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# Stereoselective synthesis of new classes of atropisomeric compounds through a tandem Michael reaction–azacyclization process. Part 2

Stéphane Le Gac,[a] Nicolas Monnier-Benoit,[a] Lionel Doumampouom Metoul,[a] Samuel Petit[b] and Ivan Jabin[a,*]

[a]*Faculté des Sciences et Techniques, URCOM, Université du Havre, 25 rue Philippe Lebon, BP 540, 76058 Le Havre Cedex, France*
[b]*Sciences et Méthodes Séparatives (SMS), UPRES EA 2659, IRCOF-Université de Rouen, F-76821 Mont Saint-Aignan Cedex, France*

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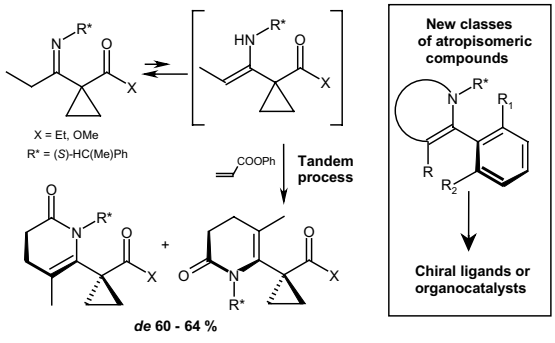
**Abstract**—Three new classes of atropisomeric compounds, that is, 6-aryl-dihydro-pyridin-2-ones, 6-aryl-pyridin-2-ones and 2-aryl-pyrroles, have been prepared from chiral imines through an efficient stereoselective tandem Michael–azacyclization process. In all cases, a study has shown that the barrier to rotation of the chiral axis is remarkably high.


## 1. Introduction

Enantiomerically pure atropisomers of axially chiral biaryls or non-biaryls compounds (i.e., chiral anilides, 1-naphthamides and benzamides) have been widely studied for their applications as chiral ligands or auxiliaries.[1] However, enantioselective syntheses of enantiomerically pure atropisomers are still rare and they are generally obtained by resolution.[2] We recently reported an efficient method for the stereoselective synthesis of non-biaryl atropisomeric compounds from chiral imines through a tandem process consisting of a Michael reaction followed by an azacyclization.[3] Thus, 5,6-disubstituted-3,4-dihydro-1*H*-pyridin-2-ones, bearing a 6-exo bulky cyclopropyl moiety, which generates the atropisomerism, were obtained in a two step sequence with good diastereoselectivities (Scheme 1, left side). The presence of the chiral auxiliary on the product permitted an easy separation of the atropisomers and an NMR study revealed that they possessed a remarkably high barrier to interconversion. However, this preliminary work also showed that the fragile cyclopropyl moiety led to degradation compounds, thus limiting the synthetic usefulness of this class of atropisomeric compounds.




**Scheme 1.**

Thus, we focused our interest on the stereoselective preparation, through the tandem Michael reaction–azacyclization process, of new classes of atropisomeric compounds consisting in five- or six-membered aza-heterocycles bearing an aryl substituent. The atropisomerism should result a priori from restricted rotation around the single bond connecting the aryl moiety to the heterocycle. Our final aim was to produce atropisomeric compounds that would be useful as either chiral ligands or organocatalysts (Scheme 1, right side).

Herein, we report a straightforward stereoselective route to the first members of these new atropisomer families, that is, 6-aryl-3,4-dihydro-1*H*-pyridin-2-ones, 6-aryl-1*H*-pyridin-2-ones and 2-aryl-pyrroles.[4]

* Corresponding author. Tel.: +33-232-74-43-94; fax: +33-232-74-43-91; e-mail: ivan.jabin@univ-lehavre.fr

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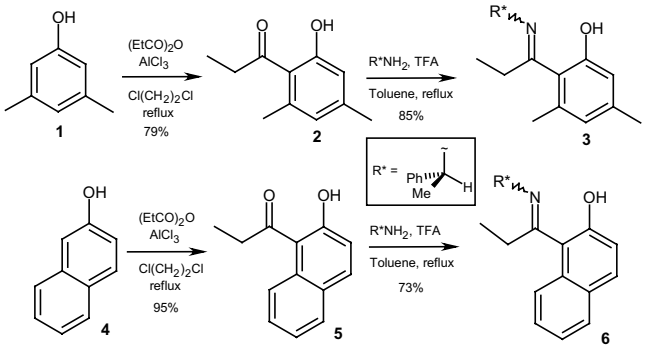
## 2. Results and discussion

The synthesis and resolution of atropisomeric pyridyl phenols has already been achieved by Chan et al.[5] These biaryl compounds have previously been used as ligands in catalytic asymmetric reactions and as starting material for the preparation of efficient P,N[6] or 2,2′-bipyridine[7] ligands. In our case, we thought that if phenol and naphthol groups were used as the aryl groups, the obtained atropisomeric compounds would possess structures close to those reported by Chan and thus would be good candidates for the preparation of chiral ligands. The required starting chiral imines **3** and **6** were prepared in two steps, respectively, from 3,5-dimethyl phenol **1** and naphthalen-2-ol **4** through a Fries rearrangement[8] and a subsequent condensation with (*S*)-1-phenylethylamine under classical conditions (i.e., azeotropic removal of water in a Dean–Stark apparatus) (Scheme 2).




