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Palladium-Catalyzed Cyclization/Carbonylation as a Direct Route to 4-[(Methoxycarbonyl)methyl]-3,4-dihydroisoquinolinones

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An efficient synthetic protocol for the preparation of 4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-ones from *N*-allylamides of 2-iodobenzoic acids has been performed under 100 atm of carbon monoxide. Pyridine ring formation occurs through an intramolecular Pd-catalyzed carbon–carbon bond formation, followed by an alkoxycarbonylation process.

Introduction

The Pd-catalyzed carbonylation of unsaturated substrates represents an attractive methodology for the entry into functionalized heterocyclic compounds.[1] These reactions can take place with carbon monoxide incorporation into the cycle by a cyclocarbonylation process[2] or with a cyclization/carbonylation process with formation of rings having an exocylic carbonyl group.[3]

In this field, despite not being as extensively studied as other Pd-catalyzed carbon–carbon bond-forming reactions, carbonylative cyclizations with vinyl or aryl halides bearing an ethylenic functionality were proven to be useful processes for the preparation of (hetero)aromatic carboxylic acid derivatives (Figure 1).[4]

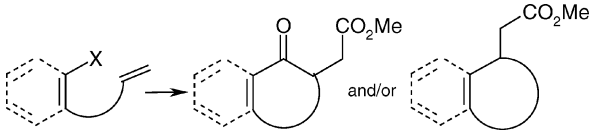


Figure 1. General Pd-catalyzed carbonylative cyclization process.

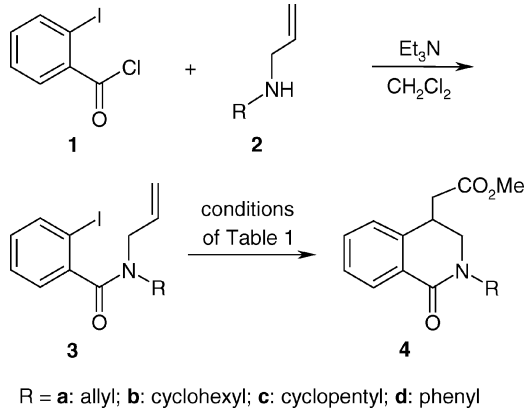
Among the nitrogen-containing heterocycles, isoquinolines represent one of the most attractive products, due to their presence in a wide range of compounds endowed with biological and pharmacological properties.[5]

Recently, we reported a protocol for the preparation of 4-spiroannulated isoquinoline derivatives in which the key step consisted of an intramolecular, Pd-catalyzed cyclization of *N*-allyl-2-iodobenzylamines, followed by a 1,3-dipolar cycloaddition.[6]

We herein report a synthetic procedure to attain 4-[(methoxycarbonyl)methyl]-substituted isoquinolin-1-ones by an intramolecular Heck-type cyclization of aryl iodides bearing a carbon–carbon double bond, carried out in the presence of carbon monoxide.

Results and Discussion

As starting materials suitable to build the isoquinolinic skeleton, we envisioned the *N*-allylamides of the 2-iodobenzoic acids **3**, easily available from the 2-iodobenzoyl chloride (**1**) and the *N*-alkyl-*N*-allylamines **2a**–**d** (Scheme 1).



R = **a**: allyl; **b**: cyclohexyl; **c**: cyclopentyl; **d**: phenyl

Scheme 1. Synthetic approach to access 4-[(methoxycarbonyl)-methyl]-3,4-dihydroisoquinolin-1-ones.

