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Michael reactions of unsubstituted aromatic chiral imines with substituted unsaturated acid esters

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Abstract—The Michael reaction of chiral imines **1**–**3**, derived from aromatic ketones' with substituted electrophilic olefins generated asymmetric tertiary carbon centers. Nevertheless, asymmetric inductions were weaker than those usually observed with cycloalkanone imines.

1. Introduction

The enantioselective Michael reaction of chiral imines with unsubstituted electrophilic olefins is limited to the creation of quaternary asymmetric carbon centers, i.e. those non-epimerisable by imine–enamine tautomerism. However, with α- or β-substituted olefins, this same reaction allows the simultaneous generation of a second tertiary asymmetric carbon in the β- or γ-position relative to the imine function, which in turn are not epimerisable.[1] It occurred to us that it could be possible to use these substituted olefins to create a compound having an asymmetric tertiary carbon center in the β and/or γ-position while the α-position would be a CH_2 group or a sp^2 carbon atom.[2] In the present study, only the latter situation is studied. Indeed, if such an extension of the imine method was possible, this reaction could allow access to 3,4-dihydropyridin-2-ones which could be useful for the preparation of pipecolic acid derivatives, key intermediates in the synthesis of many biologically active compounds.[3] For this purpose and avoiding any alkylation in the α′-position, α-tetralone or an alkylarylketone could be used, and the adduct could be cyclised into a lactam.

In the model suggested to account for the observed stereoselectivity of the Michael reaction with α-substituted chiral cycloalkanone imines, the reactive conformation of the secondary enamine is that in which the chiral moiety is on the opposite side of the double bond. This preference induces the usual diastereofacial selectivity as shown in Figure 1.[4]

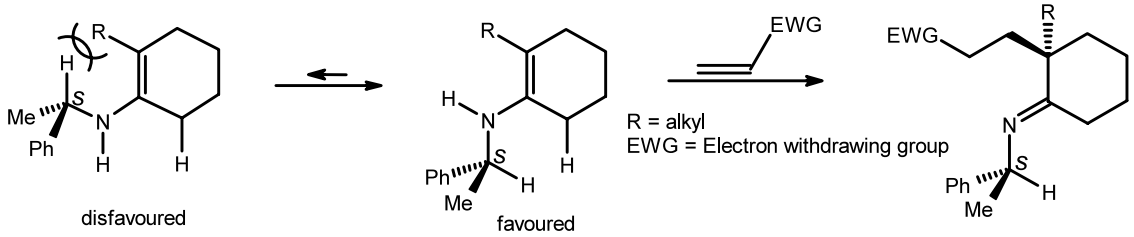

Figure 1.

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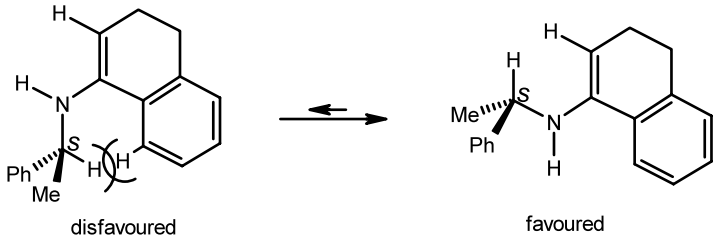


Figure 2.

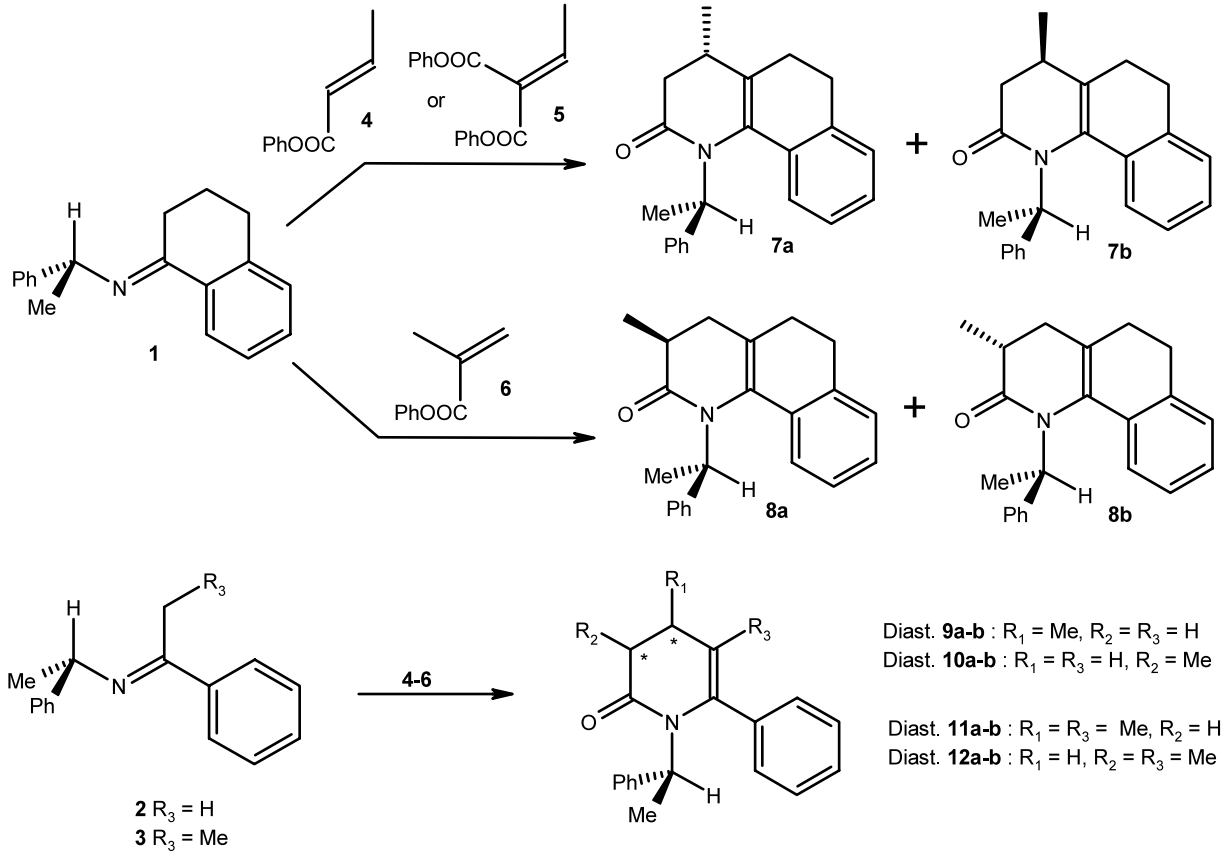
In the present instance dealing with a sterically hindered tetralone or alkylarylketone, the reactive conformation should be that in which the chiral moiety is on the same side of the double bond, thus inducing the opposite diastereofacial selectivity compared with the general case above (Fig. 2).

