.44 (s, 6H, 2 $CH_3$); 6.95 (s, 2H, H-2 and H-6); 6.97 (s, 1H, H-4); 7.51–7.58 (m, 3H, H-3′, H-4′ and H-5′); 7.95–8.05 (m, 2H, H-2′ and H-6′); 8.53 (s, 1H, CH═N). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 21.0 (2 $CH_3$); 118.4 (C-2 and C-6); 127.4 (C-4); 128.4 and 128.5 (C-3′,5′ and C-2,6′); 130.9 (C-4′); 136.0 (C-1′); 138.4 (C-3 and C-5); 151.6 (C-1); 159.7 (CH═N).

**3,5-Dimethyl-*N*-(4-methylbenzylidene)aniline (6b).** Yield: 100% as a pale red viscous liquid. IR (NaCl) $\bar{\nu}$: 1627 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.45 (s, 6H, 2 $CH_3$); 2.50 (s, 3H, $CH_3$); 6.94 (s, 2H, H-2 and H-6); 6.96 (s, 1H, H-4); 7.36 (d, $J$ = 7.9 Hz, 2H, H-3′ and H-5′); 7.88 (d, $J$ = 8.0 Hz, 2H, H-2′ and H-6′); 8.49 (s, 1H, CH═N). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 21.0 (2 $CH_3$); 21.2 ($CH_3$); 118.4 (C-2 and C-6); 127.2 (C-4); 128.4 (C-2′ and C-6′); 129.1 (C-3′ and C-5′); 133.5 (C-1′); 138.2 (C-3 and C-5); 141.2 (C-4′); 151.9 (C-1); 159.4 (CH═N).

**3,5-Dimethyl-*N*-(4-methoxybenzylidene)aniline (6c).** Yield: 100% as a pale red viscous liquid. IR (NaCl) $\bar{\nu}$: 1627 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.41 (s, 6H, 2 $CH_3$); 3.91 (s, 3H, $OCH_3$); 6.90 (s, 2H, H-2 and H-6); 6.92 (s, 1H, H-4); 7.03 (d, $J$ = 8.8 Hz, 2H, H-3′ and H-5′); 7.90 (d, $J$ = 8.8 Hz, 2H, H-2′ and H-6′); 8.43 (s, 1H, CH═N). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 21.0 (2 $CH_3$); 55.0 ($OCH_3$); 113.8 (C-3′ and C-5′); 118.4 (C-2 and C-6); 127.0 (C-4); 128.9 (C-1′); 130.1 (C-2′ and C-6′); 138.3 (C-3 and C-5); 152.0 (C-1); 159.0 (CH═N); 161.8 (C-4′).

**3,5-Dimethyl-*N*-(4-chlorobenzylidene)aniline (6d).** Yield: 100% as a pale red viscous liquid. IR (NaCl) $\bar{\nu}$: 1627 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.42 (s, 6H, 2 $CH_3$); 6.91 (s, 2H, H-2 and H-6); 6.96 (s, 1H, H-4); 7.49 (d, $J$ = 8.4 Hz, 2H, H-3′ and H-5′); 7.88 (d, $J$ = 8.4 Hz, 2H, H-2′ and H-6′); 8.46 (s, 1H, CH═N). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 21.1 (2 $CH_3$); 118.5 (C-2 and C-6); 127.7 (C-4); 128.8 (C-3′ and C-5′); 129.7 (C-2′ and C-6′); 134.6 (C-1′); 136.9 (C-4′); 138.5 (C-3 and C-5); 151.4 (C-1); 158.0 (CH═N).

**3,5-Dimethyl-*N*-(4-bromobenzylidene)aniline (6e).** Yield: 100%, as a yellow solid. IR (NaCl) $\bar{\nu}$: 1627 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.40 (s, 6H, 2 $CH_3$); 6.89 (s, 2H, H-2 and H-6); 6.94 (s, 1H, H-4); 7.64 (d, $J$ = 8.5 Hz, 2H, H-3′ and H-5′); 7.80 (d, $J$ = 8.5 Hz, 2H, H-2′ and H-6′); 8.43 (s, 1H, CH═N). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 21.2 (2 $CH_3$); 118.5 (C-2 and C-6); 125.6 (C-4′); 127.8 (C-4); 130.0 (C-3′ and C-5′); 131.8 (C-2′ and C-6′); 135.1 (C-1′); 138.7 (C-3 and C-5); 151.5 (C-1); 158.3 (CH═N).

**(±)-(2*S**,4*R**)-4-(3,5-Dimethylphenylamino)-2-phenyl-5,7-dimethyl-1,2,3,4-tetrahydroquinoline (7a).** White solid, mp 125–126 °C. IR (NaCl) $\bar{\nu}$: 3390, 1599 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.90 (td, $J$ = 12.9, 3.6 Hz, 1H, H-$3_{ax}$); 2.27 (s, 3H, $CH_3$); 2.29 (s, 9H, 3 $CH_3$); 2.41 (dt, $J$ = 12.9, 4.5, 2.3 Hz, 1H, H-$3_{eq}$); 3.84 (br s, 1H, NH); 4.14 (br s, 1H, NH-1); 4.46 (dd, $J$ = 12.9, 2.3 Hz, 1H, H-2); 4.60 (br s, 1H, H-4); 6.35 (s, 3H, H-2″, H-6″ and H-8); 6.43 (s, 1H, H-4″); 6.50 (s, 1H, H-6); 7.33–7.48 (m, 5H, Ph). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 19.1 ($CH_3$); 21.6 ($CH_3$); 22.1 (2 $CH_3$); 37.5 (C-3); 46.9 (C-4); 52.1 (C-2); 110.6 (C-2″ and C-6″); 113.5 (C-8); 117.1 (C-4a); 119.6 (C-4″); 121.3 (C-6); 127.5 (C-2′ and C-6′); 128.1 (C-4″); 129.0 (C-3′ and C-5′); 138.8 (C-7); 139.3 (C-5); 139.5 (C-3″ and C-5″); 144.3 (C-1′); 145.3 (C-8a); 147.1 (C-1″). Analysis: Calculated for $C_{25}H_{28}N_2$ (M = 356.23): C, 84.23; H, 7.92; N, 7.86. Found: C, 84.01; H, 7.80; N, 7.92.