In order to test the feasibility of the carbonylative cyclization of amides **3**, we investigated the intramolecular reaction of *N*,*N*-diallylamide **3a** in the presence of Et_3N

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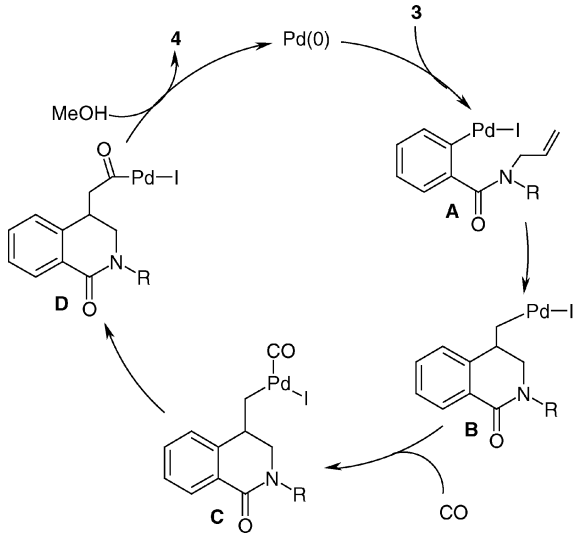
(2 equiv.), MeOH (4 equiv.) and catalytic amounts of $PdCl_2(PPh_3)_2$. The reaction was performed in MeCN at 80 °C under carbon monoxide (50 atm). Under these conditions, the desired 3,4-dihydroisoquinolinone product was obtained in 32% yield, along with the competitive acyclic methoxycarbonyl product **5** and product **6**, deriving from the shift of the C–C double bond of the initially formed Heck product **7**. The latter was detected in the ^1H NMR spectrum of the crude mixture but could not be isolated in pure form. On substrate **3a**, we screened different combinations of three parameters (catalyst, solvent and pressure) with the aim to optimize the reaction and prevent the acyclic product of alkoxycarboxylation of the iodine-substituted aromatic carbon atom.

From the conditions collected in Table 1, some features should be pointed out. First, the carbonylative cyclization was significantly accomplished only in the presence of catalytic systems with phosphane ligands. In fact, $PdCl_2(PPh_3)_2$, $PdCl_2(PTol_3)_2$, $PdCl_2(PCy_3)_2$ and $Pd(PPh_3)_4$ gave similar results, even though better results were achieved with $PdCl_2(PPh_3)_2$. The reaction required the use of polar aprotic solvents, among which MeCN was the most suitable. The addition of a co-solvent, such as toluene, DMF, THF or DMSO did not improve the yields. With MeOH as solvent, only unreacted starting material was recovered. The temperature was also important, and was optimal at 80 °C. By working at higher temperatures the yields decreased due to an increase in the amount of degradation products (Entry 5, Table 1). Finally, the conversion of the amide **3** took place in better yields by increasing the pressure to 100 atm. Having optimized the parameters, we confirmed the general effectiveness of the conditions of Entry 4 (Table 1) for the alkoxycarbonylation process on *N*-allylamides **3b–d**, starting with 2-iodobenzoyl chloride and the commercially available *N*-alkyl- and *N*-aryl-*N*-allylamines. The isoquinoline products **4b–d** were obtained in 55–61% yield.

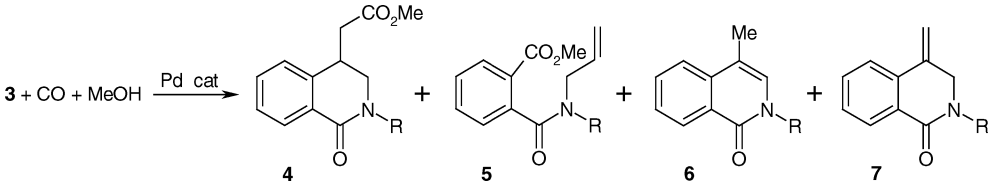
We next examined the cyclization of *N*-allylamides **9** by starting from differently substituted benzoic acids **8a–c**. The reactions occurred analogously to those of amides **3** giving rise to 4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolinones **10** (Table 2).