2. Results

The reactions of the chiral imines of α-tetralone, acetophenone and propiophenone were studied with three substituted olefins, i.e. phenyl crotonate **4**, diphenyl ethylidenemalonate **5** and phenyl methacrylate **6**. The imines **1**–**3** were prepared from the corresponding ketones and chiral (*S*)- or (*R*)-α-methylbenzylamine by azeotropic removal of water with toluene. Even in the presence of an acid catalyst (*p*TSA or TFA) the observed reaction times (48 h to 3 days) are rather long, and in some cases total conversion of the starting ketones was not observed. These experimental details reveal the low reactivity of these conjugated aromatic ketones with bulky amines. Since they are thermally unstable and cannot be purified by distillation, the crude imines were used in the Michael reactions.

Normally, the Michael reaction of the imines with substituted electrophilic olefins is slow and difficult.[1] Drastic conditions and long reaction times without solvent are required. In the present instance, the Michael reaction is followed by an aza-cyclization leading to a γ,δ-ethylenic-δ-lactam thus, as expected, avoiding any asymmetric center in the α-position (Scheme 1 and Table 1).

Conversions as well as diastereoselectivities of the reactions were evaluated by GC–MS analysis of the crude mixture. In two cases (entries 6 and 9) the diastereomers could not be separated by GC–MS and diastereomeric excesses were measured by ^{1}H NMR.



Scheme 1.

Table 1. Michael reactions of aromatic imines

Entry	Imines	Olefins	Reaction times at 100°C	Michael adducts	Diastereoselectivity	Overall yield[b]
1	**1**	**4**	5 days	**7a**/**7b**	63:37	42
2	**1**	**5**	15 h[a]	**7a**/**7b**	60:40	36
3	**1**	**6**	15 h	**8a**/**8b**	63:37	33
4	**2**	**4**	72 h	**9a**/**9b**	–	–
5	**2**	**5**	24 h[a]	**9a**/**9b**	52:48	33
6	**2**	**6**	48 h	**10a**/**10b**	64:36	19
7	**3**	**4**	10 days	**11a**/**11b**	70:30	81
8	**3**	**5**	18 h[a]	**11a**/**11b**	57:43	80
9	**3**	**6**	10 days	**12a**/**12b**	77:23	70

[a] Followed by: (i) NaOH/MeOH, 60°C, 17 h; (ii) toluene, 110°C, 4 h.
[b] Calculated from the corresponding starting ketones.

The diastereoselectivities observed in the reactions with the bicyclic imine **1** (entries 1, 2 and 3) are weak with the three olefins **4**, **5** and **6** (20–26%). The diastereomeric lactams **7a**, **7b**, **8a**, and **8b** were isolated by flash chromatography (FC). The observed diastereoselectivity of the reaction with diphenyl ethylidenemalonate **5** (entry 2) is slightly lower than that obtained with the phenyl crotonate **4** (entry 1). This fact is in agreement with the results already observed with this type of diactivated olefin.[5] Careful monitoring by GC–MS showed that the Michael reaction is relatively fast but that the aza-cyclization which follows is definitely slower (see Section 3). As long reaction times are necessary, partial degradation of the reagents takes place, thus lowering the yields.

With imine **2** (entries 5 and 6) the expected lactams **9** and **10** were obtained with olefins **5** and **6** but the observed yield was even lower with olefin **6** than in the case of imine **1**. These low yields are due to competition with self-aldolization of imine **2**. With the phenyl crotonate **4**, this last reaction was in fact the only one observed (entry 4). The diastereoselectivities are poor (entry 6) to non-existent (entry 5).