**Scheme 2.**

It is noteworthy that the $^1$H NMR spectra of imines **3** and **6** revealed the presence of three diastereomers in proportions of ca. 1:1:1 and ca. 12:1:1, respectively. A variable temperature $^1$H NMR study showed that the signals of the three diastereomers of **3** did not coalesce up to 330 K. In order to rationalize these unexpected results, we suggested that, in addition to the *E–Z* isomerism, two distinct nonplanar atropisomers with a high barrier to rotation around the aryl-imino bond are possible for the *Z*-isomer (Fig. 1, example given for imine **3**).

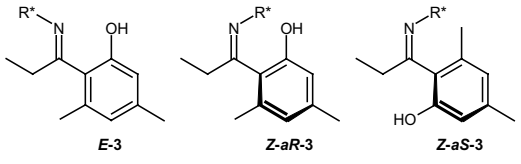
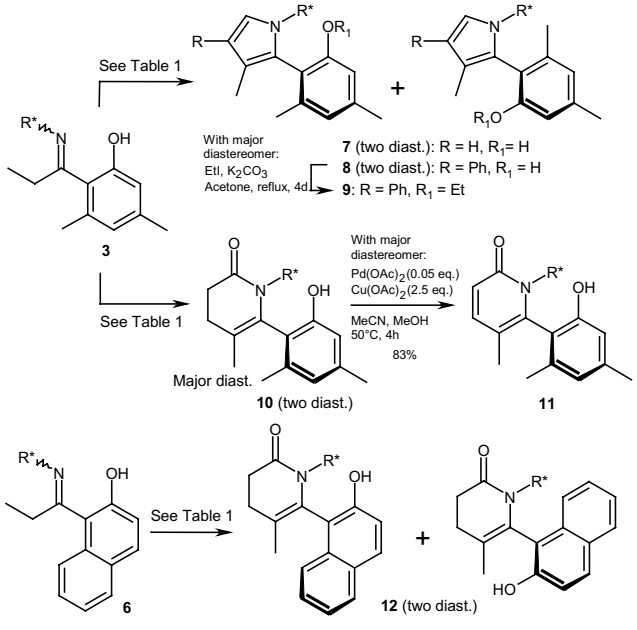



**Figure 1.** Restricted rotation of the aryl-imino bond of the *Z*-isomer leading to three diastereomers.

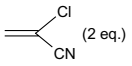
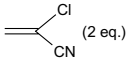
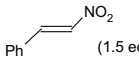
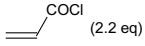
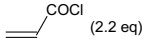
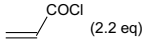
The different isomeric proportions observed for the imines **3** and **6** can be explained by the bulkiest naphthol group, which favoured the formation of the less hindered *E*-diastereomer. Moreover, this latter can be also stabilized by intramolecular hydrogen bonding between the nitrogen atom and the phenolic group. The atropisomerism of aryl imines has been already described in the 1970's[9] but, to our knowledge, no further developments have been reported.

The Michael reaction of chiral imines followed by an azacyclization step has been studied by others and ourselves. The azacyclization can take place only if the starting electrophilic olefin possesses a leaving group. For this purpose, the use of three electrophilic olefin types has been reported: Unsaturated acid derivatives (phenyl esters,[10] acyl chlorides and anhydrides[11]) which can lead to 3,4-dihydro-1*H*-pyridin-2-ones while nitroolefins[12] and chloroacrylonitrile[13] afford pyrrole derivatives through different mechanisms. We decided to investigate the possibility of using these three types of electrophilic olefins with imine **3** for the production of new classes of atropisomeric compounds. Thus, the reaction of imine **3** with chloroacrylonitrile in the presence of a base (collidine) led to the expected 2-arylpyrrole **7** in excellent yield (Scheme 3; Table 1, entry 1). The role of the base was to trap HCl and HCN formed during the reaction. The GC–MS and $^1$H NMR analyses of crude **7** were consistent with the presence of two diastereomers in close proportions (de 14%), which were separated by flash chromatography (FC) on silica gel and thus fully characterized. In order to improve the low diastereoselectivity observed, we studied the influence of a Lewis acid. When the reaction was conducted in the presence of $ZnCl_2$ (1 equiv) the diastereomeric excess rose to 44%[14] (Table 1, entry 2). Several Lewis acids were compared in the course of this study and it was observed that $ZnCl_2$ and $Mg(ClO_4)_2$ gave similar results while $TiCl_4$ and $Cu(OTf)_2$ led to complex mixtures of unidentified compounds.[15] With *trans*-β-nitrostyrene as the electrophilic olefin, imine **3** led, through the tandem process and with a poor stereoselectivity, to the pyrrole **8** as a mixture of separable atropisomers (Scheme 3;