The mechanism of the process can be rationalized as depicted in Scheme 2. The oxidative addition of the carbon–iodine bond of aryl iodides **3** to Pd^0, generated in situ from



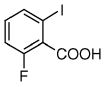
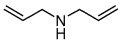
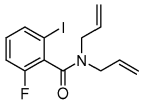
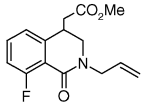
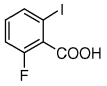
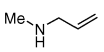
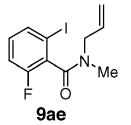
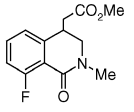
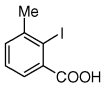
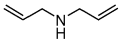
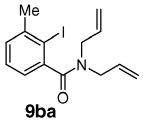
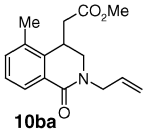
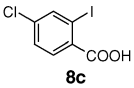
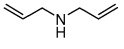
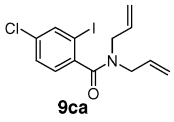
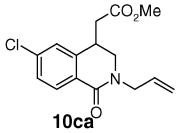
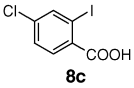
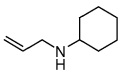
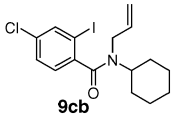
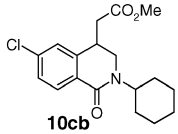
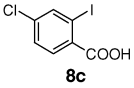
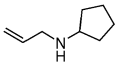
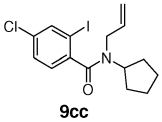
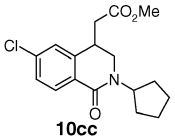
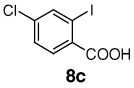
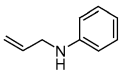
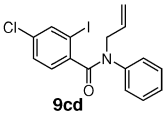
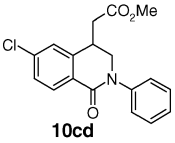
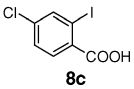
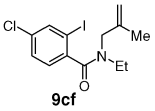
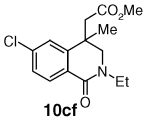
Scheme 2. Plausible mechanism for the carbonylative catalytic cycle.

Table 1. Optimization of the carbonylative cyclization conditions.



Entry	Catalyst	MeOH [equiv.]	Solvent	Pressure [atm] / *T* [°C]	R	Yield [%]		
						4	**5**	**6**
1	$PdCl_2(PPh_3)_2$	4	MeCN	50 / 80	allyl	32	40	13
2	$PdCl_2(PPh_3)_2$	4	DMF	50 / 80	allyl	15	36	21
3	$PdCl_2(PPh_3)_2$	4	MeCN	50 / 100	allyl	26	34	–
4	$PdCl_2(PPh_3)_2$	4	MeCN	100 / 80	allyl	59	4	–
5	$PdCl_2(PPh_3)_2$	4	MeCN	100 / 120	allyl	51	6	–
6	$PdCl_2(PPh_3)_2$	40	MeCN	100 / 80	allyl	13	64	–
7	$PdCl_2(PPh_3)_2$	–	MeOH	100 / 80	allyl	–	–	–
8	$PdCl_2(PTol_3)_2$	4	MeCN	100 / 80	allyl	55	6	–
9	$PdCl_2(Pcyclohexyl_3)_2$	4	MeCN	100 / 80	allyl	52	5	–
10	$Pd(PPh_3)_4$	4	MeCN	100 / 80	allyl	43	8	–
11	Pd sponge + PPh_3	4	MeCN	110 / 80	allyl	–	–	–
12	Pd black	4	MeCN	110 / 80	allyl	5	8	–
13	$PdCl_2(PPh_3)_2$	4	MeCN	100 / 80	cyclohexyl	58	–	–
14	$PdCl_2(PPh_3)_2$	4	MeCN	100 / 80	cyclopentyl	55	–	–
15	$PdCl_2(PPh_3)_2$	4	MeCN	100 / 80	phenyl	61	–	–

Table 2. Synthesis of substituted 4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolinones (under the conditions of Entry 4 of Table 1).