Finally, with imine **3** the diastereoselectivities and the yields are higher than those obtained with imines **1** and **2**. In this case self-aldolization was not observed. With phenyl methacrylate **6** (entry 9) the reaction leads to lactam with a diastereoisomeric excess higher than 50% and a 70% yield. The two diastereoisomers **12a** and **12b** were not separable by FC.

3. Discussion

As opposed to the diastereomers obtained from imines **2** and **3**, the two diastereomers **7a** and **7b** (entries 1 and 2) were separable by FC, and could be purified by recrystallization. The relative configuration of the major diastereomer **7a** was determined by single-crystal X-ray diffraction (Fig. 3).

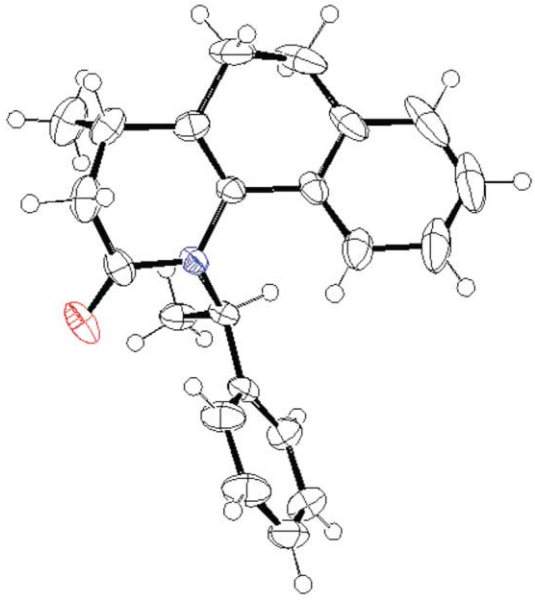


Figure 3. X-Ray structure of the major adduct **7a**.

The stereochemistry of the new stereogenic center in the major adduct **7a** is of the opposite configuration compared to the one observed with the cycloalkanone-imines in reaction with substituted olefins. This case thus represents the first example of inversion of diastereoselectivity. It can be explained if, as supposed (vide supra) the chiral moiety is located on the opposite side compared with the usual case. The observed weaker asymmetric induction, than in the normal cases, can be rationalized by the existence, in the chair transition state, of a destabilizing interaction between the methyl group of the chiral moiety and the vinyl hydrogen of the olefin. Conversely the boat transition state, while higher in energy,[4] does not present this type of interaction and can thus be in competition with the chair transition state (Fig. 4). Participation of the disfavoured structure shown in Fig. 2, can also account for the lowering of the usual diastereoselectivity.

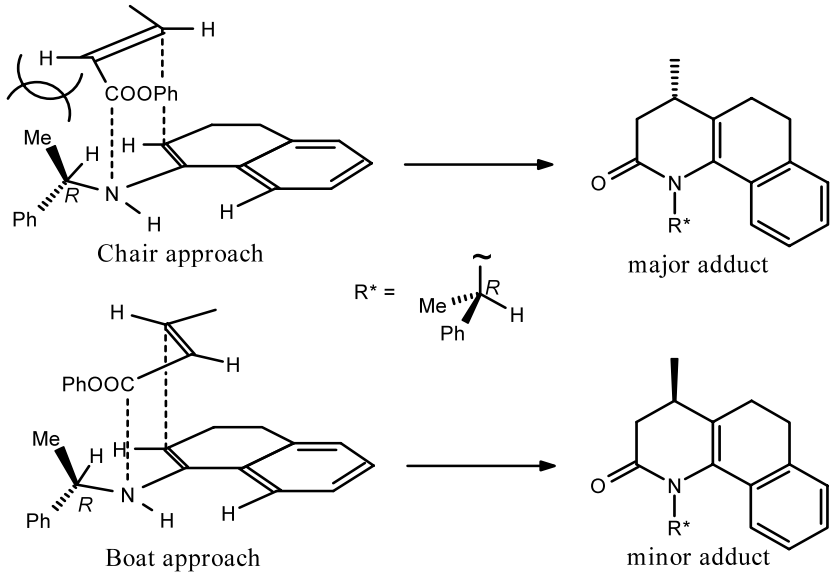


Figure 4. Possible transition states of the Michael reaction.

Finally, concerning the difficult aza-cyclization of the Michael adduct obtained from imine **1**, a similar result has already been observed for closely related compounds.[6] It may be due to the existence of a steric interaction between the chiral moiety and the aromatic ring in the ester function approach to the nitrogen atom (Fig. 5).

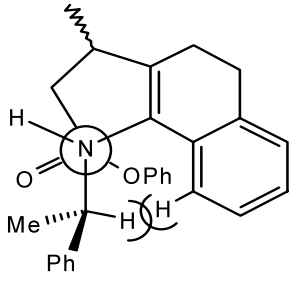


Figure 5.

4. Conclusion

The Michael reaction of aromatic imines with substituted olefins has allowed the generation only of asymmetric tertiary carbon centers in the cyclized adducts. However, the asymmetrical inductions were weaker than those usually observed with α-substituted cycloalkanones imines. Studies are in hand in our laboratory to make this process more efficient for applications in organic synthesis.

