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Rapid synthesis of quinoline-4-carboxylic acid derivatives from arylimines and 2-substituted acrylates or acrylamides under indium(III) chloride and microwave activations. Scope and limitations of the reaction

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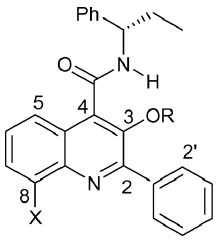
Rapid synthesis of quinoline-4-carboxylic acid derivatives has been achieved by reaction of 2-methoxy acrylates or acrylamides with *N*-arylbenzaldimines in acetonitrile under $InCl_3$ catalysis and microwave irradiation. Isolated yields up to 57% within 3 min have been obtained. The Lewis acid and the microwave activation appeared as crucial parameters for the reaction. The role of indium chloride and ytterbium triflate was specified using ^{13}C NMR data and model theoretical studies.

Introduction

Quinoline derivatives are entities often synthesised because of their occurrence in natural products and their widespread biological activities (*i.e.* inhibitor of neurokinin receptors,[1] of Na^+/H^+ exchange,[2] of caspase,[3] and phosphodiesterase enzyme[4]), their potential as chemotherapeutic agents (malaria,[5] cancer,[6] disorders of central nervous system,[7] antimicrobial agents[8]) or as imaging agents.[9] Recently, we showed that the introduction of a fluorine atom in the 8-position of the quinoline ring did not alter the affinity towards NK-3 receptors (Fig. 1) compared to Talnetant, a selective and potent NK-3 antagonist.[10] In our continuing interest for the development of NK-3 receptor radioligands,[11] for medical imaging using positron emission tomography (PET), we needed to develop a rapid synthesis of fluoroquinoline-4-carboxylic acid derivatives in order to have in hand a method for the introduction of an ^{18}F isotope ($t_{1/2}$ 110 min) from easily available radiolabeled precursors.[12]



h-NK-3	Ki, nM
X = H, R = H (Talnetant)	27
X = F, R = Me	27
X = F, R = H	24

Fig. 1 NK-3 receptors.

Several methods have been described for the synthesis of substituted quinolines. They are usually based on the reaction of primary aromatic amines with β-diketones (Combes reaction),[13] with β-keto esters[14] followed by a ring closure of the intermediate, under heating (Conrad–Limpach) or acid-catalysis (Knorr synthesis).[15] Reaction of anilines with acrolein (from glycerol and sulfuric acid) in the presence of an oxidizing agent is another common method to prepare quinolines (Skraup reaction).[16] This approach has been successfully applied to quinolines substituted on the heterocycle moiety using α,β-unsaturated ketones under indium trichloride catalysis and under microwave activation.[17] Quinoline derivatives have also been formed under basic conditions when 2-aminobenzaldehydes are condensed with ketones (Friedlander reaction).[14,16,18] However, this approach, and the previous ones, are limited to the synthesis of 4-alkyl-substituted quinolines.

The introduction of a carboxylic acid function in the 4-position of the heterocycle has only been achieved by the Pfitzinger or by the Doebner reactions. The former (Pftizinger) is based on the condensation of isatic acids with α-methylene carbonyl compounds.[14,16,19] The poor availability of isatins, the lengthy reaction times and the reaction conditions have restricted this route to the synthesis of base-stable quinolinecarboxylic acids. The Doebner reaction, a three-component reaction between benzaldehyde, pyruvic acid and an aniline, allows the preparation of various 2-phenyl-4-quinolinecarboxylic acids including those bearing a fluorine atom in the 5-, 6-,[20] 7- or 8-position.[14,21,22] However, attempts to prepare the 6-fluoro derivative with the claimed yields failed in our hands.

The aza-Diels–Alder reaction between an *N*-arylimine and vinyl ethers,[23–25] or cyclopentadiene[26] catalyzed by a Lewis acid (the Povarov reaction)[27] was studied. According to the reaction conditions alkyltetrahydroquinolines or alkylquinolines were obtained. This methodology was also applied to the preparation of 2-trifluoromethylquinolines *via* their tetrahydro intermediates.[28]

It seemed to us that the Povarov reaction could be a good alternative to the previously described methods for the rapid preparation of fluoro-substituted quinolinecarboxylic acid derivatives. Indeed, *N*-(fluorophenyl)benzaldimines or to *N*-aryl fluorobenzaldimines labeled with fluorine-18 could be easily synthesised from [2-][29] or [4-^{18}F]fluoroaniline,[30] [4-^{18}F] or [2-^{18}F]fluorobenzaldehydes.[31] We anticipated that the reaction of *N*-arylimines **1** with an acrylate bearing a leaving group at C2 (**2**–**7**) could rapidly afford quinoline-4-carboxylic derivatives

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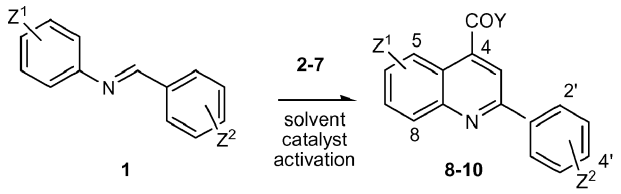
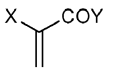
8–10 (Scheme 1) *via* an *in situ* sequence: cycloaddition, elimination and aromatization (Scheme 2).[26] Such a procedure, in which the corresponding intermediate tetrahydroquinolines are not isolated, would avoid the time-consuming oxidizing step.[25–27,38] Here, we present the scope and limitations of the reaction of imines **1** and dienophiles **2**,[32] **3**–**5**, **6**,[33] and **7**,[34] presented in Scheme 1, with an attempt to understand the reactivity of the different partners.

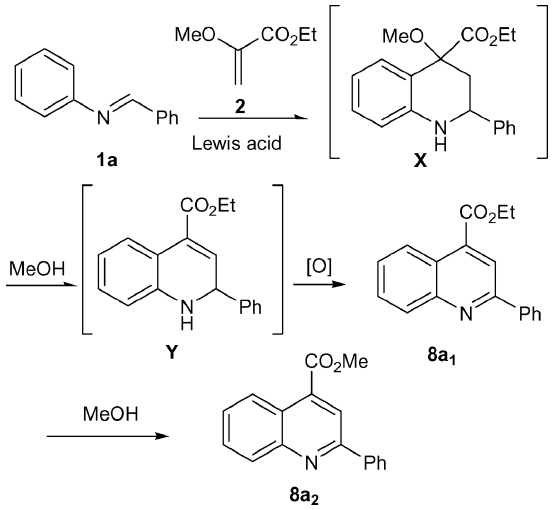


	Z^1	Z^2		Z^1	Z^2
a	H	H	**i**	H	4'-NO_2
b	H	2'-F	**j**	H	4'-F
c	H	2'-CF_3	**k**	6-F	H
d	H	3'-Br	**l**	6-Cl	H
e	H	3'-NO_2	**m**	6-Br	H
f	H	3',4'-OMe	**n**	H	3'-F
g	H	4'-Br	**o**	8-F	H
h	H	4'-CN			



	X	Y
2	OMe	OEt
3	OMe	NHiPr
(*S*)-4	OMe	NH-CH(Ph)Et
5	OMe	NHPh
6	OTf	OEt
7	Br	OMe

Scheme 1 Reaction of imines **1** with 2-substituted acrylic acid derivatives **2**–**7**.



Scheme 2 Postulated intermediates in the reaction of imine **1a** with acrylate **2**.

Results and discussion

Acrylates bearing a leaving group at C2 were chosen as dienophiles and the reaction of imine **1a** and acrylate **2** was studied as a model for the preparation of ethyl quinolinecarboxylic esters **8a**$_1$ (Scheme 2).

In our first attempts, imine **1a** was allowed to react with an excess (2.5 equiv.) of acrylate **2** either without, or in the presence of ytterbium triflate (0.1–0.4 equiv.).[24] Whatever the temperature and heating mode (room temperature, reflux of acetonitrile or microwave activation), no reaction was observed (*i.e.*, Table 1, entries 1, 2). Different Lewis acids were then tested. The starting material was completely recovered when using $BiCl_3$,[35] whereas decomposition was the major reaction with $ZnCl_2$,[36] $SnCl_4$,[37] InF_3, $In(O^tBu)_3$, $Sc(OTf)_3$,[23,38,39] the esters **8a**$_1$ and **8a**$_2$ (not separable) being obtained in yields around 10% (relative ratio: 75 : 25). The formation of this mixture of esters is not surprising due to the ability of Lewis acids to promote transesterifications.[40] The best results (yield: 57%, Table 1, entry 4) were obtained when $InCl_3$ [17] was used in conjunction with microwave irradiation. $InBr_3$ or InI_3 were less efficient (Table 1, entries 5, 6) and the use of a mixture of indium and chlorotrimethylsilane[41] did not improve the yields (Table 1, entry 9). As expected, the tetrahydroquinoline intermediate **X** was never detected in the ^{1}H NMR spectra of the crude products. In order to optimize the yields, different solvents (DMF,[42] CH_3CN, EtOH, toluene,[43] H_2O/CH_3CN [23]) or solid supports (SiO_2,[17] Al_2O_3,[44] montmorillonite [45]) were tested. Some of the results are shown in Table 2. Acetonitrile gave the best results (Table 2, entry 1). DMF and toluene (Table 2, entries 2, 4) gave no reaction. Yields of less than 40% were obtained when the reaction was performed on silica gel impregnated with indium(III) chloride and with microwave irradiation (Table 2, entries 8, 9), a method which was previously shown to be efficient for the preparation of 4-alkylquinolines from anilines and α,β-unsaturated ketones.[17]

Ionic liquids, which have been found to catalyze the three-component coupling reaction of aldehydes, amines and cyclic enol ethers at room temperature,[47] were also tested under microwave irradiation. No reaction was observed when the reaction was performed in 1,3-di-*n*-butylimidazolium bromide or tetrafluoroborate, [bbim]Br or [bbim]BF_4. However traces of the expected esters **8a** were detected in the crude ^{1}H NMR spectrum when indium(III) chloride was added to the ionic liquid (Table 2, entry 7). Using montmorillonite KSF at room temperature according to a described procedure,[48] or indium(III) chloride (0.2 equiv.) supported on alumina[49] under microwave activation (150 W, 10 min) did not allow the reaction of imine **1** with acrylate **2** to proceed.