**Scheme 3.**

**Table 1.** Conditions and results of the reactions depicted in Scheme 3

| Entry | Imine | Electrophilic olefin | Conditions | Product[a] | De[b] | Overall yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **3** |  (2 eq.) | THF, collidine, reflux, 1 h | **7** | 14 | 92 |
| 2 | **3** |  (2 eq.) | $ZnCl_2$, THF, collidine, rt, 3 days | **7** | 44 | 72 |
| 3 | **3** |  (1.5 eq.) | Toluene, collidine, molecular sieves, 90 °C, 4 h | **8** | 19 | 49[d] |
| 4 | **3** |  (2.2 eq) | (i) THF, collidine, reflux, 16 h<br>(ii) NaOH (1 M), MeOH, 55 °C, 1 h | **10** | 60 | 19 |
| 5 | **3** |  (2.2 eq) | (i) $ZnCl_2$, THF, collidine, 0 °C, 3 h<br>(ii) NaOH (1 M), MeOH, 55 °C, 1 h | **10** | 77 | 56 |
| 6 | **6** |  (2.2 eq) | (i) $ZnCl_2$, THF, collidine, 0 °C, 3 h<br>(ii) NaOH (1 M), MeOH, 55 °C, 1 h | **12** | 28 | 39 |

[a] In all cases, the products consisted of a mixture of two separable diastereomers.
[b] The diastereomeric excess was determined by GC–MS and $^1$H NMR analyses of the crude product.
[c] For the two diastereomers, calculated after flash chromatography on silica gel.
[d] $^1$H NMR estimation (see text).

Table 1, entry 3). For purification and characterization purposes,[16] the major diastereomer of **8** was alkylated by iodoethane leading to the less polar derivative **9**. Attempts to enhance the stereoselectivity in presence of a Lewis acid failed, since in this case the reaction proceeded only by heating in toluene.

Concerning the preparation of the desired 3,4-dihydro-1*H*-pyridin-2-ones, we first attempted the Michael reactions of imines **3** and **6** with phenyl acrylate but only traces of the products (i.e., **10** and **12**) were obtained even under drastic conditions (neat, high temperature, long reaction time, catalysis by a Lewis acid), with hydrolysis of the starting imine taking place preferentially. When phenyl acrylate was replaced by the more reactive acryloyl chloride, imine **3** led, under heating conditions, to the desired 6-aryl-3,4-dihydro-1*H*-pyridin-2-one **10** in low yield (Table 1, entry 4). However, to our delight, a Lewis acid catalysis by $ZnCl_2$ proved to be extremely efficient since a good 56% yield and a high diastereoselectivity (de 77%) were obtained[14] (Scheme 3; Table 1, entry 5). Under the same conditions, 6-naphthyl compound **12** was obtained as a mixture of atropisomers from imine **6** (Scheme 3; Table 1, entry 6). Surprisingly, in this case the reaction proceeded with moderate diastereoselectivity (de 28%). In both cases (i.e., imines **3** and **6**), the reactions were conducted in the presence of at least 2 equiv of acryloyl chloride since when they were performed with only 1 equiv of electrophilic olefin, phenol esterification was observed to a small extent. Consequently, a subsequent saponification step (NaOH, MeOH) was needed in order to obtain the final products **10** and **12**.

Atropisomers of **10** and **12** were separated by FC on silica gel and fully characterized. The relative configuration of the major diastereomer of **10** was determined by single-crystal X-ray diffraction (Fig. 2, left side). Its stereochemistry can be tentatively rationalized (Fig. 2, right side) if we consider that during the azacyclization step:

(i) The chiral auxiliary moiety has to be placed on the opposite side of the approaching acyl chain.
(ii) The Lewis acid chelates the hydroxy and the carbonyl groups.
(iii) The ring closing occurs on the opposite side of the bulky phenyl group borne by the chiral auxiliary.

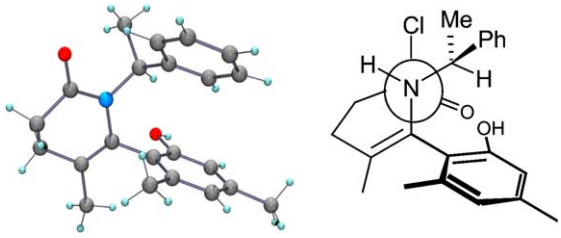



**Figure 2.** Left side: X-ray structure of the major diastereomer of **10**. Right side: proposed low energy conformation during the azacyclization step.

After all the diastereomers of compounds **7**, **8**, **10** and **12** were obtained as enantiomerically pure samples, we studied the barrier to rotation around their chiral axis by $^1$H NMR. Thus all diastereomers (majors and minors) of **7**, **8**, **10** and **12** were heated separately in refluxing toluene for 4 h. In all cases, no traces of the other atropisomeric diastereomer was detected by $^1$H NMR. These results clearly show that these compounds possess a remarkably high rotation barrier,

which prevents their interconversion into their atropisomer even at elevated temperature (ca. 110 °C). This NMR study also suggested that the observed stereoselectivities arose from asymmetric induction of the chiral auxiliary during the azacyclization step and not from slow equilibration of the final atropisomeric diastereomers.