Entry	Carboxylic acid	Allylamine	Amide	Product	Yield
1	 **8a**	 **2a**	 **9aa**	 **10aa**	86 %
2	 **8a**	 **2e**	 **9ae**	 **10ae**	67 %
3	 **8b**	 **2a**	 **9ba**	 **10ba**	52 %
4	 **8c**	 **2a**	 **9ca**	 **10ca**	87 %
5	 **8c**	 **2b**	 **9cb**	 **10cb**	71 %
6	 **8c**	 **2c**	 **9cc**	 **10cc**	68 %
7	 **8c**	 **2d**	 **9cd**	 **10cd**	83 %
8	 **8c**	 **2f**	 **9cf**	 **10cf**	55 %

$PdCl_2L_2$, resulted in the corresponding Pd^{II} complex intermediates **A**. The following intramolecular carbopalladation gave the (σ-alkyl)Pd complexes **B**. The carbon monoxide activation yielded a complex with a carbonyl ligand (**C**), and the insertion of CO into the Pd–C bond, occurring faster than β-elimination, formed the (acyl)Pd complexes **D**. The nucleophilic displacement by MeOH finally led to products **4**, with the simultaneous regeneration of the catalytically active Pd^0 species.

Conclusions

We have developed a new protocol for the direct synthesis of dihydroisoquinolinones bearing a (methoxycarbonyl)-methyl group in position 4 by means of a Pd-catalyzed carbonylative cyclization. We found that a high CO pressure and high temperatures were determinant factors in optimizing the production of the desired 4-[(methoxycarbonyl)-methyl]-3,4-dihydroisoquinolinones.

Experimental Section

General: Melting points were determined by the capillary method with a Büchi B-540 apparatus and are uncorrected. NMR spectra were recorded with an AVANCE 400 Bruker spectrometer at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR spectroscopy. Chemical shifts are given as δ values in ppm relative to the residual solvent peaks ($CHCl_3$) as the internal reference. ^{13}C NMR spectra are ^1H-decoupled, and the determination of the multiplicities was achieved by the APT pulse sequence. IR spectra were measured with a Jasco FT/IR 5300 spectrometer. Mass spectra were determined with a VG-7070 EQ-HF instrument. Elemental analyses were executed with a Perkin–Elmer CHN Analyzer Series II 2400.

Thin-layer chromatographic separations were performed with Merck silica gel 60-F_{254} (precoated). Preparative separations were performed by flash chromatography with Merck silica gel (0.035–0.070 mm). High-pressure experiments were conducted with a 100 mL PARR stainless steel autoclave reactor equipped with an Ashcroft Duralife (3000 psi) pressure gauge and a PARR 4842 temperature controller.

General Procedure for the Synthesis of *N*-Alkyl-*N*-allyl-2-iodobenzamides 3: A solution of *N*-alkyl-*N*-allylamine (3.8 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise into a solution of 2-iodobenzoyl chloride (1.0 g, 3.8 mmol) and Et_3N (0.63 mL, 4.5 mmol) in dry CH_2Cl_2 (6 mL). After stirring overnight, the mixture was washed with HCl (1 M, 30 mL) and aqueous $NaHCO_3$ (5%, 30 mL). The organic phase was dried with Na_2SO_4, and the solvent was evaporated. The products were obtained pure enough for characterization.

***N*,*N*-Diallyl-2-iodobenzamide (3a):** Yield 1.106 g (89%); pale yellow oil. IR (nujol): $\tilde{\nu}$ = 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.72 (s, 2 H), 3.77–3.83 (m, 1 H), 4.54–4.60 (m, 1 H), 5.12 (dd, J = 17.1, 1.4 Hz, 1 H), 5.20 (dd, J = 10.1, 1.4 Hz, 1 H), 5.28 (dd, J = 10.1, 1.3 Hz, 1 H), 5.33 (dd, J = 17.1, 1.3 Hz, 1 H), 5.69 (ddt, J = 17.1, 10.1, 5.7 Hz, 1 H), 5.96 (ddt, J = 17.1, 10.1, 6.2 Hz, 1 H), 7.09 (ddd, J = 7.8, 7.6, 1.7 Hz 1 H), 7.22 (dd, J = 7.6, 1.7 Hz, 1 H), 7.38 (ddd, J = 8.0, 7.8, 1.1 Hz, 1 H), 7.84 (dd, J = 8.0, 1.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.8 (t), 50.7 (t), 93.0 (s), 118.5 (t), 118.8 (t), 127.4 (d), 128.6 (d), 130.6 (d), 132.8 (d), 133.0 (d), 139.5 (d), 142.6 (s), 170.8 (s) ppm. MS: m/z = 327 $[M]^+$. $C_{13}H_{14}INO$ (327.16): calcd. C 47.73, H 4.31, N 4.28; found C 47.82, H 4.19, N 4.45.