Fig. 2 presents the yields of quinolinecarboxylic esters **8a**$_1$ and **8a**$_2$ as a function of (a) the amount of indium trichloride, (b) the microwave power, and (c) the reaction time. All the data show that the reaction is sensitive to all of these parameters. The highest yields can be reached when using 0.5 equiv. of indium

Table 1 Lewis acid screen for the reaction of imine **1a** with 2-methoxy acrylate **2** [a]

Entry	Lewis acid	Loading/equiv.[b]	Activation[c]	Time	Yield (%)[d]
1	$Yb(OTf)_3$	0.4	90 °C	24 h	0[e]
2	$Yb(OTf)_3$	0.4	150 W	3 min	Trace
3	$InCl_3$	0.5	90 °C	24 h	41
4	$InCl_3$	0.5	150 W	3 min	57
5	$InBr_3$	0.5	150 W	3 min	30
6	InI_3	0.5	150 W	3 min	36
7	$In(OTf)_3$	0.5	150 W	3 min	18
8	$In(O^tBu)_3$	0.5	150 W	3 min	0
9	In–TMSCl	0.5 : 10	150 W	3 min	24
10	$Sc(OTf)_3$	0.2	150 W	3 min	12

[a] Solvent: acetonitrile; reaction carried out with 0.1 mmol of imine **1a**, 0.25 mmol of **2**. [b] Lewis acid equivalent for one equivalent of imine. [c] Classical heating or microwave irradiation. [d] Isolated yields of esters **8a**$_1$ and **8a**$_2$. [e] The starting material was quantitatively recovered.

Table 2 Solvent and solid support screen for the reaction of imine **1a** with acrylate **2**[a]

Entry	$InCl_3$/equiv.	Reaction medium[b]	Time/min	Yield (%)[c]
1	0.5	CH_3CN	3	57
2	0.5	DMF	3	0
3	0.5	EtOH	3	18
4	0.5	Toluene	3	0
5	0.5	H_2O–CH_3CN (v : v, 1 : 1)	3	0
6	0.5	CH_3CN–perfluoro(methylcyclohexane) (v : v, 1 : 1)[46]	3	39
7	0.5	[bbim][BF_4][d]	3	<5
8	0.2	SiO_2	4	33
9	0.2	SiO_2	10	38

[a] Reaction carried out with imine **1a** (0.1 mmol), **2** (0.25 mmol), and $InCl_3$. [b] Microwave activation, 150 W, solvent (2 mL) or solid support (200 mg). [c] Isolated yields. [d] [bbim][BF_4]: 1,3-di-*n*-butylimidazolium tetrafluoroborate.

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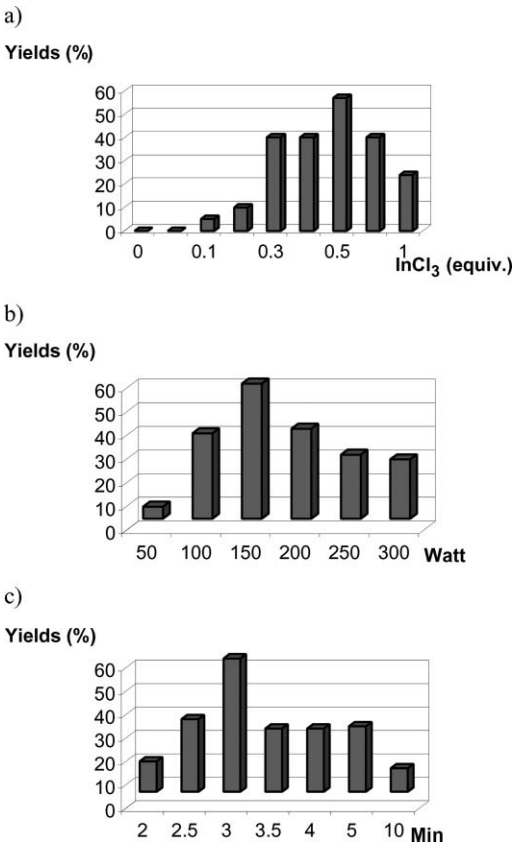

Fig. 2 Reaction of imine **1a** with acrylate **2**. Yields as a function of (a) amount of $InCl_3$, (b) power of microwave irradiation, (c) reaction time.

trichloride, and a 150 W microwave power for 3 min. Lowering or increasing the amount of indium rapidly decreased the yields (Fig. 2a). The reaction time appeared very important: the yields dropped to 30% if the time was increased to 3.5 and 5 min (Fig. 2c). A similar trend was observed with the microwave power (Fig. 2b). When going from 150 to 200 W the yields dropped from 57 to 35%.

To account for these results, the stability of the dienophile under the reaction conditions was studied. When acrylate **2** or imine **1a** was separately submitted to the reaction conditions [acetonitrile, $InCl_3$ (0.5 equiv.), 150 W microwave activation, 3 min], complete polymerization of acrylate **2** was observed whereas more than 80% of imine **1a** were recovered. Under these conditions, the quinolines $\mathbf{8a_1}$ and $\mathbf{8a_2}$ were stable.

Other acrylates were then tested. Substitution of the methoxy group of acrylate **2** for a triflyl or a bromo substituent dramatically decreased the yields of the quinoline carboxylates (Table 3, entries 1–3). The transformation of 2-methoxy acrylate into amide **3** and the reaction of the latter with imine **1a** gave the expected amide **9** in moderate yields (Table 3, entry 4). The use of one equivalent of Lewis acid (Table 3, comparison of entries 4–7) was necessary for reaching 57%. Under these conditions and starting from acrylamide **4**, the quinoline **10** was formed in 47% yield (Table 3, entry 8). No reaction was observed with the *N*-phenyl amide **5** whatever the amount of $InCl_3$ (0.5 or 1 equiv.) used (data not shown).

Acrylate **2** being formed by thermal elimination of methanol from the acetal **12** of ethyl pyruvate **13**,[32] reaction of this acetal **12** with imine **1a** was attempted under microwave activation (3 min, 150 W) and in the presence of indium trichloride (0.5 equiv.). The expected quinolines $\mathbf{8a_1}$ and $\mathbf{8a_2}$ were formed in 17% yield. Under the same conditions, ethyl pyruvate **13** and imine **1a** yielded the quinolinecarboxylic esters **8a** in 27% yield. Finally, attempts to carry out the reaction in a one-pot procedure [aniline, benzaldehyde, acrylate **2**, $InCl_3$ (0.5 equiv.), 150 W, 3 min] did not afford the expected esters **8a** but gave tars.

The scope and limitations of the reaction were studied. The results are presented in Table 4. The cycloaddition appears to be dependent on the substituent on both aromatic rings. On the aldehyde end of the imine, an electron withdrawing group in the *ortho*- or *meta*-position impeded the cycloaddition (Table 4, entries 3, 5) whereas a halogen in these positions allowed the formation of quinolines **8b**, **8d**, **9b**, **10b** and **10n** in 35–53% yields (Table 4, entries 2, 4, 15, 17 and 20). No such effect resulted from substitution in the *para*-position (Table 4, entries 7–10, 18).

Table 3 Reaction of imine **1a** with different dienophiles

Entry	X	Y	Dienophile[a]	$InCl_3$/equiv.	Yield (%)[b]
1	OMe	OEt	**2**	0.5	57
2	OTf	OEt	**6**	0.5	20
3	Br	OMe	**7**	0.5	4
4	OMe	NH^{i}Pr	**3**	0.5	36
5	OMe	NH^{i}Pr	**3**	0.8	45
6	OMe	NH^{i}Pr	**3**	1.0	57
7	OMe	NH^{i}Pr	**3**	1.5	34
8	OMe	NH–(*S*)–CH(Ph)Et	**4**	1.0	47

[a] Reaction conditions: 2.5 equiv. *vs.* imine, microwave 150 W, 3 min. [b] Isolated.

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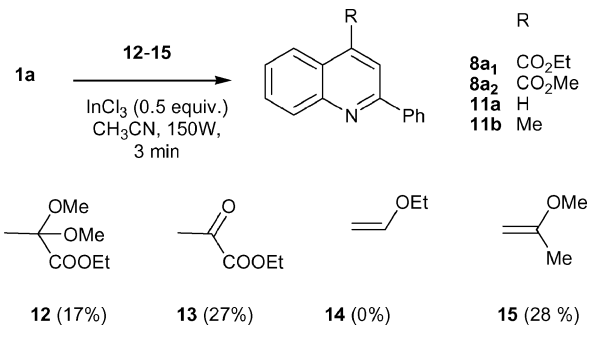
Table 4 Synthesis of quinolinecarboxylic esters and amides **8**–**10** [a]

Entry	Product	Y	Z^1	Z^2	Yield (%)[b]
1	**8a**	OR[c]	H	H	57
2	**8b**	OR[c]	H	2′-F	40
3	**8c**	OR[c]	H	2′-CF_3	0
4	**8d**	OR[c]	H	3′-Br	45
5	**8e**	OR[c]	H	3′-NO_2	0
6	**8f**	OR[c]	H	3′,4′-$(OMe)_2$	31
7	**8g**	OR[c]	H	4′-Br	20
8	**8h**	OR[c]	H	4′-CN	32
9	**8i**	OR[c]	H	4′-NO_2	23
10	**8j**	OR[c]	H	4′-F	27
11	**8k**	OR[c]	6-F	H	24
12	**8l**	OR[c]	6-Cl	H	25
13	**8m**	OR[c]	6-Br	H	52
14	**9a**	NH^{i}Pr	H	H	57
15	**9b**	NH^{i}Pr	H	2′-F	43
16	**10a**	NHCH(Ph)Et	H	H	47
17	**10b**	NHCH(Ph)Et	H	2′-F	35
18	**10j**	NHCH(Ph)Et	H	4′-F	48
19	**10k**	NHCH(Ph)Et	6-F	H	49
20	**10n**	NHCH(Ph)Et	H	3′-F	53
21	**10o**	NHCH(Ph)Et	8-F	H	53

[a] Reaction conditions: imine **1a** (0.1 mmol), **2** (0.25 mmol), and $InCl_3$ (0.5 equiv. for **2**, 1 equiv. for **3** and **4**), 150 W, acetonitrile (2 mL), 3 min. [b] Isolated yield. [c] Mixture of ethyl and methyl esters in a 75 : 25 ratio.