Finally, with an efficient preparation of the enantiomerically pure major diastereomer of **10** in hand, we tested the feasibility of converting this compound into its oxidized pyridin-2-one counterpart **11**. In fact, the pyridin-2-one cycle possessed a more planar and resistant (to oxidation and ring opening reactions) structure that was more suitable for the further development of chiral ligands and organocatalysts. Preliminary attempts, under reported conditions (*t*-BuOK–DMSO) with closely related compounds,[17] only led to moderate yields since dihydro-1*H*-pyridin-2-one ring opening was competitive. However, the oxidation of the major diastereomer of **10** was successfully performed under mild reaction conditions by Pd(II) catalysis [0.05 equiv of $Pd(OAc)_2$ and 2.5 equiv of $Cu(OAc)_2$] (Scheme 3). To our knowledge, this reaction constitutes the first example of such an oxidation catalyzed by Pd(II). The enantiomerically pure pyridin-2-one **11** was heated 4 h in refluxing toluene without any detection of its atropisomer by $^1$H NMR analyses. This result shows that, as in compounds **7**, **8**, **10** and **12**, compound **11** possesses an important barrier to rotation around its chiral axis.

## 3. Conclusion

In conclusion, new classes of atropisomeric compounds, that is, 6-aryl-dihydro-1*H*-pyridin-2-ones, 6-aryl-1*H*-pyridin-2-ones and 2-aryl-pyrroles, have been prepared from chiral imines with stereoselectivities up to 77%. The key step of their synthesis consists of an efficient tandem Michael reaction–azacyclization process. In all cases, the diastereomeric atropisomers have been separated and obtained enantiomerically pure. A study has shown that the barrier to rotation around their chiral axis was remarkably high. Work towards the use of these new classes of atropisomeric compounds for the preparation of chiral ligand or organocatalysts, in particular after the removal of the chiral auxiliary moiety (i.e., R*) are under progress in our laboratory.

## 4. Experimental

### 4.1. General

Thin layer chromatography (TLC) was performed with glass plates (0.25 mm) precoated with silica gel. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Flash chromatography separations (FC) were carried out with silica gel (230–400 mesh). GC–MS analyses were performed with a Thermofinnigan Automass Multi GC–MS apparatus (equipped with a 15 m × 0.20 mm PDMS capillary column) (GC method: 70 °C for 2 min then 15 °C/min until 280 °C). $[\alpha]_D^{20}$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$. $^1$H and $^{13}$C NMR spectra were recorded, respectively, at 200 and 50 MHz. Chemical shifts are expressed in ppm using TMS as the internal standard. Unless indicated otherwise, all reactions were performed under an argon atmosphere. Anhydrous THF and toluene were obtained by distillation over sodium/benzophenone and $P_2O_5$, respectively. For the preparation of compounds **2** and **5**, see Ref. 8. Elemental analyses were performed at the Laboratoire de Microanalyse Organique, IRCOF, France.

### 4.2. 3,5-Dimethyl-2-[1-(1-(*S*)-phenyl-ethylimino)-propyl]-phenol 3

A solution of ketone **2** (11.85 g, 66.4 mmol) and (*S*)-1-phenylethylamine (99.9% ee, 8.56 mL, 66.4 mmol) with a trace of TFA in toluene (200 mL) was heated under reflux in a Dean–Stark apparatus for 18 h. After cooling the reaction mixture to 0 °C, the resulting precipitate was isolated by suction filtration and recrystallized in toluene, giving 15.88 g (85%) of imine **3** as a mixture of three diastereomers in the proportions of ca. 1:1:1. Beige solid. EIMS *m*/*z* (rel int) 281 ($M^+$, 57), 266 (47), 162 (35), 148 (24), 105 (base), 77 (24). IR ($CHCl_3$): 3544–3189, 1629 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3/C_6D_6$, 20:1) $\delta$: spectrum of the three diastereomers: 1.00 (t, $J = 7.0$ Hz, 3H), 1.10 (t, $J = 7.0$ Hz, 3H), 1.12 (t, $J = 7.0$ Hz, 3H), 1.42 (d, $J = 7.0$ Hz, 3H), 1.51 (d, $J = 7.0$ Hz, 3H), 1.60 (d, $J = 7.0$ Hz, 3H), 1.68 (s, 3H), 2.18 (s, 3H), 2.22 (s, 3H), 2.26 (s, 6H), 2.36 (s, 3H), 2.45–2.81 (m, 6H), 4.32 (q, $J = 7.0$ Hz, 1H), 4.40 (q, $J = 7.0$ Hz, 1H), 4.97 (q, $J = 6.3$ Hz, 1H), 6.40–6.65 (m, 6H), 7.10–7.45 (m, 15H).

### 4.3. 1-[1-(1-(*S*)-Phenyl-ethylimino)-propyl]-naphthalen-2-ol 6

A solution of ketone **5** (5.54 g, 27.7 mmol) and (*S*)-1-phenylethylamine (99.9% ee, 3.57 mL, 27.7 mmol) with a trace of TFA in toluene (100 mL) was heated under reflux in a Dean–Stark apparatus for 18 h. After cooling the reaction mixture to 0 °C, the resulting precipitate was isolated by suction filtration and recrystallized in toluene, yielding 6.17 g (73%) of imine **6** as a mixture of three diastereomers in the proportions of ca. 12:1:1. Brown solid. EIMS *m*/*z* (rel int) 303 ($M^+$, 11), 198 (52), 105 (base), 79 (30), 77 (34). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: spectrum of the major diastereomer: 1.40 (t, $J = 7.0$ Hz, 3H), 1.72 (d, $J = 6.3$ Hz, 3H), 2.62–3.10 (m, 2H), 5.08 (q, $J = 6.3$ Hz, 1H), 6.93–7.80 (m, 11H).