**(±)-(2*S**,4*R**)-4-(3,5-Dimethylphenylamino)-2-(4-methylphenyl)-5,7-dimethyl-1,2,3,4-tetrahydroquinoline (7b).** White solid, mp 129–130 °C. IR (NaCl) $\bar{\nu}$: 3392, 1599 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.87 (td, $J$ = 12.5, 3.6 Hz, 1H, H-$3_{ax}$); 2.25 (s, 3H, $CH_3$); 2.28 (s, 9H, 3 $CH_3$); 2.35–2.41 (m, 1H, H-$3_{eq}$); 2.38 (s, 3H, $CH_3$); 3.81 (d, $J$ = 4.8 Hz, 1H, NH); 4.11 (br s, 1H, NH); 4.42 (dd, $J$ = 12.5, 2.1 Hz, 1H, H-2); 4.59 (br s, 1H, H-4); 6.33 (s, 3H, H-2″, H-6″ and H-8); 6.41 (br s, 1H, H-4″); 6.48 (br s, 1H, H-6); 7.19 (d, $J$ = 8.0 Hz, 2H, H-3′ and H-5′); 7.34 (d, $J$ = 8.0 Hz, 2H, H-2′ and H-6′). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 19.1 ($CH_3$); 21.5 ($CH_3$); 21.6 ($CH_3$); 22.1 (2 $CH_3$); 37.5 (C-3); 46.9 (C-4); 51.8 (C-2); 110.6 (C-2″ and C-6″); 113.5 (C-8); 117.0 (C-4a); 119.5 (C-4″); 121.2 (C-6); 127.3 (C-2′ and C-6′); 129.7 (C-3′ and C-5′); 137.8 (C-4′); 138.8 (C-7); 139.3 (C-5); 139.5 (C-3″ and C-5″); 141.3 (C-1′); 145.3 (C-8a); 147.1 (C-1″). Analysis: Calculated for $C_{26}H_{30}N_2$ (M = 370.24): C, 84.28; H, 8.16; N, 6.76. Found: C, 84.09; H, 7.98; N, 6.67.

**(±)-(2*S**,4*R**)-4-(3,5-Dimethylphenylamino)-2-(4-methoxyphenyl)-5,7-dimethyl-1,2,3,4-tetrahydroquinoline (7c).** White solid. IR (NaCl) $\bar{\nu}$: 3391, 1599 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.86 (td, $J$ = 12.5, 3.6 Hz, 1H, H-$3_{ax}$); 2.25 (s, 3H, $CH_3$); 2.28 (s, 9H, 3 $CH_3$); 2.31–2.41 (m, 1H, H-$3_{eq}$); 3.81 (d, $J$ = 6.0 Hz, 1H, NH); 3.84 (s, 3H, $OCH_3$); 4.09 (br s, 1H, NH); 4.40 (dd, $J$ = 11.9, 1.9 Hz, 1H, H-2); 4.59 (br s, 1H, H-4); 6.33 (s, 3H, H-2″, H-6″ and H-8); 6.41 (s, 1H, H-4″); 6.48 (s, 1H, H-6); 6.91 (d, $J$ = 8.7 Hz, 2H, H-3′ and H-5′); 7.37 (d, $J$ = 8.6 Hz, 2H, H-2′ and H-6′).

$^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 19.1 ($CH_3$); 21.6 ($CH_3$); 22.1 (2 $CH_3$); 37.4 (C-3); 46.9 (C-4); 51.4 (C-2); 55.8 ($OCH_3$); 110.6 (C-2″ and C-6″); 113.5 (C-8); 114.3 (C-3′ and C-5′); 117.0 (C-4a); 119.7 (C-4″); 121.2 (C-6); 128.5 (C-2′ and C-6′); 136.4 (C-1′); 138.8 (C-7); 139.3 (C-5); 139.5 (C-3″ and C-5″); 145.3 (C-8a); 147.1 (C-1″); 159.5 (C-4′). Analysis: Calculated for $C_{26}H_{30}N_2O$ (M = 386.24): C, 80.79; H, 7.82; N, 7.25. Found: C, 80.50; H, 7.64; N, 7.25.