***N*-Allyl-*N*-cyclohexyl-2-iodobenzamide (3b):** Yield 1.024 g (73%); yellow oil. IR (nujol): $\tilde{\nu}$ = 1658 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, mixture of two conformers in a 1:1 ratio): δ = 0.81–2.10 (m, 20 H), 3.14–3.24 (m, 1 H), 3.59–3.83 (m, 2 H), 3.99 and 4.23 (AB part of ABX system, J = 15.4, 5.1 Hz, 2 H), 4.45–4.51 (m, 1 H), 4.91 (d, J = 17.1 Hz, 1 H), 5.01 (d, J = 10.3 Hz, 1 H), 5.28 (d, J = 10.3 Hz, 1 H), 5.34 (d, J = 17.1 Hz, 1 H), 5.69 (ddt, J = 17.1, 10.3, 5.1 Hz, 1 H), 6.06 (ddt, J = 17.1, 10.3, 5.1 Hz, 1 H), 7.04–7.11 (m, 2 H), 7.18–7.21 (m, 2 H), 7.33–7.41 (m, 2 H), 7.81 (d, J = 8.0 Hz, 1 H), 7.86 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two conformers in a 1:1 ratio): δ = 25.5 (t), 26.0 (t), 26.1 (t), 26.4 (t), 32.2 (t), 32.4 (t), 44.4 (t), 48.3 (t), 54.8 (d), 59.7 (d), 92.9 (s), 93.3 (s), 116.8 (t), 117.2 (t), 126.8 (d), 127.9 (d), 128.3 (d), 128.6 (d), 130.2 (d), 130.4 (d), 135.5 (d), 135.7 (d), 139.3 (d) 139.7 (d), 143.4 (s), 143.5 (s), 170.8 (s), 171.2 (s) ppm. MS: m/z = 369 $[M]^+$. $C_{16}H_{20}INO$ (369.24): calcd. C 52.05, H 5.46, N 3.79l; found C 52.26, H 5.31, N 3.64.

***N*-Allyl-*N*-cyclopentyl-2-iodobenzamide (3c):** Yield 1.107 g (82%) as a mixture of two conformers in a 2:1 ratio; yellow oil. IR (nujol): $\tilde{\nu}$ = 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ major conformer): δ = 1.37–1.51 (m, 2 H), 1.54–1.82 (m, 5 H), 1.88–1.99 (m, 1 H), 3.73–3.86 (m, 1 H), 3.94 and 4.21 (AB part of ABX system, J = 15.6, 5.8 Hz, 2 H), 5.21 (d, J = 10.3 Hz, 1 H), 5.36 (d, J = 17.3 Hz, 1 H), 6.10 (ddt, J = 17.3, 10.3, 5.8 Hz, 1 H), 7.08 (dd, J = 7.9, 7.4 Hz, 1 H), 7.21 (d, J = 7.5 Hz, 1 H), 7.39 (dd, J = 7.5, 7.4 Hz, 1 H), 7.85 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major conformer): δ = 24.1 (t), 30.2 (t), 44.4 (t), 60.9 (d), 92.9 (s), 116.4 (t), 127.0 (d), 128.6 (d), 130.3 (d), 135.2 (d), 139.6 (d), 143.6 (s), 170.8 (s) ppm. ^1H NMR (400 MHz, $CDCl_3$, minor conformer): δ = 1.37–1.51 (m, 2 H), 1.54–1.82 (m, 5 H), 2.05–2.15 (m, 1 H), 3.63–3.72 (m, 2 H), 4.72–4.84 (m, 1 H), 5.01 (d, J = 17.1 Hz, 1 H), 5.08 (d, J = 10.3 Hz, 1 H), 5.69 (ddt, J = 17.1, 10.3, 5.9 Hz, 1 H), 7.05 (dd, J = 7.8, 7.4 Hz, 1 H), 7.23 (d, J = 7.6 Hz, 1 H), 7.35 (dd, J = 7.6, 7.4 Hz, 1 H), 7.80 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, minor conformer): δ = 24.6 (t), 30.2 (t), 49.0 (t), 57.0 (d), 93.2 (s), 117.0 (t), 127.7 (d), 128.3 (d), 130.3 (d), 135.3 (d), 139.2 (d), 143.4 (s), 171.4 (s) ppm. MS: m/z = 355 $[M]^+$. $C_{15}H_{18}INO$ (355.21): calcd. C 50.72, H 5.11, N 3.94; found C 50.95, H 4.93, N 3.81.