### 4.4. 3,5-Dimethyl-2-[3-methyl-1-(1-(*S*)-phenyl-ethyl)-1*H*-pyrrol-2-yl]-phenol 7

*Method A: without Lewis acid catalysis*: To a solution of imine **3** (0.20 g, 0.71 mmol) in anhydrous THF (0.4 mL) were added collidine (0.375 mL, 2.84 mmol) and chloroacrylonitrile (0.114 mL, 1.42 mmol). After refluxing for

1 h, the THF was removed under reduced pressure and the resulting residue dissolved in ethyl acetate, washed with water and dried over $MgSO_4$. After removal of the solvent under reduced pressure, a GC–MS analysis of the crude residue showed two signals corresponding to the two diastereomers of **7** (de 14%). A FC (cyclohexane/ethyl acetate, 95:5) gave product **7** (200 mg, 92%) as a mixture of two diastereomers.

*Method B: with Lewis acid catalysis*: To a solution of $ZnCl_2$ (72 mg, 0.53 mmol) in anhydrous THF (0.2 mL) were successively added imine **3** (150 mg, 0.53 mmol) in anhydrous THF (1.8 mL), collidine (0.28 mL, 2.12 mmol) and chloroacrylonitrile (0.085 mL, 1.06 mmol). The mixture was stirred for 3 days at room temperature and then the THF removed under reduced pressure. The crude mixture was dissolved in dichloromethane and washed with an aqueous solution of HCl (0.1 M). After evaporation of the solvent under reduced pressure, a GC–MS analysis of the crude residue showed two signals corresponding to the two diastereomers of **7** (de 44%). A FC (cyclohexane/ethyl acetate, 95:5) afforded product **7** (116 mg, 72%) as a mixture of two diastereomers. Analytical samples of the two diastereomers of **7** were obtained by careful FC separations.

*Major diastereomer*: Beige solid, mp = 70 °C, $[\alpha]_D^{20}$ −111.5 (*c* 0.81, $CHCl_3$). EIMS *m/z* (rel int) 305 ($M^+$, 52), 201 (base), 200 (92), 186 (51), 105 (99), 79 (61), 77 (69). IR ($CHCl_3$): 3498, 1627, 1571 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.6 (s, 3H), 1.67 (d, $J = 7.0$ Hz, 3H), 1.87 (s, 3H), 2.32 (s, 3H), 4.85 (q, $J = 7.0$ Hz, 1H), 5.02 (s, 1H), 6.18 (d, $J = 2.4$ Hz, 1H), 6.56 (s, 1H), 6.68 (s, 1H), 6.92 (d, $J = 3.1$ Hz, 1H), 6.94–7.02 (m, 2H), 7.16–7.28 (m, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 11.63, 19.69, 21.78, 22.82, 55.71, 109.9, 112.8, 115.7, 119.1, 119.8, 122.8, 123.0, 126.6 (2C), 127.5, 128.7 (2C), 140.2, 141.0, 143.1, 155.1.

*Minor diastereomer*: Colourless oil, $[\alpha]_D^{20}$ −141.8 (*c* 0.60, EtOH). EIMS *m/z* (rel int) 305 ($M^+$, 35), 201 (97), 200 (81), 186 (33), 105 (base), 79 (40), 77 (47). IR (film): 3620 (*v* OH), 1626 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.73 (d, $J = 7.0$ Hz, 3H), 1.86 (s, 3H), 2.04 (s, 3H), 2.31 (s, 3H), 4.77 (s, 1H), 4.83 (q, $J = 7.0$ Hz, 1H), 6.18 (d, $J = 3.1$ Hz, 1H), 6.55 (s, 1H), 6.68 (s, 1H), 6.88–7.0 (m, 1He, 2H), 7.15–7.3 (m, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 11.53, 20.09, 21.76, 22.10, 55.51, 110.0, 113.1, 115.6, 119.0, 119.8, 122.6, 122.7, 126.1 (2C), 127.7, 128.9 (2C), 140.0, 140.2, 143.3, 155.4. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.43; H, 7.75; N, 4.62.

### 4.5. 3,5-Dimethyl-2-[3-methyl-4-phenyl-1-(1-(*S*)-phenyl-ethyl)-1*H*-pyrrol-2-yl]-phenol 8

To a solution of imine **3** (1.00 g, 3.56 mmol) in anhydrous toluene (10 mL) were successively added *trans*-β-nitrostyrene (0.795 g, 5.33 mmol), collidine (0.47 mL, 3.90 mmol) and molecular sieves (3 Å). The reaction mixture was heated at 90 °C for 4 h and then filtered in order to remove the molecular sieves. After concentration under reduced pressure, a GC–MS analysis of the crude residue showed two signals corresponding to the two diastereomers of **8** (de 19%). A FC (cyclohexane/ethyl acetate, 96:4) yielded product **8** (748 mg, 49%) as a mixture of two diastereomers.