5. Experimental

5.1. General

Thin layer chromatography (TLC) was performed with glass plates (0.25 mm) precoated with silica gel and flash chromatography separations (FC) were carried out with silica gel (200–450 mesh), using EtOAc/cyclohexane as eluents (% EtOAc given). GLC–MS were performed with a HP 6890 GC apparatus (equipped with a 12 m×0.20 mm dimethylpolysiloxane capillary column) linked to a HP 5973 EIMS. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 200 and 50 MHz, respectively. Chemical shifts are expressed in ppm using TMS as internal standard and coupling constants (J) are given in Hz. All reactions were performed under an argon atmosphere. Unless indicated otherwise, organic phases were washed with a saturated NaCl aqueous solution, dried over $MgSO_4$, filtered, and evaporated under reduced pressure.

5.2. (3,4-Dihydro-2*H*-naphthalen-1-ylidene)-[1-(*R*)-phenyl-ethyl])-amine 1

A solution of α-tetralone (3.00 g, 20.5 mmol) and (*R*)-(+)-α-methylbenzylamine (99.9% ee, 2.64 mL, 20.5 mmol, 1 equiv.) with a trace of TFA in toluene (50 mL) was heated under reflux in a Dean–Stark apparatus for 48 h. After removal of the solvent under reduced pressure, crude imine **1** (5.67 g) was isolated and used for the next steps without purification. A GLC–MS analysis showed two signals at 4.97 min (α-tetralone, 30%) and 10.91 min (imine **1**, 70%); ^{1}H NMR δ 1.44 (d, $J=7.0$, 3H), 1.7–1.9 (m, 2H), 2.3–2.8 (m, 4H), 4.76 (q, $J=7.0$, 1H), 6.9–7.5 (m, 8H), 8.25–8.3 (m, 1H); EIMS (m/z): 249 (M$^+$, 33%), 248 (34), 234 (41), 105 (100), 77 (27).

5.3. 4-Methyl-1-(1-(*R*)-phenyl-ethyl)-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one 7a and 7b

Method A: from phenyl crotonate. Crude imine **1** (1.00 g, 4.01 mmol), phenyl crotonate **4** (0.72 mL, 4.42 mmol,

1.1 equiv.) with a trace of hydroquinone were heated at 100°C for 5 days. A GLC-MS analysis of the crude mixture showed two signals at 13.32 min (37%) and 13.56 min (63%). At rt, ether (60 mL) and 2.5 M aqueous NaOH (25 mL) were then added to the crude mixture which was stirred for 20 min. After ether extraction, washing with water to neutral pH and FC (15%), the lactams **7a** and **7b** (479 mg, 42% overall yield from α-tetralone) were isolated as a mixture of two diastereomers. *Method B: from diphenyl 2-ethylidenemalonate*. Crude imine **1** (0.50 g, 2.00 mmol), diphenyl 2-ethylidenemalonate **5** (622 mg, 2.20 mmol, 1.1 equiv.) with a trace of hydroquinone were heated at 100°C for 15 h. MeOH (20 mL) and 2.5 M aqueous NaOH (10 mL) were then added to the crude mixture which was heated at 60°C for 17 h. After evaporation of the MeOH under reduced pressure, 10% aqueous HCl was slowly added to acid pH. Ether extraction followed by usual work-up gave crude material which was dissolved in toluene (10 mL) and heated at 100°C for 3 h. A GLC–MS analysis of the crude mixture showed two signals at 13.37 (40%) and 13.63 min (60%). After toluene evaporation under reduced pression, extraction with ether and washing with 2.5 M NaOH (10 mL), usual work-up followed by FC (15%) gave the lactams **7a** and **7b** as a mixture of two diastereomers (204 mg, 36% overall yield from α-tetralone). Analytical samples of the two diastereomers were then obtained through recrystallization to give pure lactam **7a** and pure lactam **7b**; **major diastereomer 7a**: mp 130°C (AcOEt, cyclohexane); $[\alpha]_D^{20}=+54.8$, $[\alpha]_{578}^{20}=+57.7$, $[\alpha]_{546}^{20}=+68.0$, $[\alpha]_{436}^{20}=+147.5$ (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 1670 cm^{-1}; ^1H NMR: δ 1.12 (d, $J=6.3$, 3H), 1.84 (d, $J=7.0$, 3H), 2.21–2.77 (m, 7H), 4.81 (q, $J=7.0$, 1H), 7.10–7.40 (m, 9H). ^{13}C NMR: δ 17.17 (CH_3), 17.80 (CH_3), 26.09 (CH_2), 28.74 (CH_2), 30.47 (CH), 40.90 (CH_2), 57.54 (CH), 122.2 (CH), 126.3 (3CH), 126.6 (CH), 127.6 (CH), 128.0 (2CH), 130.8 (C_q), 131.0 (C_q), 136.5 ($2C_q$), 142.0 (C_q), 172.0 (C_q), EIMS (*m*/*z*): 317 (M^+, 3%), 213 (28), 198 (100), 105 (45), 77 (22); **minor diastereomer 7b**: mp 102°C (AcOEt, cyclohexane), $[\alpha]_D^{20}=-66.4$, $[\alpha]_{578}^{20}=-69.2$, $[\alpha]_{546}^{20}=-79.2$, $[\alpha]_{436}^{20}=-145.5$ (*c* 0.47, $CHCl_3$), IR ($CHCl_3$) 1662 cm^{-1}, ^1H NMR: δ 0.55 (d, $J=7.0$, 3H), 2.08 (d, $J=7.0$, 3H), 2.05–2.30 (m, 4H), 2.55 (q, $J=6.3$, 1H), 2.70–2.80 (m, 2H), 4.77 (q, $J=7.0$, 1H), 6.95–7.40 (m, 9H). ^{13}C NMR: δ 16.69 (CH_3), 17.77 (CH_3), 26.69 (CH_2), 28.88 (CH_2), 30.83 (CH), 40.53 (CH_2), 57.88 (CH), 122.3 (CH), 126.4 (CH), 126.7 (CH), 127.1 (CH), 127.6 (2CH), 127.7 (CH), 128.2 (CH) 131.1 (C_q), 131.3 (C_q), 135.1 (C_q), 136.6 (C_q) 140.3 (C_q), 172.7 (C_q); EIMS (*m*/*z*): 317 (M^+, 4%), 213 (25), 198 (100), 105 (55), 77 (28); X-ray structure determination of major diastereomer **7a**: vide infra.