***N*-Allyl-*N*-phenyl-2-iodobenzamide (3d):** Yield 924 mg (67%); pale yellow oil. IR (nujol): $\tilde{\nu}$ = 1655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.53 (d, J = 6.0 Hz, 2 H), 5.18 (d, J = 10.6 Hz, 1 H), 5.22 (d, J = 19.0 Hz, 1 H), 6.03 (ddt, J = 19.0, 10.6, 6.0 Hz, 1 H), 6.79 (dd, J = 7.8, 7.3 Hz, 1 H), 6.99–7.19 (m, 6 H), 7.28–7.48 (m, 1 H), 7.62 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.7 (t), 94.2 (s), 118.8 (t), 127.7 (d), 127.8 (d), 128.4 (d), 128.9 (d), 129.3 (d), 130.1 (d), 133.1 (d), 139.5 (d), 142.2 (s), 142.6 (s), 170.1 (s) ppm. MS: m/z = 363 $[M]^+$. $C_{16}H_{14}INO$ (363.19): calcd. C 52.91, H 3.89, N 3.86; found C 53.06, H 4.71, N 3.99.

General Procedure for the Synthesis of *N*-Alkyl-*N*-allyl-2-iodoarylamides 9. Procedure A: DCC (824 mg, 4 mmol), *N*-alkyl-*N*-allylamine (3.33 mmol) and DMAP (6 mg, 0.05 mmol) were added to a solution of 2-iodobenzoic acid **8a**–**c** (4 mmol) in dry CH_2Cl_2 (30 mL), cooled to 0 °C. The mixture was stirred at room temperature for 48 h and then filtered through Celite. The solvent was evaporated, and the crude mixture was purified by silica gel column chromatography with light petroleum/AcOEt (7:3) as the eluent. **Procedure B:** A solution of 2-iodobenzoic acid **8a**,**c** (1 mmol) in $SOCl_2$ (2 mL) was refluxed for 4 h. The solvent was removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (10 mL). After cooling the mixture to 0 °C, *N*-alkyl-*N*-allylamine (1.5 mmol) and Et_3N (0.20 mL, 1.5 mmol) were added dropwise. The mixture was stirred at room temperature for 48 h and then washed with HCl (1 M, 20 mL) and with aqueous $NaHCO_3$ (5%, 20 mL). The organic phase was dried with Na_2SO_4, and the solvent was removed under reduced pressure. The products were obtained pure enough for characterization.