*Major diastereomer*: This compound was fully characterized through its derivative **9**, see Ref. 16. EIMS *m/z* (rel int) 381 ($M^+$, 37), 277 (54), 276 (45), 105 (base), 79 (36), 77 (38). $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.65 (s, 3H), 1.70 (d, $J = 7.0$ Hz, 3H), 1.99 (s, 3H), 2.32 (s, 3H), 4.89 (q, $J = 7.0$ Hz, 1H), 5.07 (s, 1H), 6.58 (s, 1H), 6.70 (s, 1H), 7.10 (s, 1H), 7.14–7.59 (m, 10H).

*Minor diastereomer*: Beige solid, mp = 39–40 °C, $[\alpha]_D^{20}$ +9 (*c* 0.90, $CHCl_3$). EIMS *m/z* (rel int) 381 ($M^+$, 58), 277 (57), 276 (45), 105 (base), 79 (31), 77 (33). IR ($CHCl_3$): 3495, 1627, 1602 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.76 (d, $J = 7.0$ Hz, 3H), 1.97 (s, 3H), 2.07 (s, 3H), 2.31 (s, 3H), 4.80 (s, 1H), 4.86 (q, $J = 7.0$ Hz, 1H), 6.57 (s, 1H), 6.70 (s, 1H), 6.95–7.02 (m, 2H), 7.14–7.53 (m, 9H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 11.18, 20.19, 21.77, 22.09, 55.59, 113.2, 115.6, 117.4, 117.6, 122.8, 124.0, 124.8, 125.7, 126.2 (2C), 127.5 (2C), 127.8, 128.8 (2C), 128.9 (2C), 136.7, 140.0, 140.4, 143.0, 155.4. Anal. Calcd for $C_{27}H_{27}NO{\cdot}0.3H_2O$: C, 83.81; H, 7.19; N, 3.62. Found: C, 83.86; H, 7.21; N, 3.63.

### 4.6. 2-(2-Ethoxy-4,6-dimethyl-phenyl)-3-methyl-4-phenyl-1-(1-(*S*)-phenyl-ethyl)-1*H*-pyrrole 9

$K_2CO_3$ (0.66 g, 4.80 mmol) and iodoethane (0.19 mL, 2.40 mmol) were successively added to the major diastereomer of **8** (305 mg, 0.80 mmol) in 25 mL of acetone. After refluxing for 4 days, the reaction mixture was filtered in order to remove inorganic salts. After concentration under reduced pressure, the resulting residue was dissolved in dichloromethane and washed with an aqueous solution of NaOH (1 M). After solvent evaporation, a FC (cyclohexane/ethyl acetate, 97:3) afforded **9** (247 mg, 76%). Red oil, $[\alpha]_D^{20}$ +16.2 (*c* 1.05, EtOH). EIMS *m/z* (rel int) 410 (23), 409 ($M^+$, 61), 207 (25), 105 (base), 79 (25). IR ($CHCl_3$): 1602, 1571 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.27 (t, $J = 7.0$ Hz, 3H), 1.70 (s, 3H), 1.77 (d, $J = 7.0$ Hz, 3H), 1.96 (sl, 3H), 2.33 (s, 3H), 3.86–4.11 (m, 2H), 4.97 (q, $J = 7.0$ Hz, 1H), 6.61 (s, 1H), 6.63 (s, 3H), 6.86–6.96 (m, 2H), 7.07 (s, 1H), 7.11–7.26 (m, 4H), 7.34 (t, $J = 7.4$ Hz, 2H), 7.54 (d, $J = 7.4$ Hz, 2H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 11.79, 15.26, 19.83, 22.01, 22.23, 55.39, 64.37, 111.3, 114.7, 114.9, 119.2, 123.6, 125.0, 126.5 (2C), 127.1, 127.3 (2C), 127.90, 128.5 (2C), 128.6 (2C), 137.8, 139.1, 141.6, 144.0, 158.1. Anal. Calcd for $C_{29}H_{31}NO$: C, 85.04; H, 7.63; N, 3.42. Found: C, 85.08; H, 7.53; N, 3.43.

### 4.7. 6-(2-Hydroxy-4,6-dimethyl-phenyl)-5-methyl-1-(1-(*S*)-phenyl-ethyl)-3,4-dihydro-1*H*-pyridin-2-one 10

To a solution of imine **3** (0.50 g, 1.78 mmol) in anhydrous THF (10 mL) were added $ZnCl_2$ (243 mg,

1.78 mmol) in anhydrous THF (2 mL) and collidine (0.518 mL, 3.92 mmol). Then, acryloyl chloride (0.318 mL, 3.92 mmol) was added at 0 °C and the reaction mixture stirred for 3 h at this temperature. Methanol (10 mL) and an aqueous NaOH solution (1 M, 10 mL) were then added to the crude mixture, which was heated at 55 °C for 1 h. At 0 °C, an aqueous HCl solution (0.1 M) was slowly added until acidic pH after which the solvents were removed under reduced pressure. After dichloromethane extraction and concentration under reduced pressure, a GC–MS analysis of the crude mixture showed two signals corresponding to the two diastereomers of **10** (de 77%). A FC (dichloromethane/ethyl acetate, 85:15) gave the expected product **10** (337 mg, 56%) as a mixture of two diastereomers. Analytical samples of the two diastereomers of **10** were obtained by careful FC separations.