5.4. 3-Methyl-1-(1-(*R*)-phenyl-ethyl)-3,4,5,6-tetrahydro-1*H*-benzo[*h*]quinolin-2-one 8a and 8b

Crude imine **1** (1.00 g, 4.01 mmol), phenyl methacrylate **6** (0.72 mL, 4.42 mmol, 1.1 equiv.) with a trace of hydroquinone were heated at 100°C for 15 h. A GLC–MS analysis of the crude mixture showed two signals at 40.92 (37%) and 41.03 min (63%). At room temperature, ether (60 mL) and 2.5 M aqueous NaOH (25 mL) were then added to the crude mixture which was stirred for 20 min. After ether extraction and washing with water to neutral pH, usual work-up followed by FC (15%) gave the lactams **8a** and **8b** (378 mg, 33% overall yield from α-tetralone) as a diastereomeric mixture. Analytical samples of the two diastereomers were obtained by careful FC separations followed by distillation; **major diastereomer 8a**: $[\alpha]_D^{20}$ +8.4, $[\alpha]_{578}^{20}=+8.8$, $[\alpha]_{546}^{20}=+10.5$, $[\alpha]_{436}^{20}=+24.6$ (*c* 3.07, $CHCl_3$); IR (thin film) 1671 cm^{-1}; ^1H NMR: δ 1.10 (d, $J=7.0$, 3H), 1.79 (d, $J=7.0$, 3H), 2.0–2.8 (m, 7H), 4.81 (q, $J=7.0$, 1H), 7.1–7.5 (m, 9H), ^{13}C NMR: δ 14.69 (CH_3), 18.16 (CH_3), 28.40 (CH_2), 28.48 (CH_2), 33.13 (CH_2), 36.95 (CH), 57.52 (CH), 121.9 (CH), 125.5 (C_q), 126.2 (CH), 126.3 (3CH), 126.6 (CH), 127.7 (CH), 128.0 (2CH), 131.1 (C_q), 135.7 (C_q), 136.6 (C_q), 142.0 (C_q), 175.5 (C_q), EIMS (*m*/*z*): 317 (M^+, 6%), 213 (100), 198 (27), 105 (92), 77 (46); **minor diastereomer 8b**: $[\alpha]_D^{20}=-79.4$, $[\alpha]_{578}^{20}=-82.6$, $[\alpha]_{546}^{20}=-93.4$, $[\alpha]_{436}^{20}=-158.4$ (*c* 1.36, $CHCl_3$); IR (thin film) 1672 cm^{-1}; ^1H NMR: δ 1.05 (d, $J=6.3$, 3H), 2.08 (d, $J=7.0$, 3H), 2.0–2.8 (m, 5H), 4.86 (q, $J=7.0$, 1H), 6.7–7.5 (m, 9H); ^{13}C NMR: δ 14.46 (CH_3), 18.27 (CH_3), 28.11 (CH_2), 28.53 (CH_2), 33.02 (CH_2), 36.68 (CH), 57.14 (CH), 122.1 (CH), 126.0 (C_q) 126.3 (CH), 126.6 (CH), 126.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 131.2 (C_q), 136.4 (C_q), 136.7 (C_q), 142.2 (C_q), 175.6 (C_q); EIMS (*m*/*z*): 317 (M^+, 5%), 213 (98), 198 (28), 105 (100), 77 (53).