When the aniline component was substituted with a halogen on the *para*-position, the best yields were observed with less electron withdrawing atoms (Br compared to Cl and F, Table 4, entries 11–13). Finally, comparisons of the yields obtained in the formation of fluoroquinoline carboxylic esters and amides showed that higher yields were obtained with amides wherever the halogen was located (Table 4, entries 2, 10, 11, 15, 17–21). All these data significantly differ from previous observations,[50] where high yields were obtained for the Brønsted acid-catalyzed reaction of electron-deficient imines with vinyl ethers such as dihydropyran as the dienophile.

For comparison, we studied the reaction of imine **1a** with vinyl ethyl ether **14** and with 2-methoxypropene **15** (Scheme 3) under the conditions determined above ($InCl_3$, 0.5 equiv., 150 W, 3 min). Vinyl ethyl ether **14** gave no reaction whereas 2-methoxypropene **15** yielded the expected quinoline in 28% yield. These results contrast with those reported by Makioka *et al.*[24] for the preparation of **11b** (yield: 75%) using ytterbium triflate in acetonitrile at room temperature, or with those from Kobayashi *et al.*[23] who, under similar conditions (ytterbium triflate in acetonitrile, at room temperature, 20 h), described the formation of the tetrahydro derivative of quinoline **11a** (yield: 69%).



Scheme 3

In an attempt to understand how binding of the compounds **1a**, **2** and **14** to ytterbium(III) and indium(III) might be occurring, ^{13}C NMR experiments[51,52] were performed with varying catalyst loadings. Addition of increasing amounts (0.02, 0.05, 0.1, 0.2 equiv.) of $Yb(OTf)_3$ to acrylate **2** did not modify the chemical shifts of carbons C1, C7, C8, C9 (numbering in Fig. 3), the intensity of the signals being 45% of their initial value at a 0.2 equiv. loading of Lewis acid. The signals of carbons C2 (substituted ethylenic carbon) and C3 (carbonyl) disappeared as soon as 0.05 equiv. of $Yb(OTf)_3$ was added. The same experiments were carried out using $InCl_3$. Such a strong effect of the Lewis acid was not observed: carbons C2 and C3 disappeared from the spectrum only at loadings higher than 0.2 equiv. The chemical shifts of the other carbons were not modified and their intensity was around 80% of their initial value at 0.2 equiv. and 60% at 0.5 equiv. of Lewis acid. Complexation of enol ether **14** was then studied. Addition of 0.05 equiv. of $Yb(OTf)_3$ has no effect on the ^{13}C NMR chemical shifts. However, at 0.1 and 0.2 equiv. Lewis acid loadings, important modifications of the ^{13}C NMR spectra between 10 and 70 ppm were observed as well as the disappearance of the C1 and C2 signals. At 0.5 equiv. of $Yb(OTf)_3$, all the carbons of enol ether **14** have disappeared. With $InCl_3$, the ^{13}C NMR spectrum of enol ether **14** was modified as soon as 0.05 equiv. of the Lewis acid was added, and higher amounts of the indium salt led to a complete removal of the signals. Finally, the spectra of imine **1a** in the presence of Lewis acid at different loadings were recorded. The results are presented in Table 5. Here again, a different behavior of $Yb(OTf)_3$ and $InCl_3$ was observed. Comparison of the data shows that $Yb(OTf)_3$ is a stronger chelating agent than $InCl_3$. For example, the ^{13}C chemical shift of C2 (imine carbon) is deshielded by 3.4 ppm and carbon C4′ by 3.7 ppm with a 0.5 equiv. loading of $Yb(OTf)_3$ (Table 5, entry 5). In the presence of $InCl_3$ the same carbons are shifted by 0.4 and 0.5 ppm respectively (Table 5, entry 10). At 0.2 equiv., the intensity of the remaining signals was around 30% of their initial value.

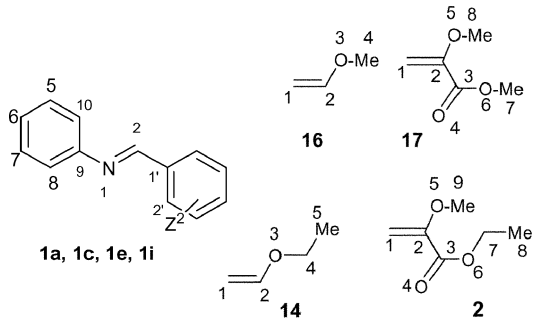


Fig. 3 Structures and numbering considered in the ^{13}C NMR and computational modelling. The dihedral angles Θ_i reported in Table 6 are defined according to: $\Theta_1 = (10, 9, 1, 2)$, $\Theta_2 = (1, 2, 1', 2')$ and $\Theta_3 = (10, 9, 1', 2')$ for imines **1** and $\Theta_1 = (1, 2, 3, 4)$ for compounds **16** and **17**.

The comparison of entries 11–14 with entries 5 and 10 (Table 5) shows that the ^{13}C chemical shifts of the mixture imine **1a**, Lewis acid and dienophile are strongly modified. With the acrylate **2**, the major effect is observed with $Yb(OTf)_3$, whereas with enol ether **14** the largest modifications were observed with $InCl_3$. The strong chelation of both partners in the reaction of imine **1a** and acrylate **2** in the presence of $Yb(OTf)_3$ or in the reaction of imine **1a** and enol ether **14** catalyzed by $InCl_3$ explain why the expected adduct was not obtained in our reactions (Table 1, entries 1 and 2, and Scheme 3) whereas Makioka *et al.*,[24] Kobasyashi *et al.*[23] and Reddy *et al.*[53] observed the cycloaddition of enol ethers.

Theoretical modelling

Computational procedure

In order to get another point of view liable to clarify the role of Lewis acids, some computations have been performed on model systems. Semiquantitative conclusions can be drawn using the well-known semiempirical AM1 method,[54] the results of which can then be used within the framework of Fukui's theory,[55] which, in its simplest formulation, requires the determination

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Table 5 Differences between the ^{13}C NMR chemical shift values of imine **1a** at various loadings of Lewis acid in d_3-acetonitrile[a]

			Δδ	Δδ	Δδ	Δδ	Δδ	Δδ	Δδ	Δδ	Δδ
Entry	Lewis acid	Loading/equiv.	C2	C9	C1′	C4′	C2′	C7	C3′	C6	C10
Imine **1a** + Lewis acid[b]											
1	$Yb(OTf)_3$	0.02	0.1	−0.2	−0.1	0.1	0.0	0.0	0.1	0.1	0.0
2	$Yb(OTf)_3$	0.05	0.3	[c]	−0.6	0.4	0.1	0.0	0.2	0.3	0.0
3	$Yb(OTf)_3$	0.1	0.2	[c]	−0.4	0.4	0.2	0.2	0.3	0.2	0.0
4	$Yb(OTf)_3$	0.2	1.6	[c]	[c]	1.7	0.4	0.7	0.5	1.3	0.1
5	$Yb(OTf)_3$	0.5	3.4	[c]	[c]	3.7	1.7	0.9	0.9	2.7	0.2
6	$InCl_3$	0.02	0.1	−0.1	−0.1	0.1	0.0	0.0	0.0	0.0	0.0
7	$InCl_3$	0.05	0.1	−0.1	−0.1	0.2	0.0	0.0	0.1	0.0	0.0
8	$InCl_3$	0.1	0.0	−0.2	−0.1	0.1	0.0	0.0	0.1	0.0	0.0
9	$InCl_3$	0.2	0.1	−0.2	−0.2	0.1	0.0	0.0	0.1	0.0	0.0
10	$InCl_3$	0.5	0.4	[c]	−0.6	0.5	0.1	0.2	0.3	0.3	0.0
Imine **1a** + acrylate **2** + Lewis acid[b]											
11	$Yb(OTf)_3$	0.5	[c]	[c]	[c]	[c]	[c]	[c]	[c]	[c]	[c]
12	$InCl_3$	0.5	1.4	−0.6	0.1	[d]	[d]	[d]	[d]	0.6	−0.1
Imine **1a** + ether **14** + Lewis acid[b]											
13	$Yb(OTf)_3$	0.5	−0.0	−0.2	[d]	[d]	[d]	[d]	[d]	−0.1	−0.1
14	$InCl_3$	0.5	[c]	[c]	[c]	[c]	[c]	[c]	[c]	[c]	[c]

[a] $\Delta\delta = \delta\{[\text{reagent(s)} + \text{Lewis acid}] - \delta[\text{reagent(s)}]\}$. [b] Ratio imine–acrylate **2** or enol ether **14**–Lewis acid = 1 : 2.5 : 0.5. [c] The signal of the carbon disappears when adding Lewis acid. [d] The different signals cannot be assigned.

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of HOMO/LUMO gaps between the reagents (frontier molecular orbital approximation[56]): the smaller this gap, the more favourable the associated reaction. In the present case, whether the normal or inverse electron demand is involved may depend on whether or not the process is concerted. The ground principle of such an analysis must, however, always be kept in mind: it states that the reaction must be under orbital control, which is far from certain when dealing with aza-Diels–Alder cycloadditions or with substituents combined in such a way that subtle captodative effects appear, as might here be the case for dienophiles such as **2**, for example.[57]

A series of AM1 calculations has thus been performed[58] on the compounds presented in Fig. 3, or on some of their substituted analogues. The geometries of these species have been fully optimized at the AM1 level of calculation, and the nature of the stationary structures found, namely transition states or not, has been characterized by the mean of a vibrational analysis performed within the harmonic approximation: only minimum energy structures are reported here, and, when several stable conformers were found, only that of lowest energy was considered. We then qualitatively investigated the role of catalysts using two very simple models of Lewis acids: H^+ and $AlCl_3$.[59] Using H^+ and $AlCl_3$ as models precludes accounting precisely for the possible π interactions occurring between the catalyst and the chelated species. However, it is clear for both $InCl_3$ and $Yb(OTf)_3$ – analogues to BF_3 [60,61] or to $B(OR)_3$,[62] and it seems established for $Yb(OTf)_3$ [63,64] – that coordination to the catalyst involves the σ skeleton, namely the in-plane lone pair of nitrogen (N) of imine **1a**, and the lone pair(s) of oxygens O_3, O_4 (in-plane lone pairs), O_5 and O_6 in **16** and **17**.