**(±)-(2*S**,4*R**)-4-(3,5-Dimethylphenylamino)-2-(4-chlorophenyl)-5,7-dimethyl-1,2,3,4-tetrahydroquinoline (7d).** White solid, mp 137–138 °C. IR (NaCl) $\bar{\nu}$: 3390 (NH), 1598 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.84 (td, $J$ = 12.5, 3.5 Hz, 1H, H-3$_{ax}$); 2.25 (s, 3H, $CH_3$); 2.29 (s, 9H, 3 $CH_3$); 2.31–2.41 (m, 1H, H-3$_{eq}$); 3.79 (d, $J$ = 5.3 Hz, 1H, NH); 4.08 (br s, 1H, NH-1); 4.44 (dd, $J$ = 12.0, 2.1 Hz, 1H, H-2); 4.59 (br s, 1H, H-4); 6.33 (s, 2H, H-2″ and H-6″); 6.36 (s, 1H, H-8); 6.43 (s, 1H, H-4″); 6.50 (s, 1H, H-6); 7.30–7.43 (m, 4H, H-2′, H-3′, H-5′ and H-6′). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 19.1 ($CH_3$); 21.6 ($CH_3$); 22.0 (2 $CH_3$); 37.6 (C-3); 46.8 (C-4); 51.6 (C-2); 110.5 (C-2″ and C-6″); 113.6 (C-8); 117.1 (C-4a); 119.7 (C-4″); 121.5 (C-6); 128.8 (C-3′ and C-5′); 129.1 (C-2′ and C-6′); 133.6 (C-4′); 138.8 (C-7); 139.3 (C-5); 139.6 (C-3″ and C-5″); 142.8 (C-1′); 145.0 (C-8a); 147.0 (C-1″). Analysis: Calculated for $C_{25}H_{27}ClN_2$ (M = 390.19): C, 76.80; H, 6.96; N, 7.17. Found: C, 76.35; H, 6.78; N, 7.30.

**(±)-(2*S**,4*R**)-4-(3,5-Dimethylphenylamino)-2-(4-bromophenyl)-5,7-dimethyl-1,2,3,4-tetrahydroquinoline (7e).** White solid, mp 130–131 °C. IR (NaCl) $\bar{\nu}$: 3389.6 (NH), 1598.6 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.84 (td, $J$ = 12.5, 3.5 Hz, 1H, H-3$_{ax}$); 2.25 (s, 3H, $CH_3$); 2.29 (s, 9H, 3 $CH_3$); 2.31–2.41 (m, 1H, H-3$_{eq}$); 3.79 (d, $J$ = 4.9 Hz, 1H, NH); 4.08 (br s, 1H, NH); 4.43 (dd, $J$ = 11.8, 1.6 Hz, 1H, H-2); 4.58 (br s, 1H, H-4); 6.33 (s, 2H, H-2″ and H-6″); 6.36 (s, 1H, H-8); 6.43 (s, 1H, H-4″); 6.50 (s, 1H, H-6); 7.33 (d, $J$ = 8.4 Hz, 2H, H-2′ and H-6′); 7.50 (d, $J$ = 8.4 Hz, 2H, H-3′ and H-5′). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 19.1 ($CH_3$); 21.6 ($CH_3$); 22.1 (2 $CH_3$); 37.6 (C-3); 46.8 (C-4); 51.6 (C-2); 110.6 (C-2″ and C-6″); 113.6 (C-8); 117.1 (C-4a); 119.7 (C-4″); 121.6 (C-6); 121.7 (C-4′) 129.2 (C-2′ and C-6′); 132.1 (C-3′ and C-5′); 138.9 (C-7); 139.3 (C-5); 139.6 (C-3″ and C-5″); 143.4 (C-1′); 145.0 (C-8a); 147.0 (C-1″). Analysis: Calculated for $C_{25}H_{27}BrN_2$ (M = 434.14): C, 68.96; H, 6.25; N, 6.43. Found: C, 68.68; H, 6.12; N, 6.61.

**(±)-(2*S**,4*R**)-4-(4-Chlorophenylamino)-2-phenyl-5,7-dimethyl-1,2,3,4-tetrahydroquinoline (8a).** White solid, mp 114–115 °C. IR (NaCl) $\bar{\nu}$: 3395, 1598 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.89 (td, $J$ = 12.8, 3.6 Hz, 1H, H-3$_{ax}$); 2.22 (s, 3H, $CH_3$); 2.28 (s, 3H, $CH_3$); 2.29–2.36 (m, 1H, H-3$_{eq}$); 3.95 (br s, 1H, NH); 4.13 (br s, 1H, NH-1); 4.43 (dd, $J$ = 12.1, 2.3 Hz, 1H, H-2); 4.55 (br s, 1H, H-4); 6.36 (s, 1H, H-8); 6.49 (s, 1H, H-6); 6.62 (d, $J$ = 8.8 Hz, 2H, H-2″ and H-6″); 7.17 (d, $J$ = 8.8 Hz, 2H, H-3″ and H-5″); 7.32–7.46 (m, 5H, Ph). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.9 ($CH_3$); 21.5 ($CH_3$); 37.2 (C-3); 47.2 (C-4); 52.0 (C-2); 113.5 (C-8); 113.7 (C-2″ and C-6″); 116.5 (C-4a); 121.3 (C-6); 122.0 (C-4″); 127.3 (C-2′ and C-6′); 128.1 (C-4′); 129.0 (C-3′ and C-5′); 129.7 (C-3″ and C-5″); 139.0 (C-7); 139.1 (C-5); 143.9 (C-1′); 145.2 (C-8a); 145.5 (C-1″). Analysis: Calculated for $C_{23}H_{23}ClN_2$ (M = 362.15): C, 76.12; H, 6.39; N, 7.72. Found: C, 75.85; H, 6.26; N, 7.89.