5.5. [1-(*S*)-Phenyl-ethyl)-(1-phenyl-ethylidene]-amine 2

A solution of acetophenone (3.00 mL, 25.6 mmol) and (*S*)-(−)-α-methylbenzylamine (99.9% ee, 3.30 mL, 25.6 mmol, 1 equiv.) with a trace of pTSA in toluene (50 mL) was heated under reflux in a Dean-Stark apparatus for 3 days. After removal of the solvent under reduced pressure, crude imine **2** (6.40 g) was obtained and used for the next steps without purification. A GLC–MS analysis of this crude imine showed three signals at 1.51, 1.63 min (starting materials) and 8.69 min (imine **2**, 77% conversion); ^1H NMR δ 1.60 (d, $J=7.0$, 3H), 2.30 (s, 3H), 4.90 (q, $J=7.0$, 1H), 7.1–7.6 (m, 9H), 7.9 (m, 1H); EIMS (*m*/*z*): 223 (M^+, 28%), 222 (37), 208 (21), 105 (100), 77 (34).

5.6. 4-Methyl-6-phenyl-1-(1-(*S*)-phenyl-ethyl)-3,4-dihydro-1*H*-pyridin-2-one 9a and 9b

Crude imine **2** (253 mg, 1.13 mmol), diphenyl 2-ethylidenemalonate **5** (346 mg, 1.22 mmol, 1.1 equiv.) with a trace of hydroquinone were heated at 100°C for 24 h. MeOH (20 mL) and 2.5 M aqueous NaOH (10 mL) were then added to the crude mixture which was heated at 60°C for 17 h. After evaporation of the MeOH under reduced pressure, 10% aqueous HCl was slowly added to acid pH. Ether extraction followed by usual work-up gave crude material which was dissolved in toluene (10 mL) and heated at 100°C for 3 h. A GLC–MS analysis of the crude mixture showed two signals at 27.51 (48%) and 27.68 min (52%). After toluene evaporation under reduced pressure, extraction with ether and washing with 2.5 M aqueous NaOH (10 mL), usual work-up followed by FC (15%) gave the lactams as a mixture of

two diastereomers **9a** and **9b** (98 mg, 33% overall yield from acetophenone); IR (thin film) 1644 cm^{-1}; ^1H NMR (two diastereomers mixture): δ 0.90 and 1.05 (d, $J=7.0$, 3H), 1.64 and 1.71 (d, $J=7.0$, 3H), 2.2–2.7 (m, 6H), 4.70 and 4.95 (q, $J=7.0$, 1H), 5.18 and 5.22 (d, $J=4$, 1H) 7.0–7.4 (m, 10H). ^{13}C NMR (two diastereomers mixture): δ 17.04 (CH_3), 17.27 (CH_3), 18.98 (CH_3), 19.51 (CH_3), 26.19 (CH), 26.27 (CH), 40.86 (CH_2), 41.41 (CH_2), 54.82 (CH), 55.14 (CH), 118.0 (2CH), 122.4 (2CH), 126.4 (CH), 126.5 (2CH), 126.9 (2CH), 127.7 (3CH), 127.9 (2CH), 128.0, 128.1 (2CH), 128.2 (CH), 128.4 (2CH), 136.7 (C_q), 136.8 (C_q), 141.0 (C_q), 141.9 (C_q), 142.7 (C_q), 143.3 (C_q), 171.8 (C_q), 172.0 (C_q); EIMS (m/z): 291 (M^+, 14%), 187 (38), 172 (100), 105 (40), 77 (17).

5.7. 3-Methyl-6-phenyl-1-(1-(*S*)-phenyl-ethyl)-3,4-dihydro-1*H*-pyridin-2-one 10a and 10b

Crude imine **2** (1.02 g, 4.57 mmol), phenyl methacrylate **6** (0.85 mL, 5.24 mmol, 1.14 equiv.) with a trace of hydroquinone were heated at 100°C for 48 h. A GLC–MS analysis of the crude mixture showed one signal at 27.41 min. At room temperature, THF (15 mL), ether (35 mL) and 2.5 M aqueous NaOH (25 mL) were then added to the crude mixture which was stirred for 30 min. After ether extraction and washing with water to neutral pH, usual work-up followed by FC (15%) gave the lactams **10a** and **10b** (226 mg, 19% overall yield from acetophenone) as a diastereomeric mixture; IR (thin film) 1680 cm^{-1}; ^1H NMR (64:36 two diastereomers mixture): δ 1.18 and 1.30 (d, $J=7.0$, 3H), 1.67 and 1.79 (d, $J=7.0$, 3H), 2.0–2.8 (m, 3H), 4.81 and 5.00 (q, $J=7.0$, 1H), 5.25 and 5.40 (dd, $J=5.5$ and 6.3, 4.7 and 3.1, 1H), 7.0–7.7 (m, 10H), ^{13}C NMR: δ 14.96 (CH_3), 15.30 (CH_3), 17.21 (CH_3), 17.48 (CH_3), 27.63 (CH_2), 27.67 (CH_2), 36.58 (CH), 36.79 (CH), 54.59 (CH), 55.0 (CH), 110.3 (CH), 110.6 (CH), 121.4 (CH), 125.8 (CH), 126.3 (2CH), 126.4 (CH), 126.9 (CH), 127.3 (CH), 127.6 (CH), 127.8 (2CH), 127.9 (2CH), 128.0 (2CH), 128.1 (2CH), 128.3 (CH), 128.6 (CH), 129.4 (CH), 133.1 (CH), 137.1 (C_q), 137.2 (C_q), 141.6 (C_q), 142.3 (C_q), 143.4 (C_q), 144.4 (C_q), 174.4 ($2C_q$); EIMS (m/z): 291 (M^+, 26%), 187 (100), 172 (61), 159 (23), 105 (74), 77 (27).