*Major diastereomer*: White solid, mp = 191 °C, $[\alpha]_D^{20}$ −121.8 (*c* 1.02, EtOH). EIMS *m*/*z* (rel int) 335 ($M^+$, 12), 231 (82), 216 (76), 105 (base), 77 (31). IR ($CHCl_3$): 1649 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.46 (d, $J = 7.0$ Hz, 3H), 1.50 (s, 3H), 2.07 (s, 3H), 2.18–2.64 (m, 4H), 2.24 (s, 3H), 4.35 (s, 1H), 5.10 (q, $J = 7.0$ Hz, 1H), 6.43 (s, 1H), 6.54 (s, 1H), 7.04–7.12 (m, 2H), 7.15–7.30 (m, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 17.20, 19.13, 19.89, 21.62, 26.79, 33.34, 53.82, 113.8, 118.6, 122.5, 123.2, 127.0 (2C), 127.2, 128.6 (2C), 130.1, 138.9, 140.3, 141.7, 154.1, 171.5. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.66; H, 7.82; N, 4.16. X-ray structure determination of this major diastereomer: vide infra.

*Minor diastereomer*: White solid, mp = 241 °C, $[\alpha]_D^{20}$ −93.4 (*c* 0.99, EtOH). EIMS *m*/*z* (rel int) 335 ($M^+$, 17), 231 (91), 216 (83), 105 (base), 103 (34), 77 (44). IR ($CHCl_3$): 1651 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.56 (s, 3H), 1.58 (d, $J = 7.8$ Hz, 3H), 2.05–2.20 (m, 1H), 2.11 (s, 3H), 2.25 (s, 3H), 2.34–2.58 (m, 3H), 4.47 (q, $J = 7.0$ Hz, 1H), 5.50 (s, 1H), 6.55, (s, 1H), 6.59 (s, 1H), 7.05–7.35 (m, 5H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 17.16, 19.21, 19.56, 21.62, 26.45, 33.15, 55.44, 113.8, 118.5, 120.0, 123.3, 126.7, 127.1 (2C), 128.1 (2C), 131.3, 138.2, 140.1, 142.5, 154.3, 171.1. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.87; H, 7.66; N, 4.15.

### 4.8. 6-(2-Hydroxy-4,6-dimethyl-phenyl)-5-methyl-1-(1-(*S*)-phenyl-ethyl)-1*H*-pyridin-2-one 11

Under an air atmosphere, acetonitrile (30 mL), methanol (10 mL), $Pd(OAc)_2$ (17 mg, 0.0746 mmol) and $Cu(OAc)_2$, $H_2O$ (744 mg, 3.725 mmol) were successively added to the major diastereomer of **10** (0.50 g, 1.49 mmol). After 4 h at 50 °C, the solvents were removed under reduced pressure. The crude mixture was then dissolved in dichloromethane and washed with an aqueous HCl solution (0.1 M). The aqueous layer was extracted with dichloromethane and the combined organic layers concentrated under reduced pressure. A FC (dichloromethane/ethyl acetate, 40:60) yielded product **11** (411 mg, 83%). Yellow solid, mp = 270 °C (dec), $[\alpha]_D^{20}$ −155.6 (*c* 0.99, $CHCl_3$). EIMS *m*/*z* (rel int) 333 ($M^+$, 17), 229 (41), 214 (base), 105 (55), 104 (57), 103 (43), 77 (41). IR ($CHCl_3$): 1648 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.76 (s, 3H), 1.89 (d, $J = 7.0$ Hz, 3H), 2.00 (s, 3H), 2.18 (s, 3H), 5.21 (q, $J = 7.0$ Hz, 1H), 6.47 (d, $J = 9.4$ Hz, 1H), 6.47 (s, 1H), 6.53 (s, 1H), 7.10–7.25 (m, 5H), 7.29 (d, $J = 9.4$ Hz, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 17.84, 18.09, 19.97, 21.61, 59.61, 114.7, 116.8, 118.7, 120.9, 122.6, 126.4 (2C), 126.6, 128.3 (2C), 137.4, 140.8, 141.6, 143.0, 144.7, 155.0, 163.8. Anal. Calcd for $C_{22}H_{25}NO_2 \cdot H_2O$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.25; H, 6.92; N, 4.16.

### 4.9. 6-(2-Hydroxy-naphthalen-1-yl)-5-methyl-1-(1-(*S*)-phenyl-ethyl)-3,4-dihydro-1*H*-pyridin-2-one 12

To a solution of imine **6** (0.50 g, 1.65 mmol) in anhydrous THF (9 mL) were added $ZnCl_2$ (225 mg, 1.65 mmol) in anhydrous THF (2 mL) and collidine (0.444 mL, 3.63 mmol). Acryloyl chloride (0.295 mL, 3.63 mmol) was then added at 0 °C, and the reaction mixture stirred for 3 h at this temperature. Methanol (10 mL) and an aqueous NaOH solution (1 M, 10 mL) were then added to the reaction mixture, which was then heated at 55 °C for 1 h. At 0 °C, an aqueous HCl solution (0.1 M) was slowly added until acidic pH after which the solvents were removed under reduced pressure. After dichloromethane extraction and evaporation of the solvent under reduced pressure, a $^1H$ NMR analysis of the crude mixture allowed us to calculate the relative proportions of the two diastereomers of **12** (de 28%). A FC (dichloromethane/ethyl acetate, 85:15) led to product **12** (230 mg, 39%) as a mixture of two diastereomers. Analytical samples of the two diastereomers of **12** were obtained by careful FC separations.