**(±)-(2*S**,4*R**)-4-(4-Bromophenylamino)-2-phenyl-5,7-dimethyl-1,2,3,4-tetrahydroquinoline (8b).** White solid, mp 119–120 °C. IR (NaCl) $\bar{\nu}$: 3407, 1590 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.90 (td, $J$ = 12.5, 3.5 Hz, 1H, H-3$_{ax}$); 2.23 (s, 3H, $CH_3$); 2.27 (s, 3H, $CH_3$); 2.33–2.38 (m, 1H, H-3$_{eq}$); 3.96 (br s, 1H, NH); 4.17 (br s, 1H, NH-1); 4.45 (dd, $J$ = 12.1, 2.3 Hz, 1H, H-2); 4.56 (br s, 1H, H-4); 6.35 (s, 1H, H-8); 6.48 (s, 1H, H-6); 6.60 (d, $J$ = 7.9 Hz, 2H, H-2″ and H-6″); 7.30–7.46 (m, 7H, H-3″, H-5″ and Ph). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.9 ($CH_3$); 21.5 ($CH_3$); 37.1 (C-3); 47.1 (C-4); 52.0 (C-2); 108.9 (C-4″); 113.5 (C-8); 114.2 (C-2″ and C-6″); 116.4 (C-4a); 121.3 (C-6); 127.3 (C-2′ and C-6′); 128.1 (C-4′); 129.0 (C-3′ and C-5′); 132.5 (C-3″ and C-5″); 139.1 (C-5 and C-7); 143.9 (C-1′); 145.2 (C-8a); 145.9 (C-1″). Analysis: Calculated for $C_{23}H_{23}BrN_2$ (M = 407.35): C, 67.82; H, 5.69; N, 6.88. Found: C, 67.45; H, 5.53; N 7.25.

**(±)-(2*S**,4*R**)-4-(3,5-Dichlorophenylamino)-2-phenyl-5,7-dimethyl-1,2,3,4-tetrahydroquinoline (8c).** White solid, mp 145–146 °C. IR (NaCl) $\bar{\nu}$: 3404, 1589 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.91 (td, $J$ = 12.8, 3.6 Hz, 1H, H-3$_{ax}$); 2.22 (s, 3H, $CH_3$); 2.27 (s, 3H, $CH_3$); 2.27–2.33 (m, 1H, H-3$_{eq}$); 4.08 (d, $J$ = 6.0 Hz, 1H, NH); 4.16 (br s, 1H, NH-1); 4.38 (dd, $J$ = 12.0, 2.1 Hz, 1H, H-2); 4.53 (br s, 1H, H-4); 6.35 (s, 1H, H-8); 6.49 (s, 1H, H-6); 6.53 (d, $J$ = 1.7 Hz, 2H, H-2″ and H-6″); 6.70 (t, $J$ = 1.7 Hz, 1H, H-4″); 7.33–7.46 (m, 5H, Ph). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.9 ($CH_3$); 21.6 ($CH_3$); 36.9 (C-3); 46.9 (C-4); 52.1 (C-2); 110.8 (C-2″ and C-6″); 113.6 (C-8); 115.7 (C-4a); 117.4 (C-4″); 121.4 (C-6); 127.3 (C-2′ and C-6′); 128.3 (C-4′); 129.1 (C-3′ and C-5′); 136.1 (C-3″ and C-5″); 139.1 (C-7); 139.4 (C-5); 143.7 (C-1′); 145.2 (C-8a); 148.3 (C-1″). Analysis: Calculated for $C_{23}H_{22}Cl_2N_2$ (M = 397.34): C, 69.52; H, 5.58; N, 7.05. Found: C, 69.83; H, 5.79; N, 6.97.

**Synthesis of 2-arylquinolines 10. General procedure.** To a stirred solution of the suitable aniline (3 mmol), the suitable aromatic aldehyde (1 equiv.) and CAN (10 mol%) in acetonitrile (10 mL) was added dropwise a mixture of the same or a different aniline (1 equiv.) and ethyl vinyl ether (1 equiv.) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h and upon completion, as judged by TLC, it was diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). In some cases where an emulsion was formed, the dichloromethane extracts were shaken with brine (10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (30 mL), and $FeCl_3{\cdot}6H_2O$ (2.5 equiv.) was added. The solution was stirred at room temperature for 3 h and evaporated to dryness. The residue was taken up with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated, and the residue was purified by chromatography on silica gel, eluting with a 97 : 3 petroleum ether–ethyl acetate mixture.

**2-Phenyl-5,7-dimethylquinoline (10a).** White solid, mp 89–90 °C. IR (NaCl) $\bar{\nu}$: 1619, 1598 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.57 (s, 3H, $CH_3$); 2.70 (s, 3H, $CH_3$); 7.23 (s, 1H, H-6); 7.45–7.63 (m, 3H, H-3′, H-4′ and H-5′); 7.85 (d, $J$ = 8.7 Hz, 1H, H-3); 7.86 (s, 1H, H-8); 8.18 (dd, $J$ = 8.4, 1.6 Hz, 2H, H-2′

and H-6′); 8.35 (d, $J$ = 8.7 Hz, 1H, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.5 ($CH_3$); 21.8 ($CH_3$); 117.6 (C-3); 124.5 (C-4a); 126.9 (C-6); 127.4 (C-3′ and C-5′); 128.7 (C-2′ and C-6′); 129.1 (C-4′ and C-8); 132.9 (C-4); 133.9 (C-5); 139.4 and 139.7 (C-1′ and C-7); 148.8 (C-8a); 156.7 (C-2). Analysis: Calculated for $C_{17}H_{15}N_2$ (M = 233.31): C, 87.52; H, 6.48; N, 6.00. Found: C, 87.22; H, 6.59; N, 5.97.