As our calculations have evidenced that strong deformations of the skeletons might occur when chelating one reagent to the model catalysts, we also report the value of some critical dihedral angles Θ_i, the definitions of which are given in Fig. 3. Such variations in the geometries, and, consequently, the sometimes significant distortion with respect to (quasi-) planarity in the vicinity of the relevant π bond(s), made it sometimes difficult to unambiguously identify the π HOMOs and LUMOs: in such cases, the orbital(s) having the proper symmetry with respect to the double bond local plane, and also having the most evident localization on the π bond(s) concerned, has (have) been retained.

The above-mentioned dihedral angles have been collected with the π HOMO/LUMO energy values in Table 6. The HOMO/LUMO gaps, ΔE, are shown in Table 7 for a selected set of reactions, normal or inverse Diels–Alder:

Normal Electron Demand (NED):

$$\Delta E_{NED} = |\,HO^{diene} - LU^{dienophile}\,|$$

Inverse Electron Demand (IED):

$$\Delta E_{IED} = |\,HO^{dienophile} - LU^{diene}\,|$$

The 26 reactions summarised in Table 7 have been selected so that both reagents are not positively charged simultaneously (an unfavourable Coulomb repulsion might occur in that case), and also ensure that these reagents do not bind to $AlCl_3$ simultaneously. However, Table 6 reports any quantity required to investigate the full set of reactions being susceptible to arising from the sets of non-substituted reagents.

Analysis and discussion

In the absence of any catalyst, **16** (methoxyethylene as a model of ethoxyethylene) and **17** (methyl methoxyacrylate as a model of acrylate **2**) behave differently with respect to **1a**. As seen from Table 7 (entries 1 and 5), **16** undergoes an IED reaction, whereas **17** favours the NED reaction. For the reaction between **1a** and **17** there is, however, only a small difference between the ΔE_{NED} and ΔE_{IED} gaps (less than 0.6 eV, to be compared with the 1.45 eV found for the reaction with **16**). Consequently, substitution effects on **1a** might easily make the reaction become of IED nature. Substitutions of the phenyl group with electron withdrawing groups (NO_2 and CF_3 on **1a**: *cf.* Table 7, entries 2–4 and 6–8) decrease the energy of both the HOMO and LUMO of diene **1a**, which results in reversing the electronic demand when opposed to **17**: the corresponding reactions become IED reactions. Of course, when the substituted analogues of diene **1a** are opposed to **16**, the corresponding reactions remain of IED type. The fact that, for the **1a** + **17** reaction, only a very small difference between ΔE_{NED} and ΔE_{IED} is observed appears especially interesting as theoretical calculations have shown that the closer these gaps, the less control and the less reactivity.[65] This might help to explain why no reaction of the imine **1a** and acrylate **2** was observed in the absence of catalyst and without microwave activation.

Table 6 HOMO and LUMO energy levels (eV), and dihedral angles Θ_i for the model reagents, with or without catalyst

Entry	Reagent	HO	LU	Θ_1	Θ_2	Θ_3
No catalyst						
1	**1a** (diene)	−8.90	−0.50	35	7	−142
2	**1a**–NO_2 (3′)	−9.30	−1.21	31	0	−152
3	**1a**–NO_2 (4′)	−9.38	−1.50	30	0	−152
4	**1a**–CF_3 (2′)	−9.17	−0.87	32	−23	−171
5	**16** (dienophile)	−9.41	+1.46	180	—	—
6	**17** (dienophile)	−9.99	+0.06	180	—	—
H^+ as a catalyst						
7	**1a**–H^+ (N_3)	−13.09	−5.51	33	3	−147
8	**16**–H^+ (O_3)	−16.27	−4.57	116	—	—
9	**17**–H^+ (O_4)	−14.53	−6.15	177	—	—
10	**17**–H^+ (O_5)	−16.22	−5.09	177	—	—
11	**17**–H^+ (O_6)	−14.57	−5.49	171	—	—
$AlCl_3$ as a catalyst						
12	**1a**–$AlCl_3$ (N_3)	−10.10	−1.63	62	−36	−164
13	**16**–$AlCl_3$ (O_3)	−11.15	−0.14	115	—	—
14	**17**–$AlCl_3$ (O_4)	−11.31	−1.65	173	—	—
15	**17**–$AlCl_3$ (O_5)	−11.70	−0.96	168	—	—
16	**17**–$AlCl_3$ (O_6)	−10.40	−0.92	170	—	—
17	**1e**–$AlCl_3$ (N_3)	−10.56	−2.09	−60	40	168
18	**1i**–$AlCl_3$ (N_3)	−10.63	−2.20	−60	50	176
19	**1c**–$AlCl_3$ (N_3)	−10.34	−1.88	−57	46	174

Table 7 HOMO/LUMO gaps (ΔE_{NED} and ΔE_{IED} in eV) for selected reactions involving model reagents, with or without catalysis

Entry	Reaction	ΔE_{NED}	ΔE_{IED}
No catalyst			
1	**1a** + **16**	10.36	8.91
2	**1a**–NO_2 (3′) + **16**	10.76	8.20
3	**1a**–NO_2 (4′) + **16**	10.84	7.91
4	**1a**–CF_3 (2′) + **16**	10.63	8.54
5	**1a** + **17**	8.96	9.49
6	**1a**–NO_2 (3′) + **17**	9.36	8.78
7	**1a**–NO_2 (4′) + **17**	9.44	8.49
8	**1a**–CF_3 (2′) + **17**	10.05	9.12
H^+ as a catalyst			
9	**1a**–H^+ (N_3) + **16**	14.55	3.90
10	**1a**–H^+ (N_3) + **17**	13.15	4.48
11	**1a** + **16**–H^+ (O_3)	4.33	15.77
12	**1a** + **17**–H^+ (O_4)	2.75	14.03
13	**1a** + **17**–H^+ (O_5)	3.81	15.72
14	**1a** + **17**–H^+ (O_6)	3.41	14.07
$AlCl_3$ as a catalyst			
15	**1a**–$AlCl_3$ (N_3) + **16**	11.56	7.78
16	**1a**–$AlCl_3$ (N_3) + **17**	10.16	8.36
17	**1a** + **16**–$AlCl_3$ (O_3)	8.76	10.65
18	**1a** + **17**–$AlCl_3$ (O_4)	7.25	10.81
19	**1a** + **17**–$AlCl_3$ (O_5)	7.94	11.20
20	**1a** + **17**–$AlCl_3$ (O_6)	7.98	9.90
21	**1e**–$AlCl_3$ (N_3) + **16**	12.02	7.32
22	**1i**–$AlCl_3$ (N_3) + **16**	12.09	7.21
23	**1c**–$AlCl_3$ (N_3) + **16**	11.80	7.53
24	**1e**–$AlCl_3$ (N_3) + **17**	10.62	7.90
25	**1i**–$AlCl_3$ (N_3) + **17**	10.69	7.79
26	**1c**–$AlCl_3$ (N_3) + **17**	10.40	8.11

If we now consider the role of a proton H^+, the simplest model of Lewis acid, we first observe (Table 6, entries 7–11) a huge decrease of the HOMO and LUMO energies of the protonated reagents when compared to those of their neutral precursors. Moreover, significant geometrical distortions with respect to the unprotonated species appear, which implies large modifications in the conjugation effects within the reagents, and thus variations in the HOMO/LUMO energy values. In all cases (Table 7, entries 9–14), and in contrast with the previous results, a large difference now appears between the ΔE_{NED} and ΔE_{IED} gaps (more than 10 eV). Such variations are unlikely to be reversed by substitution effects. It is thus clear that using the protonated diene **1a**–H^+ always will lead to IED reactions when reacting with **16** (the same result as without a catalyst) and also with **17** (the opposite result to that obtained without a catalyst). In contrast, if the O-protonated **16** and **17** species are considered, the reactions with **1a** turn out to become of NED type.

Very similar conclusions can be drawn if using a more realistic Lewis catalyst such as $AlCl_3$ (Table 7, entries 15–26). It is worth noting, however, that the numerical decreases of the HOMOs and the LUMOs are by far less pronounced than when using H^+: the differences between the ΔE_{NED} and ΔE_{IED} gaps remain at about only 2–4 eV. Consequently, substitution effects on either the chelated diene or the chelated dienophile might be able to reverse the type of the reaction. We point out that, because of the steric hindrance induced by $AlCl_3$, the structure of **1a**–$AlCl_3$ is strongly distorted when compared to that of **1a** and **1a**–H^+. Complexing structure **1a** when substituted by electroattractive groups reinforces the conclusions found when no catalyst is used (Table 7, entries 2–4 and 6–8): in these cases, an IED reaction is still expected to occur with both **16** and **17** (Table 7, entries 21–26). The corresponding IED gaps suggest that the reaction will be more efficient if catalyzed.

If we consider $AlCl_3$ as a model of $Yb(OTf)_3$ or of $InCl_3$, a preferential complexation of imine **1a** with respect to the acrylate should favor an IED Diels–Alder reaction (Table 7, entry 16). The ^{13}C NMR data which show a stronger complexation of imine **1a** than that of acrylate **2** in the presence of $InCl_3$, and of imine **1a** *vs.* enol ether **14** in the presence of $Yb(OTf)_3$ are in good agreement with this hypothesis. However, further investigations are necessary to clarify the exact molecular mechanism of these reactions.

Conclusion

Substituted quinoline 4-carboxylic esters or amides have been synthesised in a one-pot procedure from *N*-arylimines and 2-methoxyacrylic acid derivatives. The choice of the catalyst and the microwave activation were crucial in obtaining satisfactory yields and in determining the reactivity of the partners in the formal aza-Diels–Alder reaction.

The described procedure, allowing the introduction of a functional group in the 4-position of the heterocyclic ring,

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complements well the previously described synthesis of quinoline derivatives. The conditions (3 min, excess of acrylic derivative *versus* the fluoro imine) could be easily adapted to the synthesis of fluorine-18 ligands for medical imaging.