5.8. (1-(*S*)-Phenyl-ethyl)-(1-phenyl-propylidene)-amine 3

A solution of propiophenone (6.80 mL, 48.2 mmol) and (*S*)-(−)-α-methylbenzylamine (99.9% ee, 6.20 mL, 48.2 mmol, 1 equiv.) with a trace of pTSA in toluene (50 mL) was heated under reflux in a Dean–Stark apparatus for 96 h. After removal of the toluene under reduced pressure, crude imine **3** (11.5 g) was obtained and used for the next steps without purification. A GLC–MS analysis of this crude imine showed two signals at 2.66 (12.5%, propiophenone) and 8.49 min (imine **3**, 87.5% conversion); ^1H NMR (*Z* and *E* isomers mixture) δ 1.02 and 1.07 (t, $J=7.8$, 3H), 1.34 and 1.51 (d, $J=6.3$ and 7.0, 3H), 2.53 and 2.70 (q, $J=7.8$, 2H), 4.36 and 4.86 (q, $J=7.0$ and 6.3, 1H), 7.1–8.0 (m, 10H); EIMS (m/z): 237 (M^+, 21%), 105 (100), 77 (27).

5.9. 4,5-Dimethyl-6-phenyl-1-(1-(*S*)-phenyl-ethyl)-3,4-dihydro-1*H*-pyridin-2-one 11a and 11b

Method A: from phenyl crotonate. Crude imine **3** (1.50 g, 6.23 mmol), phenyl crotonate **4** (1.23 mL, 7.56 mmol, 1.2 equiv.) with a trace of hydroquinone were heated at 100°C for 10 days. A GLC–MS analysis of the crude mixture showed two signals at 25.37 (70%) and 25.51 min (30%). At room temperature, ether (60 mL) and 2.5 M aqueous NaOH (25 mL) were added to the crude mixture which was stirred for 20 min. After ether extraction, washing with water to neutral pH, usual work-up followed by FC (15%) gave the lactams **11a** and **11b** (1.57 g, 81% overall yield from propiophenone).

Method B: from diphenyl 2-ethylidenemalonate. Crude imine **3** (531 mg, 2.24 mmol), diphenyl 2-ethylidenemalonate **5** (642 mg, 2.27 mmol, 1 equiv.) with a trace of hydroquinone were heated at 100°C for 18 h. MeOH (30 mL) and 2.5 M aqueous NaOH (20 mL) were then added to the crude mixture which was heated at 60°C for 17 h. After evaporation of the MeOH under reduced pressure, 10% aqueous HCl was slowly added to the mixture at 0°C until acid pH. Ether extraction followed by usual work-up gave crude material which was dissolved in toluene (10 mL) and heated at 100°C for 3 h. A GLC–MS analysis of the crude mixture showed two signals at 25.19 (57%) and 25.34 min (43%). After toluene evaporation under reduced pression, extraction with ether and washing with 2.5 M aqueous NaOH, usual work-up followed by FC (15%) gave the lactams **11a** and **11b** as a mixture of two diastereomers (545 mg, 80% overall yield from propiophenone); IR (thin film) 1650 cm^{-1}; ^1H NMR (two diastereomeric mixture): δ 0.95 and 1.15 (d, $J=7.0$, 3H), 1.55 and 1.63 (s, 3H), 1.58 and 1.64 (d, $J=7.0$, 3H), 2.2–2.4 (m, 2H), 2.6–2.8 (m, 1H), 4.68 and 4.80 (q, $J=7.0$, 1H), 7.1–7.5 (m, 10H); ^{13}C NMR: δ 16.42 (CH_3), 16.84 ($2CH_3$), 17.01 (CH_3), 17.61 (CH_3), 18.08 (CH_3), 31.90 (CH), 32.43 (CH), 39.73 (CH_2), 40.14 (CH_2), 53.97 (CH), 54.33 (CH), 121.5 (C_q), 121.6 (C_q), 126.2 (CH), 126.4 (2CH), 127.1 (CH), 127.6 (CH), 127.7 (CH), 127.8 (2CH), 128.1 (2CH), 128.3 (2CH), 135.2 (C_q), 135.4 (C_q), 135.6 ($2C_q$), 141.8 (C_q), 141.9 (C_q), 169.7 (C_q), 169.9 (C_q); EIMS (m/z): 305 (M^+, 17%), 201 (40), 186 (100), 105 (27), 77 (18).