**2-(4-Chlorophenyl)-5,8-dimethylquinoline (10b).** Pale yellow viscous oil. IR (NaCl) $\bar{\nu}$: 1602, 1563 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.70 (s, 3H, $CH_3$); 2.89 (s, 3H, $CH_3$); 7.28 (d, $J$ = 7.6 Hz, 1H, H-6); 7.45–7.57 (m, 3H, H-7, H-3′ and H-5′); 7.91 (d, $J$ = 8.8 Hz, 1H, H-3); 8.25 (d, $J$ = 8.5 Hz, 2H, H-2′ and H-6′); 8.39 (d, $J$ = 8.8 Hz, 1H, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 17.8 ($CH_3$); 18.4 ($CH_3$); 117.1 (C-3); 126.4 (C-4a); 126.6 (C-6); 128.5 (C-2′ and C-6′); 128.8 (C-3′ and C-5′); 129.4 (C-7); 131.9 (C-5); 133.5 (C-4); 135.2 (C-4′); 135.4 (C-8); 138.1 (C-1′); 147.2 (C-8a); 153.5 (C-2). Analysis: Calculated for $C_{17}H_{14}ClN$ (M = 267.75): C, 76.26; H, 5.27; N, 5.23. Found: C, 75.94; H, 5.15; N, 5.37.

**2-(4-Methylphenyl)-5,7-dimethylquinoline (10c).** Pale yellow solid, mp 101–102 °C. IR (NaCl) $\bar{\nu}$: 1621, 1598 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.47 (s, 3H, $CH_3$); 2.56 (s, 3H, $CH_3$); 2.70 (s, 3H, $CH_3$); 7.22 (s, 1H, H-6); 7.36 (d, $J$ = 8.3 Hz, 2H, H-3′ and H-5′); 7.84 (s, 1H, H-8); 7.85 (d, $J$ = 8.7 Hz, 1H, H-3); 8.10 (d, $J$ = 8.2 Hz, 2H, H-2′ and H-6′); 8.34 (d, $J$ = 8.8 Hz, 1H, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.5 ($CH_3$); 21.3 ($CH_3$); 21.8 ($CH_3$); 117.5 (C-3); 124.4 (C-4a); 126.8 (C-6); 127.3 (C-3′ and C-5′); 128.9 (C-8); 129.5 (C-2′ and C-6′); 132.9 (C-4); 133.9 (C-5); 136.8 (C-4′); 139.2 (C-1′); 139.4 (C-7); 148.7 (C-8a); 156.7 (C-2). Analysis: Calculated for $C_{18}H_{17}N$ (M = 247.33): C, 87.41; H, 6.93; N, 5.66. Found: C, 87.12; H, 6.97; N, 5.58.

**2-(4-Methoxyphenyl)-5,7-dimethylquinoline (10d).** Pale yellow solid, mp 118–119 °C. IR (NaCl) $\bar{\nu}$: 1620, 1599 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.56 (s, 3H, $CH_3$); 2.69 (s, 3H, $CH_3$); 3.92 (s, 3H, $OCH_3$); 7.08 (dd, $J$ = 6.8, 2.1 Hz, 2H, H-3′ and H-5′); 7.21 (s, 1H, H-6); 7.81 (d, $J$ = 8.7 Hz, 1H, H-3); 7.83 (s, 1H, H-8); 8.17 (dd, $J$ = 6.8, 2.0 Hz, 2H, H-2′ and H-6′); 8.32 (d, $J$ = 8.8 Hz, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.5 ($CH_3$); 21.8 ($CH_3$); 55.3 ($OCH_3$); 114.1 (C-3′ and C-5′); 117.2 (C-3); 124.2 (C-4a); 126.7 (C-6); 128.7 (C-2′ and C-6′); 128.8 (C-8); 132.3 (C-1′); 132.8 (C-4); 133.8 (C-5); 139.3 (C-7); 148.7 (C-8a); 156.3 (C-2); 160.6 (C-4′). Analysis: Calculated for $C_{18}H_{17}NO$ (M = 263.33): C, 82.10; H, 6.51; N, 5.32. Found: C, 81.84; H, 6.60; N, 5.28.

**2-(4-Chlorophenyl)-5,7-dimethylquinoline (10e).** Pale yellow solid, mp 133–134 °C. IR (NaCl) $\bar{\nu}$: 1620, 1597 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.57 (s, 3H, $CH_3$); 2.71 (s, 3H, $CH_3$); 7.25 (s, 1H, H-6); 7.52 (dd, $J$ = 6.7, 1.8 Hz, 2H, H-3′ and H-5′); 7.82 (d, $J$ = 8.7 Hz, 1H, H-3); 7.84 (s, 1H, H-8); 8.15 (dd, $J$ = 6.7, 1.8 Hz, 2H, H-2′ and H-6′); 8.37 (d, $J$ = 8.8 Hz, 1H, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.5 ($CH_3$); 21.8 ($CH_3$); 117.2 (C-3); 124.6 (C-4a); 126.8 (C-6); 128.7 (C-2′ and C-6′); 128.9 (C-3′ and C-5′); 129.3 (C-8); 133.2 (C-4); 133.9 (C-5); 135. 3 (C-4′); 138.1 (C-1′); 139.7 (C-7); 148.8 (C-8a); 155.4 (C-2). Analysis: Calculated for $C_{17}H_{14}ClN$ (M = 267.75): C, 76.26; H, 5.27; N, 5.23. Found: C, 75.95; H, 5.26; N, 5.16.