Experimental

^{1}H NMR, ^{13}C NMR (62.9 MHz, with decoupling ^{1}H broad band) and ^{19}F NMR (235 MHz) spectra were recorded on a Bruker DPX 250 MHz instrument, with chloroform ($CDCl_3$) as the solvent and TMS (^{1}H, ^{13}C) or freon (^{19}F) as the internal standard. Data appear in the following order: chemical shift in ppm, multiplicity (s: singlet, d: doublet, t: triplet, q: quadruplet, sept: septuplet, m: multiplet), coupling constant *J* in Hz. GC–MS analyses were recorded on Varian 3800 (GC) and Saturn 2000 (MS) instruments; CP-SIL 8CB (Low BLEED/MS) column (30 m × 0.32 mm), with 5% phenyl 95% dimethoxypolysiloxane as the stationary phase, was used for the analysis. High resolution mass spectra (HRMS) were recorded using a QTOF Micro spectrometer (Waters). Infrared spectra (IR) were recorded on a Perkin-Elmer spectrometer 16 PC-FT-IR. The conditions of analysis are specified in each case. The melting points were obtained from a Kofler bench. Thin-layer chromatography (TLC) was performed on silica gel $60F_{254}$ plates and visualized by UV irradiation. A Synthewave 402 Prolabo was used for the microwave irradiations. The reactions were carried out in an open glass tube (id: 1.5 cm). Optical rotation, measured with a Perkin Elmer 241 polarimeter, are given in 10^{-1} deg cm^2 g^{-1}. Microanalyses were carried out with a ThermoQuest CHNS-O apparatus. Tetrahydrofuran (THF) was dried and distilled from sodium benzophenone ketyl under nitrogen prior to use. Acetonitrile (CH_3CN) was dried over CaH_2 and distilled. Dimethylformamide (DMF) was dried over CaH_2 and distilled under vacuum prior to use (0.02 bar). Ytterbium triflate was dried at 200 °C for 48 h under reduced pressure (0.02 bar). All the reagents commercially available were used without further purification. Imines **1** were prepared by reaction of the appropriate aniline and aldehyde. Spectroscopic and analytical data of imines **1** are in agreement with the literature: (**1a**, **1g**, **1h**),[66] **1b**,[67] **1c**,[68] (**1d**, **1l**),[69] **1e**,[70] **1f**,[71] **1j**,[72] **1k**,[73] **1m**,[74] **1n**,[75] **1o**.[72] Ethyl-2-methoxypropenoate **2**[76] was prepared from the methoxyacetal of ethyl pyruvate **13**.[32]

N-(Isopropyl)-2-methoxypropenamide (3)[77]

Isopropylamine (429 mg, 7.8 mmol) was added to a solution of ethyl-2-methoxypropenoate **2** (500 mg, 3.9 mmol) in methanol (10 mL). The solution was heated under reflux for two days. The solvent was evaporated under vacuum and the crude product extracted with dichloromethane. The organic layers were washed with aqueous HCl 5% (10 mL) then with brine (10 mL). After drying over $MgSO_4$, filtration and evaporation of the solvent, the crude product was purified by chromatography over silica gel (pentane–ethyl acetate 60 : 40) to yield the pure title compound **3** (167 mg, 30%) as a white solid, mp 52 °C. IR ν_{max}/cm^{-1} (KBr): 3500, 3000, 1746, 1628, 1518, 1380, 1170. ^{1}H NMR: δ_H 6.64 (1H, br s), 5.37 (1H, d, *J* 2.1), 4.41 (1H, d, *J* 2.1), 4.14 (1H, sept, *J* 6.7), 3.65 (3H, s), 1.23 (6H, d, *J* 6.7). ^{13}C NMR: δ_C 161.7, 154.6, 90.1, 55.8, 42.3, 23.0. MS (EI, GC–MS) *m*/*z* 144 (M$^{+\bullet}$, 85%), 128 (100), 110 (49), 100 (49), 57 (82). CHN requires for $C_7H_{13}NO_2$: C, 58.7; H, 9.2; N, 9.8%. Found: C, 58.8; H, 9.4; N, 9.6%.

(*S*)-*N*-(1-Phenylpropyl)-2-methoxypropenamide (4)

2-Methoxypropenoic acid[78] (3.2 g, 32 mmol), *N*-hydroxysuccinimide (4.3 g, 1.2 equiv.) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl, 7.4 g, 1.2 equiv.) and anhydrous DMF (50 mL) were stirred under nitrogen at −5 °C for 1 h then at room temperature for 12 h. The solvent was evaporated and the residue was extracted with dichloromethane (25 mL). The organic layers were washed with aqueous citric acid 5% (3 × 25 mL), then with aqueous $NaHCO_3$ 50% (3 × 25 mL) and with water (1 × 25 mL). After drying over $MgSO_4$, filtration then evaporation of the solvent, the residue was diluted with dichloromethane (25 mL). (*S*)-Phenylpropylamine (4.7 mL, 1.3 equiv.) and triethylamine (4.2 mL, 1.2 equiv.) were added to the solution. The mixture was stirred under reflux for 4 h. After cooling to room temperature, it was poured into aqueous citric acid 5% (25 mL). The organic layer was successively washed with aqueous citric acid 5% (2 × 25 mL), with saturated aqueous $NaHCO_3$ (1 × 25 mL), with brine (1 × 25 mL) and with water (1 × 25 mL). It was then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography over silica gel (pentane–ethyl acetate 80 : 20) to yield the title compound **4** (4.9 g, 90%) as a white solid, mp 88 °C. $[a]_D^{20} = -143$ (*c* 1 in MeOH). IR ν_{max}/cm^{-1} (KBr): 3053, 2985, 1421, 1265, 896, 743. ^{1}H NMR: δ_H 7.35–7.23 (5H, m), 6.80 (1H, s, NH), 5.37 (1H, d, *J* 1.5), 4.92 (1H, q, *J* 7.4), 4.42 (1H, d, *J* 1.5), 3.64 (3H, s, OMe), 1.89–1.85 (2H, m), 0.91 (3H, t, *J* 7.4). ^{13}C NMR: δ_C 161.9, 154.4, 142.3, 129.0, 127.7, 127.1, 90.2, 55.9, 55.1, 29.5, 11.1. MS (EI, GC–MS) *m*/*z* 219 (M$^{+\bullet}$, 55%), 204 (46), 190 (100, M − CH_2CH_3), 176 (36), 159 (21), 131 (37), 106 (44), 91 (65). CHN requires for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4%. Found: C, 71.5; H, 8.2; N, 6.4%. HRMS calc.: 219.1259, found: 219.1266.

N-Phenyl-2-methoxypropenamide (5)

Using the same method as described above, the amide **5** was obtained from 2-methoxypropenoic acid (1 g, 9.8 mmol) and aniline (1.52 mL, 11.7 mmol) as a white solid (300 mg, 17%), mp 78 °C. IR ν_{max}/cm^{-1} (KBr): 3053, 2986, 1695, 1600, 1530, 1443, 1265, 1047, 895, 738. ^{1}H NMR: δ_H 8.38 (1H, br s, NH), 7.60 (2H, d, *J* 7.7), 7.35 (2H, t, *J* 7.7), 7.12 (1H, t, *J* 7.7), 5.51 (1H, d, *J* 2.5), 4.56 (1H, d, *J* 2.5), 3.74 (3H, s, OMe). ^{13}C NMR: δ_C 159.8, 153.7, 137.2, 128.8, 124.3, 119.7, 90.5, 55.6. MS (EI, GC–MS) *m*/*z* 177 (M$^{+\bullet}$, 100%), 162 (25), 146 (55), 134 (32), 57 (47). HRMS ($C_{10}H_{12}NO_2$) calc.: 178.0868, found: 178.0858.

General procedure for the preparation of 2-arylquinoline-4-carboxylates

Ethyl-[79] and methyl-2-phenylquinoline-4-carboxylate[80] (8a$_1$, 8a$_2$). *N*-(Benzyliden)aniline **1a** (0.4 mmol) and ethyl 2-methoxypropenoate **2** (130 mg, 1 mmol) were added to indium trichloride (44 mg, 0.2 mmol) in acetonitrile (2 mL). The mixture was irradiated in a microwave oven at 150 W for 3 min. The temperature of the reaction was recorded as a function of time (Fig. 4).

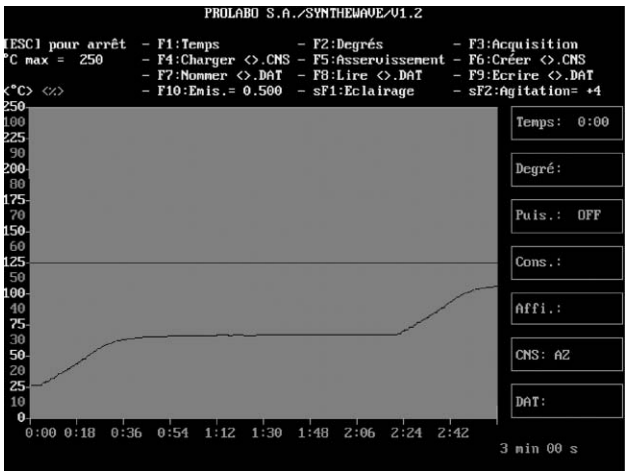

Fig. 4 Temperature (°C) as a function of time (min) inside the microwave oven (irradiation power: 150 W).

After cooling to room temperature, the residue was poured into water (20 mL) and extracted with dichloromethane (20 mL).

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The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent evaporated under vacuum. The residue was purified by column chromatography over silica gel (pentane–ethyl acetate 95 : 5) to yield a mixture of the two esters **8a$_1$** and **8a$_2$** (63 mg, 57%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8a$_1$**: ^{1}H NMR: δ_H 8.66 (1H, d, *J* 8.5, H arom), 8.30 (s, H3), 8.16–8.11 (3H, m), 7.69–7.60 (1H, m), 7.57–7.40 (4H, m), 4.45 (2H, q, *J* 7, OCH_2CH_3), 1.39 (3H, t, *J* 7, OCH_2CH_3). MS (EI, GC–MS) *m*/*z* (t_R = 23.3 min) 277 ($M^{+\bullet}$, 100%), 206 (46, M − OCH_2CH_3). **8a$_2$**: ^{1}H NMR: δ_H 8.66 (1H, d, *J* 8.5, H arom), 8.33 (s, H3), 8.16–8.11 (3H, m), 7.69–7.60 (1H, m), 7.57–7.40 (4H, m), 3.99 (3H, s, OCH_3). MS (EI, GC–MS) *m*/*z* (t_R = 22.6 min) 263 ($M^{+\bullet}$, 100%), 206 (46, M − OCH_3).