*Major diastereomer*: Amorphous solid. $[\alpha]_D^{20}$ −173.1 (*c* 1.1, EtOH). EIMS *m*/*z* (rel int) 357 ($M^+$, 19), 253 (base), 252 (73), 238 (48), 105 (76), 104 (33), 77 (39). IR ($CHCl_3$): 3272, 1638 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.12 (d, $J = 7.0$ Hz, 3H), 1.49 (s, 3H), 2.28–2.45 (m, 1H), 2.51–2.86 (m, 3H), 4.62 (s, 1H), 5.25 (q, $J = 7.0$ Hz, 1H), 6.92–7.03 (m, 2H), 7.14–7.25 (m, 4H), 7.26–7.48 (m, 2H), 7.63 (d, $J = 7.8$ Hz, 1H), 7.70–7.78 (m, 2H) $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 17.07, 19.19, 26.84, 33.15, 53.33, 113.8, 117.7, 123.7, 124.1, 126.8 (2C), 126.9, 127.2, 128.3 (2C), 128.4, 128.7, 128.8, 131.0, 133.5, 141.4, 152.4, 171.3.

*Minor diastereomer*: White solid, mp = 213 °C (dec), $[\alpha]_D^{20}$ −141.8 (*c* 0.36, EtOH). EIMS *m*/*z* (rel int) 357 ($M^+$, 18), 253 (99), 252 (73), 238 (51), 105 (base), 104 (58), 77 (55). IR ($CHCl_3$): 3437, 1613 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.40 (d, $J = 7.0$ Hz, 3H), 1.59 (s, 3H), 2.24–2.38 (m, 1H), 2.49–2.90 (m, 3H), 4.35 (q, $J = 7.0$ Hz, 1H), 5.61 (s, 1H), 7.08–7.27 (m, 6H), 7.29–7.48 (m, 2H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.74–7.82 (m, 2H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 17.65, 19.62, 26.93, 33.52, 56.11, 113.9, 117.6, 122.1, 124.2 (2C), 126.9, 127.1 (2C), 127.5, 128.3 (2C), 128.7, 129.3, 129.9, 131.4, 132.8, 142.1, 151.9, 170.7.

### 4.10. X-ray structure determination of the major diastereomer of 10

Formula: $C_{22}H_{25}NO_2$, MW = 335.43, monoclinic, space group $C2$; $a = 14.951(2)$, $b = 7.610(1)$, $c = 16.453(2)$ Å, $\beta = 92.439(1)°$, $V = 1870(3)$ Å$^3$, $Z = 4$, $Z' = 1$; $D_c = 1.191\,g\,cm^{-3}$; $T = 296(2)$ K, crystal habit = prismatic, crystal colour = colourless, approximate crystal size = 0.10 × 0.46 × 0.60 mm, $F(000) = 720$, $\mu(MoK\alpha) = 0.076\,mm^{-1}$. Structure solution and refinement: The program package SHELXTL (V6.10) was used for space group determination, structure solution and refinement. The space group $C2$ was reliably determined from systematic extinctions and the relative $F_0^2$ of equivalent reflections (XPREP). The structure was solved by direct methods (SHELXS). An ORTEP view of the title compound is presented in Figure 2 and provides a representation of the stereochemistry of this compound. The absolute configuration of the stereogenic centre of the methylbenzylamine moiety is (*S*). Anisotropic displacement parameters were refined for nonhydrogen atoms. Some hydrogen atoms could not be located from subsequent difference Fourier synthesis and refined. Ideal positions were calculated for each one (SHELXL). The final cycle of full-matrix least-square refinement on $F^2$ was based on 3763 observed reflections and 296 variable parameters and converged with unweighted and weighted agreement factors of $R_1 = \sum(||F_0| - |F_C||)/\sum|F_0| = 0.0390$ [0.0352 for 3445 $F_0 > 4.0\sigma(F_0)$], $wR_2 = \{\sum[w(F_0^2 - F_C^2)^2]/\sum[w(F_0^2)^2]\}^{1/2} = 0.1001$. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 218213. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

## Supplementary material

Detailed crystal structure determination of major diastereomer of **10** is available free of charge from the author.

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14. In both cases (i.e., under heating conditions or with a Lewis acid catalysis), the obtained major diastereomer was identical.
15. The comparison between the different Lewis acids was made on the reaction of imine **3** with acryloyl chloride.
16. We were unable to obtain an analytical sample of the major diastereomer of **8** since this compound was inseparable, by FC on silica gel, from traces of ketone **2** formed during the reaction. Thus, the 49% yield, given for the mixture of diastereomers of **8**, was determined by an $^1H$ NMR purity estimation of major diastereomer of **8**.
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