**2-(4-Bromophenyl)-5,7-dimethylquinoline (10f).** Pale yellow solid, mp 116–117 °C. IR (NaCl) $\bar{\nu}$: 1619, 1598 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.57 (s, 3H, $CH_3$); 2.71 (s, 3H, $CH_3$); 7.25 (s, 1H, H-6); 7.68 (dd, $J$ = 6.8, 2.0 Hz, 2H, H-3′ and H-5′); 7.82 (d, $J$ = 8.8 Hz, 1H, H-3); 7.84 (s, 1H, H-8); 8.08 (dd, $J$ = 6.8, 2.0 Hz, 2H, H-2′ and H-6′); 8.38 (d, $J$ = 8.7 Hz, 1H, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.5 ($CH_3$); 21.8 ($CH_3$); 117.2 (C-3); 123.7 (C-4′); 124.6 (C-4a); 126.8 (C-6); 128.9 (C-2′ and C-6′); 129.4 (C-8); 131.9 (C-3′ and C-5′); 133.2 (C-4); 133.9 (C-5); 138.5 (C-1′); 139.8 (C-7); 148.7 (C-8a); 155.4 (C-2). Analysis: Calculated for $C_{17}H_{14}BrN$ (M = 312.20): C, 65.40; H, 4.52; N, 4.49. Found: C, 63.77; H, 4.47; N, 4.35.

**2-(2-Furyl)-5,7-dimethylquinoline (10g).** Pale yellow oil. IR (NaCl) $\bar{\nu}$: 1619, 1598 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.54 (s, 3H, $CH_3$); 2.67 (s, 3H, $CH_3$); 6.58–6.63 (m, 1H, H-4′); 7.19 (s, 1H, H-6); 7.23 (d, $J$ = 3.4 Hz, 1H, H-3′); 7.65 (s, 1H, H-5′); 7.79 (d, $J$ = 8.9 Hz, 1H, H-3); 7.81 (s, 1H, H-8); 8.28 (d, $J$ = 8.3 Hz, 1H, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.4 ($CH_3$); 21.7 ($CH_3$); 109.6 (C-4′); 112.0 (C-3′); 116.0 (C-3); 124.4 (C-4a); 126.5 (C-6); 129.0 (C-8); 132.7 (C-4); 133.8 (C-5); 139.6 (C-7); 143.8 (C-5′); 148.4 and 148.5 (C-2′ and C-8a); 153.7 (C-2). Analysis: Calculated for $C_{15}H_{13}NO$ (M = 223.27): C, 80.69; H, 5.87; N, 6.27. Found: C, 75.33; H, 5.68; N, 6.01.

**2-(2-Thienyl)-5,7-dimethylquinoline (10h).** White solid, mp, 96–97 °C. IR (NaCl) $\bar{\nu}$: 1619, 1597 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.51 (s, 3H, $CH_3$); 2.63 (s, 3H, $CH_3$); 7.10–7.20 (m, 2H, H-6 and H-4′); 7.45 (d, $J$ = 6.3 Hz, 1H, H-3′); 7.72 (m, 3H, H-3, H-8 and H-5′); 8.22 (d, $J$ = 11.0 Hz, 1H, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.4 ($CH_3$); 21.7 ($CH_3$); 116.3 (C-3); 124.5 (C-4a); 125.5 (C-5′); 126.5 (C-6); 127.9 and 128.2 (C-3′ and C-4′); 129.0 (C-8); 132.8 (C-4); 133.9 (C-5); 139.6 (C-7); 145.5 (C-2′); 148.6 (C-8a); 151.7 (C-2). Analysis: Calculated for $C_{15}H_{13}NS$ (M = 239.34): C, 75.28; H, 5.47; N, 5.85; S, 13.40. Found: C, 74.99; H, 5.48; N, 6.01; S, 13.33.

**2-[3-[(2*R**,4*S**)-4-Methoxy-5,7-dimethyl-1,2,3,4-tetrahydroquinolin-2-yl]phenyl]-5,7-dimethylquinoline (12).** A mixture of 3,5-dimethylaniline (2.42 g, 20 mmol) and isophthalaldehyde (1.34 g, 10 mmol) was stirred vigorously with a glass rod for 5 min and then it was kept overnight at room temperature over filter paper to afford the corresponding imine **11** as a pale brown solid (3.40 g, 100%), which was used for the next step without further purification. IR (NaCl) $\bar{\nu}$: 1628 cm$^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 2.40 (s, 12H, 4 $CH_3$); 6.89 (s, 4H, H-2′ and H-6′); 6.95 (s, 2H, H-4′); 7.61 (t, $J$ = 7.6 Hz, 1H, H-5); 8.06 (dd, $J$ = 7.7, 1.6 Hz, 2H, H-4 and H-6); 8.41 (s, 1H, H-2); 8.70 (s, 2H, 2 CH=N). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 21.3 (4 $CH_3$); 118.6 (C-2′ and C-6′); 127.8 (C-4′); 129.2 and 129.3 (C-2 and C-5); 130.9 (C-4 and C-6); 136.8 (C-1 and C-3); 138.8 (C-3′ and C-5′); 151.7 (C-1′); 154.2 (2 CH=N).