Ethyl-[81] and methyl-2-(2′-fluorophenyl)-quinoline-4-carboxylate (8b$_1$, 8b$_2$). Using the general procedure, imine **1b** (0.4 mmol) afforded a mixture of esters **8b$_1$** and **8b$_2$** (42 mg, 40%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8b$_1$**: ^{1}H NMR: δ_H 8.77 (1H, d, *J* 8.0), 8.41–8.39 (1H, m), 8.23 (1H, d, *J* 8.3), 8.12 (1H, td, *J* 6.1 *J* 1.6), 7.79 (1H, td, *J* 7.2, *J* 1.2), 7.69–7.65 (1H, m), 7.50–7.44 (1H, m), 7.32 (1H, td, *J* 7.2, *J* 1.2), 7.22–7.18 (1H, m), 4.54 (2H, q, *J* 7.1, OCH_2CH_3), 1.48 (3H, t, *J* 7.1, OCH_2CH_3). ^{19}F NMR: δ_F −116.9. MS (EI, GC–MS) *m*/*z* (t_R = 17 min) 295 (100%, $M^{+\bullet}$), 223 (56). HRMS ($C_{18}H_{15}FNO_2$) calc.: 296.1087, found: 296.1082. **8b$_2$**: ^{1}H NMR: δ_H 8.77 (1H, d, *J* 8.0), 8.41–8.39 (1H, m), 8.23 (1H, d, *J* 8.3), 8.12 (1H, td, *J* 6.1 *J* 1.6), 7.79 (1H, td, *J* 7.2, *J* 1.2), 7.69–7.65 (1H, m), 7.50–7.44 (1H, m), 7.32 (1H, td, *J* 7.2, *J* 1.2), 7.22–7.18 (1H, m), 4.05 (3H, s, OCH_3). ^{19}F NMR: δ_F −116.9. MS (EI, GC–MS) *m*/*z* (t_R = 16.3 min) 281 ($M^{+\bullet}$, 100%), 223 (36). HRMS ($C_{17}H_{13}FNO_2$) calc.: 282.0919, found: 282.0924.

Ethyl- and methyl 2-(3′-bromophenyl)-quinoline-4-carboxylate (8d$_1$, 8d$_2$). Using the general procedure, imine **1d** (0.4 mmol) afforded a mixture of esters **8d$_1$** and **8d$_2$** (64 mg, 45%). Attempts to separate these two esters were unsuccessful but because of the product distribution (3: 1 ratio), the NMR could nevertheless be resolved. **8d$_1$**: ^{1}H NMR: δ_H 8.74 (1H, d, *J* 8.5), 8.39–8.32 (2H, m), 8.21 (1H, d, *J* 8.4), 8.11 (1H, d, *J* 7.5), 7.79 (1H, t, *J* 7.8), 7.66–7.58 (2H, m), 7.39 (1H, t, *J* 7.8), 4.55 (2H, q, *J* 7.1, OCH_2CH_3), 1.51 (3H, t, *J* 7.1, OCH_2CH_3). MS (EI, GC–MS) *m*/*z* (t_R = 18.7 min), 357 ($M^{+\bullet}$, $C_{18}H_{14}{}^{81}BrNO_2$, 69%), 355 ($M^{+\bullet}$, $C_{18}H_{14}{}^{79}BrNO_2$, 69%), 285 (100), 283 (97), 203 (25). HRMS ($C_{18}H_{15}{}^{79}BrNO_2$) calc.: 356.0286, found: 356.0288. **8d$_2$**: ^{1}H NMR: δ_H 8.74 (1H, d, *J* 8.5), 8.39–8.32 (2H, m), 8.21 (1H, d, *J* 8.4), 8.11 (1H, d, *J* 7.5), 7.79 (1H, t, *J* 7.8), 7.66–7.58 (2H, m), 7.39 (1H, t, *J* 7.8), 4.07 (3H, s, OCH_3). MS (EI, GC–MS) *m*/*z* (t_R = 18.5 min) 343 ($M^{+\bullet}$, $C_{17}H_{12}{}^{81}BrNO_2$, 72%), 341 ($M^{+\bullet}$, $C_{17}H_{12}{}^{79}BrNO_2$, 68%), 285 (98), 283 (100), 203 (40). HRMS ($C_{17}H_{13}{}^{79}BrNO_2$) calc.: 342.0130, found: 342.0130.

Ethyl-[82] and methyl-2-(3′,4′-dimethoxyphenyl)-quinoline-4-carboxylate[82] (8f$_1$, 8f$_2$). Using the general procedure, imine **1f** (0.4 mmol) afforded a mixture of esters **8f$_1$** and **8f$_2$** (40 mg, 31%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8f$_1$**: ^{1}H NMR: δ_H 8.69 (1H, dt, *J* 8.5, *J* 1.6), 8.34 (1H, s), 8.20 (1H, dd, *J* 7.5, *J* 0.9), 7.9 (1H, d, *J* 1.7), 7.90 (1H, s), 7.62–7.56 (1H, m), 7.00 (1H, dd, *J* 7.5, *J* 0.9), 4.56 (2H, q, *J* 7.1, OCH_2CH_3), 4.05 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 1.53 (3H, t, *J* 7.1, OCH_2CH_3). MS (EI, GC–MS) *m*/*z* (t_R = 21.3 min) 337 (100%, $M^{+\bullet}$), 309 (18). **8f$_2$**: ^{1}H NMR: δ_H 8.69 (1H, d, *J* 8.5), 8.36 (1H, s), 8.20 (1H, dd, *J* 7.5, *J* 0.9), 7.91 (1H, s), 7.78–7.68 (1H, m), 7.62–7.56 (1H, m), 7.00 (1H, dd, *J* 7.5, *J* 0.9), 4.07 (3H, s, $COOCH_3$), 4.05 (3H, s, OCH_3), 3.96 (3H, s, OCH_3). MS (EI, GC–MS) *m*/*z* (t_R = 20.1 min) 323 ($M^{+\bullet}$, 100%), 308 (16), 293 (20), 278 (34), 265 (12).

Ethyl- and methyl-2-(4′-bromophenyl)-quinoline-4-carboxylate (8g$_1$, 8g$_2$). Using the general procedure, imine **1g** (0.4 mmol) afforded a mixture of esters **8g$_1$** and **8g$_2$** (27 mg, 20%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8g$_1$**: ^{1}H NMR: δ_H 8.92 (1H, d, *J* 8.3), 8.35 (1H, d, *J* 6.4), 8.20 (1H, d, *J* 8.3), 8.08 (2H, d, *J* 7.6), 7.78 (1H, t, *J* 1.1), 7.69–7.63 (3H, m), 7.43 (1H, d, *J* 8.3), 4.55 (2H, q, *J* 7.1, OCH_2CH_3), 1.51 (3H, t, *J* 7.1, OCH_2CH_3). MS (EI, GC–MS) *m*/*z* (t_R = 18.8 min) 357 ($M^{+\bullet}$, $C_{18}H_{14}{}^{81}BrNO_2$, 99%), 355 ($M^{+\bullet}$, $C_{18}H_{14}{}^{79}BrNO_2$, 99%), 285 (89), 284 (100), 204 (28), 203 (28). HRMS ($C_{18}H_{15}{}^{79}BrNO_2$) calc.: 356.0286, found: 356.0274. **8g$_2$**: ^{1}H NMR: δ_H 8.92 (1H, d, *J* 8.3), 8.35 (1H, d, *J* 6.4), 8.20 (1H, d, *J* 8.3), 8.08 (2H, d, *J* 7.6), 7.78 (1H, t, *J* 1.1), 7.69–7.63 (3H, m), 7.43 (1H, d, *J* 8.3), 4.08 (3H, s, OCH_3). MS (EI, GC–MS) *m*/*z* (t_R = 18.1 min) 343 ($M^{+\bullet}$, $C_{17}H_{12}{}^{81}BrNO_2$, 97%), 341 ($M^{+\bullet}$, $C_{17}H_{12}{}^{79}BrNO_2$, 98%), 286 (13), 285 (98), 284 (37), 283 (100), 203 (30). HRMS ($C_{17}H_{13}{}^{79}BrNO_2$) calc.: 342.0130, found: 342.0114.

Ethyl- and methyl-2-(4′-cyanophenyl)-quinoline-4-carboxylate (8h$_1$, 8h$_2$). Using the general procedure, imine **1h** (0.4 mmol) afforded a mixture of esters **8h$_1$** and **8h$_2$** (27 mg, 20%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8h$_1$**: ^{1}H NMR: δ_H 8.75 (1H, d, *J* 9.5), 8.39–8.32 (3H, m), 8.23 (1H, d, *J* 7.8), 7.85–7.82 (3H, m), 7.68–7.64 (1H, m), 4.56 (2H, q, *J* 7.1, OCH_2CH_3), 1.44 (3H, t, *J* 7.1, OCH_2CH_3). MS (EI, GC–MS) *m*/*z* 302 ($M^{+\bullet}$, 100%). 288 ($M^{+\bullet}$, 100%), 231 (33) 230 (53). HRMS ($C_{19}H_{15}N_2O_2$) calc.: 303.1134, found: 303.1129. **8h$_2$**: ^{1}H NMR: δ_H 8.75 (1H, d, *J* 9.5), 8.39–8.32 (3H, m), 8.23 (1H, d, *J* 7.8), 7.85–7.82 (3H, m), 7.68–7.64 (1H, m), 3.99 (3H, s, OCH_3). MS (EI, GC–MS) *m*/*z* 288 ($M^{+\bullet}$, 100%), 231 (33), 230 (53). HRMS ($C_{18}H_{12}N_2O_2$) calc.: 288.0899, found: 288.0886.