***N*,*N*-Diallyl-6-fluoro-2-iodobenzamide (9aa):** Procedure A; yield 1.0 g (87%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (d, J = 6.1 Hz, 2 H), 3.98 and 4.42 (AB part of ABX system, J = 15.0, 6.0 Hz, 2 H), 5.12 (d, J = 17.1 Hz, 1 H), 5.18 (d, J = 10.2 Hz, 1 H), 5.27 (d, J = 10.2 Hz, 1 H), 5.27 (d, J = 17.4 Hz, 1 H), 5.73 (ddt, J = 17.1, 10.2, 6.1 Hz, 1 H), 5.92 (ddt, J = 17.4, 10.2, 6.0 Hz, 1 H), 7.06–7.11 (m, 2 H), 7.62 (d, J = 7.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.8 (t), 51.0 (t), 93.9 (s), 116.0 (d), 116.2 (d), 118.7 (t), 119.3 (t), 131.0 (d, $J_{C,F}$ = 21.4 Hz), 131.8 (dd, $J_{C,F}$ = 8.1 Hz), 132.7 (dd, $J_{C,F}$ = 28.2 Hz), 135.4 (d), 158.3 (d, $J_{C,F}$ = 249.9 Hz), 166.2 (s) ppm. MS: m/z = 345 $[M]^+$. $C_{13}H_{13}FINO$ (345.15): calcd. C 45.24, H 3.80, N 4.06; found C 44.99, H 3.92, N 3.79.

***N*-Allyl-6-fluoro-2-iodo-*N*-methylbenzamide (9ae):** Procedure B; yield 252 mg (79%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, mixture of two conformers in a 1:1 ratio): δ = 2.83 (s, 3 H), 3.12 (s, 3 H), 3.73 and 3.78 (AB part of ABX system, J = 18.4, 6.3 Hz, 2 H), 4.16 and 4.30 (AB part of ABX system, J = 14.5, 5.7 Hz, 2 H), 5.19 (d, J = 11.8 Hz, 1 H), 5.23 (d, J = 10.3 Hz, 1 H), 5.30 (d, J = 10.2 Hz, 1 H), 5.36 (d, J = 17.2 Hz, 1 H), 5.76 (ddt, J = 17.2, 10.2, 5.7 Hz, 1 H), 5.92 (ddt, J = 11.8, 10.3, 6.3 Hz, 1 H), 7.04–7.16 (m, 4 H), 7.62–7.66 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.6 (q), 35.6 (q), 49.8 (t), 54.0 (t), 93.2 (s), 93.6 (s), 116.0 (d), 116.2 (d), 118.5 (t), 119.3 (t), 129.6 (d, $J_{C,F}$ = 22.8 Hz), 131.0 (d, $J_{C,F}$ = 21.4 Hz), 131.3 (dd, $J_{C,F}$ = 8.2 Hz), 131.7 (dd, $J_{C,F}$ = 7.8 Hz), 132.2 (dd, $J_{C,F}$ = 28.5 Hz), 132.6 (dd, $J_{C,F}$ = 27.7 Hz), 132.8 (d), 133.3 (d), 158.3 (d, $J_{C,F}$ = 249.9 Hz), 163.8 (d, $J_{C,F}$ = 242.1 Hz), 166.0 (s), 166.2 (s) ppm. MS:

m/*z* = 319 [M]$^+$. $C_{11}H_{11}FINO$ (319.11): calcd. C 41.40, H 3.47, N 4.39; found C 41.65, H 3.23, N 4.45.

***N*,*N*-Diallyl-2-iodo-3-methylbenzamide (9ba):** Procedure A; yield 977 mg (86%); pale yellow oil. IR (nujol): $\tilde{\nu}$ = 1686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 3.68 (d, *J* = 4.9 Hz, 2 H), 3.77 and 4.56 (AB part of ABX system, *J* = 14.8, 5.0 Hz, 2 H), 5.09 (d, *J* = 17.1 Hz, 1 H), 5.15 (d, *J* = 10.2 Hz, 1 H), 5.25 (d, *J* = 10.2 Hz, 1 H) 5.30 (d, *J* = 16.2 Hz, 1 H), 5.66 (ddt, *J* = 17.2, 10.2, 4.9 Hz, 1 H), 5.95 (ddt, *J* = 16.2, 10.2, 5.0 Hz, 1 H), 6.96 (d, *J* = 7.1 Hz, 1 H), 7.19–7.28 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3 (q), 46.7 (t), 50.7 (t), 99.8 (s), 118.5 (t), 118.8 (t), 124.6 (d), 128.7 (d), 130.0 (d), 132.9 (d), 133.1 (d), 143.0 (s), 143.7 (s), 171.5 (s) ppm. MS: *m*/*z* = 341 [M]$^+$. $C_{14}H_{16}INO$ (341.19): calcd. C 49.28, H 4.73, N 4.11; found C 49.07, H 4.84, N 4.26.