To a stirred solution of the imine **11** (1.02 g, 3 mmol) and CAN (10 mol%) in acetonitrile (10 mL) was added dropwise a mixture of 3,5-dimethylaniline (726 mg, 6 mmol) and ethyl vinyl ether (450 mg, 6 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h. Then, it was diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined dichloromethane extracts were shaken with brine (1 × 10 mL), dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure. The residue

was dissolved in methanol (30 mL), and $FeCl_3 \cdot 6H_2O$ (2.03 g, 7.5 mmol) was added. The solution was stirred at room temperature for 3 h and then evaporated to dryness. The residue was taken up with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated, and the residue was purified by chromatography on silica gel, eluting with a petroleum ether–ethyl acetate (95 : 5, v/v) mixture, yielding 976 mg (77%) of **12** as a pale orange solid, mp 133 °C. IR (NaCl) $\tilde{\nu}$: 3390; 1619, 1599 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.89 (td, $J$ = 13.8, 3.0 Hz, 1H, H-3″$_{ax}$); 2.24 (s, 3H, $CH_3$); 2.35 (s, 3H, $CH_3$); 2.47 (dt, $J$ = 13.8, 2.3 Hz, 1H, H-3″$_{eq}$); 2.57 (s, 3H, $CH_3$); 2.71 (s, 3H, $CH_3$); 3.53 (s, 3H, $OCH_3$); 4.21 (br s, 1H, NH); 4.38 (t, $J$ = 2.5 Hz, 1H, H-4″); 4.60 (dd, $J$ = 11.5, 1.5 Hz, 1H, H-2″); 6.35 (s, 1H, H-8″); 6.47 (s, 1H, H-6″); 7.25 (s, 1H, H-6); 7.53–7.63 (m, 2H, H-4′ and H-5′); 7.86 (s, 1H, H-8); 7.88 (d, $J$ = 8.7 Hz, 1H, H-3); 8.10 (dt, $J$ = 6.9, 1.8 Hz, 1H, H-6′); 8.31 (s, 1H, H-2′); 8.38 (d, $J$ = 9.0 Hz, 1H, H-4). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.5 ($CH_3$); 18.6 ($CH_3$); 21.1 ($CH_3$); 21.8 ($CH_3$); 34.9 (C-3″); 51.4 (C-2″); 55.4 ($OCH_3$); 71.7 (C-4″); 113.2 (C-8″); 116.0 (C-4a″); 117.8 (C-3); 120.9 (C-6″); 124.6 (C-4a); 126.2 (C-6′); 126.8 (C-6); 127.8 (C-4′); 128.3 (C-5′); 129.1 (C-8); 129.2 (C-2′); 133.1 (C-4); 133.9 (C-5); 138.7 (C-5″, C-7″ and C-1′); 144.6 (C-7); 144.8 (C-1′); 148.7 (C-8a″); 149.3 (C-8a); 156.5 (C-2). Analysis: Calculated for $C_{29}H_{30}N_2O_2$ (M = 422.56): C, 82.43; H, 7.16; N, 6.63. Found: C, 82.31; H, 7.18; N, 6.58.

**(±)-(2*S**,4*R**)-4-Methoxy-2-(4-methylphenyl)quinoline (13).** A solution of compound **7b** (386.3 mg, 1 mmol) and CAN or $InCl_3$ (10 mol%) in MeOH (5 mL) was stirred at room temperature until no starting material was detected by TLC (5 h) and then it was diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated, and the residue was purified by chromatography on silica gel, eluting with a petroleum ether–ethyl acetate (99 : 1, v/v) mixture, yielding 292 mg (98%) of **13** as a yellow viscous liquid. IR (NaCl) $\tilde{\nu}$: 3392; 1600 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 250 MHz) $\delta$: 1.78 (td, $J$ = 13.1, 3.1 Hz, 1H, H-3$_{ax}$); 2.21–2.27 (m, 1H, H-3$_{eq}$); 2.23 (s, 3H, $CH_3$); 2.34 (s, 3H, $CH_3$); 2.40 (s, 3H, $CH_3$); 3.50 (s, 3H, $OCH_3$); 4.06 (br s, 1H, NH); 4.35 (t, $J$ = 2.6 Hz, 1H, H-4); 4.42 (dd, $J$ = 12.4, 2.4 Hz, 1H, H-2); 6.30 (s, 1H, H-8); 6.46 (s, 1H, H-6); 7.22 (d, $J$ = 7.8 Hz, 2H, H-3′ and H-5′); 7.39 (d, $J$ = 8.0 Hz, 2H, H-2′ and H-6′). $^{13}$C-NMR ($CDCl_3$, 63 MHz) $\delta$: 18.5 ($CH_3$); 21.0 ($CH_3$); 21.1 ($CH_3$); 34.8 (C-3); 50.9 (C-2); 55.2 ($OCH_3$); 71.7 (C-4); 113.2 (C-8); 116.0 (C-4a); 120.8 (C-6); 126.8 (C-2′ and C-6′); 129.2 (C-3′ and C-5′); 137.3 (C-4′); 138.6 and 138.7 (C-5 and C-7); 140.9 (C-1′); 144.9 (C-8a). Calculated for $C_{19}H_{23}NO_2$ (M = 297.39): C, 76.73; H, 7.80; N, 4.71. Found: C, 76.34; H, 7.49; N, 4.65.

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## Notes and references

1 For reviews, see: (*a*) A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031; (*b*) V. Sridharan, P. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157.

2 For reviews on related topics that contain information on tetrahydroquinolines, see: (*a*) V. Kouznetsov, A. Palma, C. Ewert and A. Varlamov, *J. Heterocycl. Chem.*, 1998, **35**, 761; (*b*) A. Mitchinson and A. Nadin, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2553; (*c*) A. Mitchinson and A. Nadin, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2862.

3 (*a*) J. A. Sikorski, *J. Med. Chem.*, 2006, **49**, 1; (*b*) M. DePasquale, G. Cadelina, D. Knight, W. Loging, S. Winter, E. Blasi, D. Perry and J. Keiser, *Drug Dev. Res.*, 2009, **70**, 35.