Ethyl- and methyl-2-(4′-nitrophenyl)-quinoline-4-carboxylate (8i$_1$, 8i$_2$). Using the general procedure, imine **1i** (0.4 mmol) afforded a mixture of esters **8i$_1$** and **8i$_2$** (29 mg, 23%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8i$_1$**: ^{1}H NMR: δ_H 8.77 (1H, d, *J* 8), 8.44–8.38 (5H, m), 8.24 (1H, d, *J* 8), 7.82 (1H, t, *J* 0.8), 7.69 (1H, t, *J* 0.8), 4.56 (2H, q, *J* 8, OCH_2CH_3), 1.52 (3H, t, *J* 8, OCH_2CH_3). MS (EI, GC–MS) *m*/*z* (t_R = 23.1 min) 322 ($M^{+\bullet}$, 100%), 251 (70), 250 (23). HRMS ($C_{18}H_{14}N_2O_4$) calc.: 323.1032, found: 323.1038. **8i$_2$**: ^{1}H NMR: δ_H 8.77 (1H, d, *J* 8), 8.44–8.38 (5H, m), 8.24 (1H, d, *J* 8), 7.82 (1H, t, *J* 0.8), 7.69 (1H, t, *J* 0.8), 4.10 (3H, s, OCH_3). MS (EI, GC–MS) *m*/*z* (t_R = 21.5 min) 308 ($M^{+\bullet}$, 100%), 251 (66), 250 (42). HRMS ($C_{17}H_{12}N_2O_4$) calc.: 309.0875, found: 309.0886.

Ethyl- and methyl-2-(4′-fluorophenyl)-quinoline-4-carboxylate (8j$_1$, 8j$_2$). Using the general procedure, imine **1j** (0.4 mmol) afforded a mixture of esters **8j$_1$** and **8j$_2$** (32 mg, 27%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8j$_1$**: ^{1}H NMR: δ_H 8.75 (1H, dd, *J* 4.0 *J* 1.2), 8.36 (1H, s), 8.25–8.21 (3H, m), 7.79 (1H, td, *J* 6.4, *J* 1.2), 7.65 (1H, td, *J* 7.2, *J* 1.6), 7.25 (2H, t, *J* 6.4), 4.57 (q, *J* 7.2, OCH_2CH_3), 1.53 (t, *J* 7.2, OCH_2CH_3). ^{19}F NMR: δ_F −112.1. MS (EI, GC–MS) *m*/*z* (t_R = 16.7 min) 295 ($M^{+\bullet}$, 100%), 223 (38). HRMS ($C_{18}H_{14}FNO_2$) calc.: 296.1087, found: 296.1086. **8j$_2$**: ^{1}H NMR: δ_H 8.75 (1H, dd, *J* 4.0 *J* 1.2), 8.38 (1H, s), 8.25–8.21 (3H, m), 7.79 (1H, td, *J* 6.4, *J* 1.2), 7.65 (1H, td, *J* 7.2, *J* 1.6), 7.25 (2H, t, *J* 6.4), 4.10 (3H, s, OCH_3). ^{19}F NMR: δ_F −112.1. MS (EI, GC–MS) *m*/*z* (t_R = 16.1 min) 281 ($M^{+\bullet}$,100%), 223 (20). HRMS ($C_{17}H_{12}FNO_2$) calc.: 282.0930, found: 282.0935.

Ethyl- and methyl-6-fluoro-2-phenylquinoline-4-carboxylate (8k$_1$, 8k$_2$). Using the general procedure, imine **1k** (0.4 mmol) afforded a mixture of esters **8k$_1$** and **8k$_2$** (28 mg, 24%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8k$_1$**: ^{1}H NMR δ_H 8.39 (2H, m), 8.17–8.09 (3H, m),

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7.50–7.41 (4H, m), 4.51 (2H, q, *J* 7.1, OCH_2CH_3), 1.43 (3H, t, *J* 7.1, OCH_2CH_3). MS (EI, GC–MS) *m/z* 295 ($M^{+\bullet}$, 100%), 223 (56). HRMS ($C_{18}H_{15}FNO_2$) calc.: 296.1087, found: 296.1078. **8k$_2$**: ^{1}H NMR: δ_H 8.39 (2H, m), 8.17–8.09 (3H, m), 7.50–7.41 (4H, m), 3.99 (3H, s, OCH_3). MS (EI, GC–MS) *m/z* 281 ($M^{+\bullet}$, 100%), 224 (32), 223 (21). HRMS ($C_{17}H_{13}FNO_2$) calc.: 282.0930, found: 282.0918.

Ethyl- and methyl-6-chloro-2-phenylquinoline-4-carboxylate[83] (8l$_1$, 8l$_2$). Using the general procedure, imine **1l** (0.4 mmol) afforded a mixture of esters **8l$_1$** and **8l$_2$** (31 mg, 25%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8l$_1$**: ^{1}H NMR: δ_H 8.83 (1H, s), 8.43 (1H, d, *J* 4.2), 8.20–8.12 (3H, m), 7.71–7.68 (1H, m), 7.55–7.32 (3H, m), 4.54 (2H, q, *J* 7.1, OCH_2CH_3), 1.50 (3H, t, *J* 7.1, OCH_2CH_3). MS (EI, GC–MS) *m/z* (t_R = 25.1 min) 311 ($M^{+\bullet}$, 100%), 297 (10), 239 (81), 241 (29), 240 (21), 204 (17), 203 (20). HRMS ($C_{18}H_{14}ClNO_2$) calc.: 312.0791, found: 312.0791. **8l$_2$**: ^{1}H NMR: δ_H 8.83 (1H, s), 8.43 (1H, d, *J* 4.2), 8.20–8.11 (3H, m), 7.71–7.68 (1H, m), 7.55–7.32 (3H, m), 4.07 (3H, s, OCH_3). MS (EI, GC–MS) *m/z* (t_R = 24.1 min) 297 ($M^{+\bullet}$, 100%), 241 (26), 240 (23), 239 (82), 204 (15). HRMS ($C_{17}H_{13}ClNO_2$) calc.: 298.0635, found: 298.0654.

Ethyl-[84] and methyl-6-bromo-2-phenylquinoline-4-carboxylate[84] (8m$_1$, 8m$_2$). Using the general procedure, imine **1m** (0.4 mmol) afforded a mixture of esters **8m$_1$** and **8m$_2$** (78 mg, 52%). Attempts to separate these two esters were unsuccessful, but because of the product distribution (3 : 1 ratio) the NMR could nevertheless be resolved. **8m$_1$**: ^{1}H NMR: δ_H 9.00 (1H, d, *J* 2.1, H5), 8.43 (1H, s, H3 arom), 8.21–8.17 (2H, m), 8.06 (1H, s), 7.85 (1H, d, *J* 1.2, H8 arom), 7.58–7.49 (2H, m), 7.35–7.21 (2H, m), 4.55 (2H, q, *J* 7.1, OCH_2CH_3), 1.51 (3H, t, *J* 7.1, OCH_2CH_3). MS (EI, GC–MS) *m/z* (t_R = 27.1 min) 357 ($M^{+\bullet}$, $C_{18}H_{14}{}^{81}BrNO_2$, 100%), 355 ($M^{+\bullet}$, $C_{18}H_{14}{}^{79}BrNO_2$, 99%), 285 (81), 284 (77), 203 (28). HRMS ($C_{18}H_{15}{}^{79}BrNO_2$) calc.: 356.0286, found: 356.0283. **8m$_2$**: ^{1}H NMR: δ_H 9.00 (1H, d, *J* 2.1, H5), 8.45 (1H, s, H3 arom), 8.21–8.17 (2H, m), 8.09 (1H, s), 7.81 (1H, d, *J* 1.2, H8 arom), 7.58–7.49 (2H, m), 7.35–7.21 (2H, m), 4.07 (3H, s, OCH_3). MS (EI, GC–MS) *m/z* (t_R = 26.0 min) 343 ($M^{+\bullet}$, $C_{17}H_{12}{}^{81}BrNO_2$, 96%), 341 ($M^{+\bullet}$, $C_{17}H_{12}{}^{79}BrNO_2$, 68%), 285 (99), 284 (87), 203 (40). HRMS ($C_{17}H_{13}{}^{79}BrNO_2$) calc.: 342.0130, found: 342.0123.

General procedure for the preparation of 2-arylquinoline-4-carboxamides

A solution of imine **1a** (72 mg, 0.4 mmol) and amide **3** (219 mg, 1 mmol) or **4** (159 mg, 1 mmol) was added to indium chloride (88 mg, 0.4 mmol) in acetonitrile (2 mL) in a reaction tube. The solution was heated in a microwave oven (150 W) for 3 min. The mixture was cooled to room temperature, poured into water (20 mL) and extracted with dichloromethane (20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by column chromatography over silica gel (pentane–ethyl acetate 95 : 5 to 80 : 20) to yield the expected quinoline 4-carboxamide.

***N*-Isopropyl-2-phenylquinoline-4-carboxamide (9a).** Yellow solid (66 mg, 57%), mp 148–150 °C. IR ν_{max}/cm^{-1} (KBr): 3270, 2990, 2950, 1634, 1595, 1570, 785. ^{1}H NMR: δ_H 8.22–8.15 (4H, m), 7.88 (1H, s), 7.76 (1H, t, *J* 6.0), 7.58–7.50 (4H, m), 5.91 (1H, br s), 4.46 (1H, sept, *J* 6.7), 1.36 (6H, d, *J* 6.7). ^{13}C NMR: δ_C 171.1, 166.8, 154.2, 148.7, 143.9, 138.9, 130.1, 129.7, 128.9, 127.9, 124.9, 123.4, 116.4, 41.9, 22.4. MS (EI) *m/z* 290 ($M^{+\bullet}$, 100%), 275 (M − CH_3, 48%), 247 (11), 232 [65, M − $NHCH(CH_3)_2$], 204 [33, M − $CONHCH(CH_3)_2$], 176 (12). HRMS ($C_{19}H_{19}N_2O$) calc.: 291.1497, found: 291.1487.

***N*-Isopropyl-2-(2′-fluorophenyl)-quinoline-4-carboxamide (9b).** Yellow oil (53 mg, 43%). IR ν_{max}/cm^{-1} (NaCl): 3058, 1634, 1610, 1546, 1265, 741. ^{1}H NMR: δ_H 8.12 (2H, dd, *J* 5.4, *J* 1.2), 8.00 (1H, dt, *J* 7.8, *J* 1.8), 7.80 (1H, d, *J* 2.3), 7.66 (1H, dt, *J* 7, *J* 1.2), 7.51 (1H, dt, *J* 8.1, *J* 0.9), 7.37–7.31 (1H, m), 7.25–7.07 (2H, m), 6.10 (1H, s), 4.04 (1H, sept, *J* 6.6), 1.23 (3H, d, *J* 6.6). ^{13}C NMR: δ_C 167.1, 161.7, 161.1 (d, ^1J 249), 149.1, 143.0, 131.8 (d, $^4J_{CF}$ 2.5), 131.5 (d, $^3J_{CF}$ 8.1), 130.5, 127.9, 127.7, 127.5, 125.4, 125.1 (d, $^4J_{CF}$ 3.7), 123.9, 120.1, 119.9, 116.6 (d, $^2J_{CF}$ 22.6), 42.7, 23.1. ^{19}F NMR: δ_F −117.3 (m). MS (EI, GC–MS) *m/z* 308 ($M^{+\bullet}$, 93%), 293 (56), 250 (100), 222 (67), 202 (12). HRMS ($C_{19}H_{18}FN_2O$) calc.: 309.1403, found: 309.1396.