5.10. 3,5-Dimethyl-6-phenyl-1-(1-(*S*)-phenyl-ethyl)-3,4-dihydro-1*H*-pyridin-2-one 12a and 12b

Crude imine **3** (1.50 g, 6.23 mmol), phenyl methacrylate **6** (1.23 mL, 7.56 mmol, 1.2 equiv.) with a trace of hydroquinone were heated at 100°C for 10 days. A GLC–MS analysis of the crude mixture showed one signal at 12.96 min. At room temperature, ether (40 mL) and 2.5 M aqueous NaOH (25 mL) were then added to the crude mixture which was stirred for 20 min. After ether extraction and washing with water to neutral pH, usual work-up followed by FC (15%) gave the lactams **12a** and **12b** (1.35 g, 70% overall yield from propiophenone) as a diastereomeric mixture; IR (thin film) 1650 cm^{-1}; ^1H NMR (77:23 diastereomeric mix-

ture): δ 1.20 and 1.25 (d, $J=6.3$, 3H), 1.53 and 1.63 (d, $J=7.0$, 3H), 1.58 and 1.65 (s, 3H), 2.1–2.5 (m, 2H), 2.5–2.8 (m, 1H), 4.80 and 5.0 (q, $J=7.0$, 1H), 6.8–7.4 (m, 10H), ^{13}C NMR (77:23 diastereomeric mixture): δ 14.87 (CH_3), 15.05 (CH_3), 16.82 (CH_3), 17.05 (CH_3), 19.45 (CH_3), 19.53 (CH_3), 34.58 (CH_2), 34.67 (CH_2), 36.02 (CH), 36.21 (CH), 53.63 (CH), 54.13 (CH), 115.3 (CH), 116.5 (C_q), 116.7 (C_q), 119.4 (CH), 126.1 (2CH), 126.2 (CH), 126.4 (CH), 127.7 (2CH), 127.8 (CH), 127.9 (2CH), 128.1 (CH), 129.2 (CH), 130.0 (2CH), 135.4 (C_q), 135.5 ($2C_q$), 136.3 (C_q), 141.8 (C_q), 142.5 (C_q), 173.4 (C_q), 173.5 (C_q); EIMS (m/z): 305 (M^+, 26%), 201 (100), 186 (70), 172 (32), 105 (51), 77 (29).

5.11. X-Ray structure determination of lactame 7a

Formula: $C_{22}H_{23}NO$, MW = 317.43, monoclinic, space group $P2_1$; $a=9.132(1)$, $b=14.702(1)$, $c=13.501(1)$ Å, $\beta=102.83(1)$, $V=1767.8(3)$ Å^3, $Z=4$; $M=317.4$ g; $D_{calcd}=1.193$ g cm^{-3}; $F(000)=680$. The structure was solved by direct methods using SHELXS97.[7] Refinement, based on F,[8] was carried out by full matrix least squares with SHELXL97 software. An ORTEP[9] diagram is given in Figure 3. Non hydrogen atoms were refined anisotropically. The hydrogen atoms were positioned geometrically and refined riding on their carrier atom with isotropic thermal displacement parameters fixed at 1.2 times those of their parent atoms. Convergence was reached at $R_1=0.033$ for 5768 reflections ($I>2\sigma(I)$), $wR_2=0.077$ for all data and $S=1.023$ for 437 parameters. The residual electron density in the final difference Fourrier does not show any feature above 0.139 e Å^{-3} and below –0.198 e Å^{-3}.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 205637. 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].

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References

1. (a) Pfau, M.; Tomas, A.; Lim, S.; Revial, G. *J. Org. Chem.* **1995**, *60*, 1143–1147; (b) Jabin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795–1812; (c) Jabin, I.; Revial, G.; Pfau, M.; Decroix, B.; Netchitaïlo, P. *Org. Lett.* **1999**, *1*, 1901–1904; (d) Revial, G.; Jabin, I.; Pfau, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4975–4983; (e) Jabin, I.; Redolfi, M.; Pfau, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1683–1688.
2. One example of this concept with chiral enaminoesters was already described: Revial, G.; Lim, S.; Viossat, B.; Lemoine, P.; Tomas, A.; Duprat, A. F.; Pfau, M. *J. Org. Chem.* **2000**, *65*, 4593–4600.
3. (a) Agami, C.; Bihan, D.; Morgentin, R.; Puchot-Kadouri, C. *Synlett* **1997**, 799–800; (b) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2000**, *65*, 4435–4439; (c) Maldaner, A.; Pilli, R. *Tetrahedron* **1999**, *55*, 13321–13332.
4. (a) Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.* **1986**, *51*, 2671–2675; (b) Sevin, A.; Masure, D.; Giessner-Prettre, C.; Pfau, M. *Helv. Chim. Acta* **1990**, *73*, 552–573.
5. Jabin, I.; Revial, G.; Monnier-Benoit, N.; Netchitaïlo, P. *J. Org. Chem.* **2001**, *66*, 256–261.
6. (a) Jabin, I.; Monnier-Benoit, N.; Le Gac, S.; Netchitaïlo, P. *Tetrahedron Lett.* **2003**, *44*, 611–614; (b) Monnier-Benoit, N. Ph.D. Thesis, Le Havre University, Jan. 31, 2003.
7. Sheldrick, G. M. SHELXS97. Program for solution of crystal structures. University of Göttingen, Germany, 1990.
8. Sheldrick, G. M.; Schneider, T. R. SHELXL97: high resolution refinement, Methods in Enzymology, 277, Carter, C. W., Jr.; Sweet, L. M., Eds.; Academic Press: San Diego, pp. 319–343.
9. Johnson, C. K. ORTEP. A thermal Ellipsoid Plotting Program; Oak Ridge National, Laboratories: Oak Ridge, TN, 1976.