4 (*a*) T. A. Rano, E. Sieber-McMaster, P. D. Pelton, M. Yang, K. T. Demarest and G.-H. Kuo, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2456; (*b*) G.-H. Kuo, T. A. Rano, P. D. Pelton, K. T. Demarest, A. C. Gibbs, W. V. Murray, B. P. Damiano and M. A. Connelly, *J. Med. Chem.*, 2009, **52**, 1768; (*c*) A. Escribano, A. I. Mateo, E. M. Martín de la Nava, D. R. Mayhugh, S. L. Cockerham, T. P. Beyer, R. J. Schmidt, G. Cao, Y. Zhang, T. M. Jones, A. G. Borel, S. A. Sweetana, E. A. Cannady and N. B. Mantlo, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3671.

5 J. Liu, Y. Wang, Y. Sun, D. Marshall, S. Miao, G. Tonn, P. Anders, J. Tocker, H. L. Tang and J. Medina, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6840.

6 L. S. Povarov, *Russ. Chem. Rev.*, 1967, **36**, 656.

7 S. Kobayashi, H. Ishitani and S. Nakagawa, *Synthesis*, 1995, 1195.

8 For reviews, see: (*a*) V. A. Glushkov and A. G. Tolstikov, *Russ. Chem. Rev.*, 2008, **77**, 137; (*b*) V. V. Kouznetsov, *Tetrahedron*, 2009, **65**, 2721; (*c*) D. Bello, R. Ramón and R. Lavilla, *Curr. Org. Chem.*, 2010, **14**, 332.

9 For a representative example of Povarov reactions involving nitrogen-substituted cyclic dienophiles, see: R. A. Batey and D. A. Powell, *Chem. Commun.*, 2001, 2362.

10 For representative examples of reactions involving *N*-vinylamides and leading to *cis*-2,4-disubstituted products, see: (*a*) G. Stevenson, P. Leeson, M. Rowley, I. Sanderson and I. Stansfield, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 371; (*b*) B. Crousse, J. Bégué and D. Bonnet-Delpon, *J. Org. Chem.*, 2000, **65**, 5009; (*c*) S. Talukdar, C.-T. Chen and J.-M. Fang, *J. Org. Chem.*, 2000, **65**, 3148; (*d*) P. J. Stevenson and I. Graham, *Arkivoc*, 2003 (vii), 139; (*e*) V. V. Kouznetsov, F. I. Zubkov, U. M. Cruz and L. G. Voskressensky, *Lett. Org. Chem.*, 2004, **1**, 37; (*f*) D. B. Damon, R. W. Dugger, G. Magnus-Aryitey, R. B. Ruggeri, R. T. Wester, M. Tu and Y. Abramov, *Org. Process Res. Dev.*, 2006, **10**, 464; (*g*) G. Savitha and P. T. Perumal, *Tetrahedron Lett.*, 2006, **47**, 3589.

11 H. Xu, S. J. Zuend, M. G. Woll, Y. Tao and E. N. Jacobsen, *Science*, 2010, **327**, 986.

12 V. Sridharan, C. Avendaño and J. C. Menéndez, *Tetrahedron*, 2007, **63**, 673.

 

13 For a review, see: D. Tejedor and F. García-Tellado, *Chem. Soc. Rev.*, 2007, **36**, 484.
14 Crystallographic data (excluding structure factors) for compound **7b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication under the reference CCDC 894715.
15 For a review of the synthetic applications of CAN, with emphasis on those that employ stoichiometric amounts of the reagent, see: V. Nair and A. Deepthi, *Chem. Rev.*, 2007, **107**, 1862.
16 For a review of the use of CAN as a catalyst in organic synthesis, see: V. Sridharan and J. C. Menéndez, *Chem. Rev.*, 2010, **110**, 3805.
17 V. Sridharan, C. Avendaño and J. C. Menéndez, *Synthesis*, 2008, 1039.
18 P. Leeson, R. W. Carling, K. W. Moore, A. M. Moseley, J. D. Smith, G. Stevenson, T. Chan, R. Baker, A. C. Foster, S. Grimwood, J. A. Kemp, G. R. Marshall and K. Hoogsteen, *J. Med. Chem.*, 1992, **35**, 1954.
19 For representative examples, see: (*a*) G. Manfroni, B. Gatto, O. Tabarrini, S. Sabatini, V. Cecchetti, G. Giaretta, C. Parolin, C. del Vecchio, A. Calistri, M. Palumbo and A. Fravolini, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 714; (*b*) M. Krishnamurthy, N. T. Schirle and P. A. Beal, *Bioorg. Med. Chem.*, 2008, **16**, 8914; (*c*) A. Borloni, C. Mustazza, I. Sestili, M. Sbraccia, L. Turchetto and M. R. del Giudice, *Arch. Pharm.*, 2007, **340**, 17.
20 For representative examples, see: (*a*) S. Kikuchi, M. Iwai and S.-i. Fukuzawa, *Synlett*, 2007, 2639; (*b*) F. Xiao, Y. Chen, Y. Liu and J. Wang, *Tetrahedron*, 2008, **64**, 2755; (*c*) H. Huang, H. Jiang, K. Chen and H. Liu, *J. Org. Chem.*, 2009, **74**, 5476; (*d*) S. K. Guchhait, K. Jadeja and C. Madaan, *Tetrahedron Lett.*, 2009, **50**, 6861; (*e*) M. Zhu, W. Fu, C. Xun and G. Zou, *Bull. Korean Chem. Soc.*, 2012, **33**, 43.
21 See, for instance: W.-W. Li, Y. Bing, M.-Q. Zha, T.-H. Li and X. Li, *Acta Crystallogr., Sect. E Struct. Rep. Online*, 2011, **67**, m1464.