(*S*)-*N*-(1-Phenylpropyl)-2-phenylquinoline-4-carboxamide (10a)[1]. White solid (67 mg, 47%), mp 158 °C (lit.[1]: 140–141 °C) $[\alpha]_D^{20}$ = −24.2 (*c* 0.5, MeOH, lit.[1] $[\alpha]_D^{20}$ = −26.7). ^{1}H NMR: δ_H 8.03–8.00 (2H, m), 7.99 (1H, dd, *J* 7.6, *J* 0.8), 7.69 (1H, s), 7.63 (1H, dt, *J* 5.5, *J* 1.5), 7.46–7.31 (10H, m), 6.80 (d, 1H, *J* 8.4), 5.16 (1H, q, *J* 8.1), 0.98 (3H, t, *J* 8.1). ^{13}C NMR: δ_C 167.4, 157.0, 148.9, 143.4, 141.9, 139.2, 130.4, 130.1, 129.1, 128.1, 127.9, 127.6, 127.2, 126.9, 125.3, 123.7, 116.6, 56.1, 29.5, 11.6.

(*S*)-*N*-(1-Phenylpropyl)-2-(2′-fluorophenyl)-quinoline-4-carboxamide (10b). White solid (53 mg, 35%), mp 160 °C. $[\alpha]_D^{20}$ = −46 (*c* 1, MeOH). IR ν_{max}/cm^{-1} (KBr): 3260, 2964, 1705, 1641, 1555, 1467, 1260. ^{1}H NMR: δ_H 8.16–8.07 (3H, m), 7.88 (1H, s), 7.72 (1H, t, *J* 2.1), 7.52 (1H, d, *J* 1), 7.36–7.14 (7H, m), 6.49 (1H, d, *J* 8.3), 5.16 (1H, q, *J* 7.5), 2.01–1.90 (2H, m), 0.85 (3H, t, *J* 7.5). ^{13}C NMR: δ_C 165.4, 159.3 (d, $^1J_{CF}$ 249), 152.1, 147.3, 140.9, 140.1, 129.9 (d, $^3J_{CF}$ 8.1), 129.7, 128.7, 128.6, 127.4, 127.2, 126.2, 125.2, 123.6, 123.3 (d, $^4J_{CF}$ 3.7), 122.1, 118.1 (d, $^3J_{CF}$ 8.1), 114.8 (d, $^2J_{CF}$ 22.6), 54.1, 27.7, 9.1. ^{19}F NMR: δ_F −105.6 (m). MS (EI, GC–MS) *m/z* 384 ($M^{+\bullet}$, 12%), 355 (16, M − CH_2CH_3), 270 (33), 255 (23), 250 (48), 222 [35, M − $CONHCH(PhCH_2CH_3)$], 99 (100). HRMS ($C_{25}H_{21}FN_2O$) calc.: 384.1638, found: 384.1620.

(*S*)-*N*-(1-Phenylpropyl)-2-(4′-fluorophenyl)-quinoline-4-carboxamide (10j). White solid (74 mg, 48%), mp 160 °C. $[\alpha]_D^{20}$ = −27 (*c* 1, MeOH). IR ν_{max}/cm^{-1} (KBr): 3053, 2986, 1701, 1670, 1421, 1264, 738. ^{1}H NMR: δ_H 8.00–7.94 (3H, m), 7.61 (1H, s), 7.38–7.24 (6H, m), 7.13 (2H, t, *J* 8.6), 6.76 (1H, d, *J* 8.3), 5.15 (1H, q, *J* 7.6), 2.00–1.89 (2H, m), 0.98 (3H, t, *J* 7.6). ^{13}C NMR: δ_C 167.3, 164.3 (d, $^1J_{CF}$ 249), 155.8, 148.8, 143.3, 141.9, 135.2 (d, $^4J_{CF}$ 3.1), 130.5, 130.3, 129.7 (d, $^3J_{CF}$ 8.2), 129.2, 129.1, 128.1, 127.6, 127.2, 125.2, 123.5, 116.3, 116.2 (d, $^2J_{CF}$ 21.4), 56.2, 29.8, 11.8. ^{19}F NMR: δ_F −112.1 (m). MS (EI, GC–MS) *m/z* 384 ($M^{+\bullet}$, 25%), 363 (31), 355 (31, M − CH_2CH_3), 250 (100), 222 [69, M − $CONHCH(PhCH_2CH_3)$], 190 (64). HRMS ($C_{25}H_{21}FN_2O$) calc.: 384.1638, found: 384.1652.

(*S*)-*N*-(1-Phenylpropyl)-6-fluoro-2-phenylquinoline-4-carboxamide (10k). White solid (75 mg, 49%), mp 160 °C. $[\alpha]_D^{20}$ = −24.8 (*c* 1, MeOH). IR ν_{max}/cm^{-1} (KBr): 3258, 2964, 1705, 1641, 1555, 1467, 1260. ^{1}H NMR: δ_H 8.03–7.97 (3H, m), 7.70 (1H, s), 7.62–7.50 (1H, dd, *J* 6.9, *J* 2.8), 7.50–7.26 (9H, m), 6.57 (1H, d, *J* 8.4), 5.19 (1H, q, *J* 7.5), 2.06–1.97 (2H, m), 1.01 (3H, t, *J* 7.5). ^{13}C NMR: δ_C 166.5, 160.1 (d, $^1J_{CF}$ 249), 156.0, 145.8, 142.2, 141.4, 138.5, 132.4 (d, $^3J_{CF}$ 9.4), 129.8, 128.9, 128.8, 128.6, 128.0, 127.8, 127.3, 126.8, 126.6, 120.4 (d, $^2J_{CF}$ 25.8), 116.8, 108.8 (d, $^2J_{CF}$ 23.4), 55.8, 24.4, 10.9. ^{19}F NMR: δ_F −111.5 (m). *m/z* (EI, GC–MS) 384 ($M^{+\bullet}$, 12%), 355 (16, M − CH_2CH_3), 333 (14), 288 (15), 270 (33), 250 (48), 222 [31, M − $CONHCH(PhCH_2CH_3)$], 99 (100). HRMS ($C_{25}H_{22}FN_2O$) calc.: 385.1716, found: 385.1705.

(*S*)-*N*-(1-Phenylpropyl)-2-(3′-fluorophenyl)-quinoline-4-carboxamide (10n). White solid (81 mg, 53%), mp 160 °C. $[\alpha]_D^{20}$ = −27.6 (*c* 1 in MeOH). IR ν_{max}/cm^{-1} (KBr): 3260, 3060, 1705, 1641, 1467, 1353, 1260. ^{1}H NMR: δ_H 8.05 (1H, d, *J* 8.4), 7.95 (1H, d, *J* 7.8), 7.82–7.77 (2H, m), 7.70–7.66 (2H, m), 7.46–7.15 (8H, m), 6.68 (1H, d, *J* 7.7), 5.19 (1H, q, *J* 7.7), 2.13–2.04 (2H, m), 1.02 (3H, t, *J* 7.7). ^{13}C NMR: δ_C 164.4, 160.5 (d, $^1J_{CF}$ 246), 153.0, 152.9, 146.3, 141.0, 139.3, 138.9, 128.1 (d, $^3J_{CF}$ 10.7),

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127.9, 126.7, 126.4, 125.6, 125.4, 124.6, 122.7, 121.3, 120.8 (d, $^4J_{CF}$ 3.1), 114.4 (d, $^2J_{CF}$ 21.4), 113.8, 112.2 (d, $^2J_{CF}$ 22.7), 53.4, 27.0, 8.8. ^{19}F NMR: δ_F −115.3 (m). MS (EI, GC–MS) *m/z* 384 ($M^{+\bullet}$, 20%), 363 (56), 355 (27, M − CH_2CH_3), 250 (81), 222 [54, M − CONHCH($PhCH_2CH_3$)], 190 (51), 134 (100). HRMS ($C_{25}H_{21}FN_2O$) calc.: 384.1712, found: 384.1702.

(*S*)-*N*-(1-Phenylpropyl)-8-fluoro-2-phenylquinoline-4-carboxamide (10o). White solid (80 mg, 53%), mp 160 °C. $[a]_D^{20}$ = −9.4 (*c* 1, MeOH). IR ν_{max}/cm^{-1} (KBr): 3260, 2964, 1705, 1641, 1555, 1467, 1260. ^{1}H NMR: δ_H 8.04–8.00 (3H, m), 7.74 (1H, s), 7.73–7.72 (1H, m), 7.45–7.22 (10H, m), 6.68 (1H, d, *J* 7.5), 5.18 (1H, q, *J* 7.5), 2.02–1.93 (2H, m), 1.00 (3H, t, *J* 7.5). ^{13}C NMR: δ_C 166.9, 158.5 (d, $^1J_{CF}$ 257), 157.1, 143.3, 141.8, 139.1, 138.6, 130.4, 129.3, 129.0 (d, $^3J_{CF}$ 6.9), 128.4, 128.1, 127.9, 127.3, 127.2, 126.9, 125.3, 121.0 (d, $^4J_{CF}$ 5), 117.4, 114.5 (d, $^2J_{CF}$ 18.9), 53.6, 29.5, 11.4. ^{19}F NMR: δ_F −124.3 (m). MS (EI, GC–MS) *m/z* 384 ($M^{+\bullet}$, 17%,), 355 (23, M − CH_2CH_3), 250 (67), 233 (32), 222 [35, M − CONHCH($PhCH_2CH_3$)], 204 (76), 72 (100). HRMS ($C_{25}H_{21}FN_2O$) calc. 384.1638, found: 384.1656.

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