***N*,*N*-Diallyl-4-chloro-2-iodobenzamide (9ca):** Procedure A; yield 975 mg (81%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1663 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63–3.75 (m, 3 H), 4.45–4.55 (m, 1 H), 5.07 (d, *J* = 17.1 Hz, 1 H), 5.18 (d, *J* = 10.3 Hz, 1 H), 5.23 (d, *J* = 10.1 Hz, 1 H), 5.28 (d, *J* = 17.1 Hz, 1 H), 5.58–5.66 (m, 1 H), 5.86–5.94 (m, 1 H), 7.10 (d, *J* = 8.1 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 1 H), 7.79 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.0 (t), 50.7 (t), 93.3 (s), 118.6 (t), 119.0 (t), 128.1 (d), 128.9 (d), 132.6 (d), 132.8 (d), 135.4 (s), 139.0 (d), 141.1 (s), 170.0 (s) ppm. MS: *m*/*z* = 361 [M]$^+$. $C_{13}H_{13}ClINO$ (361.61): calcd. C 43.18, H 3.62, N 3.87; found C 43.19, H 3.84, N 3.76.

***N*-Allyl-4-chloro-*N*-cyclohexyl-2-iodobenzamide (9cb):** Procedure A; yield 739 mg (55%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1654 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two conformers in a 1:1 ratio): δ = 0.98–2.05 (m, 20 H), 3.10–3.18 (m, 1 H), 3.49–3.81 (m, 2 H), 3.96 and 4.19 (AB part of ABX system, *J* = 15.4, 5.8 Hz, 2 H), 4.39–4.49 (m, 1 H), 4.92 (d, *J* = 18.3 Hz, 1 H), 5.03 (d, *J* = 10.3 Hz, 1 H), 5.16 (d, *J* = 10.3 Hz, 1 H), 5.32 (d, *J* = 17.3 Hz, 1 H) 5.61–5.70 (m, 1 H), 5.97–6.07 (m, 1 H), 7.09 (d, *J* = 8.2 Hz, 1 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 7.32 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.36 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.79 (d, *J* = 2.0 Hz, 1 H), 7.84 (d, *J* = 2.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2 (t), 25.5 (t), 25.9 (t), 26.0 (t), 26.1 (t), 30.5 (t), 31.3 (t), 32.2 (t), 32.4 (t), 33.2 (t), 44.5 (t), 48.3 (t), 54.9 (d), 59.8 (d), 93.1 (s), 93.5 (s), 117.0 (t), 117.4 (t), 128.2 (d), 128.6 (d), 128.7 (d), 129.0 (d), 135.0 (s), 135.1 (s), 135.3 (d), 135.5 (d), 138.7 (d), 139.1 (d), 141.2 (s), 142.1 (s), 169.9 (s), 170.4 (s) ppm. MS: *m*/*z* = 403 [M]$^+$. $C_{16}H_{19}ClINO$ (403.69): calcd. C 47.61, H 4.74, N 3.47; found C 47.84, H 4.66, N 3.61.

***N*-Allyl-4-chloro-*N*-cyclopentyl-2-iodobenzamide (9cc):** Procedure B; yield 335 mg (86%); pale yellow oil. IR (nujol): $\tilde{\nu}$ = 1669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two conformers in a 1:1 ratio): δ = 1.25–2.10 (m, 16 H), 3.50–3.80 (m, 3 H), 3.93 and 4.19 (AB part of ABX system, *J* = 15.6, 5.5 Hz, 2 H), 4.71–4.77 (m, 1 H), 5.04 (d, *J* = 10.4 Hz, 1 H), 5.12 (d, *J* = 10.1 Hz, 1 H), 5.21 (d, *J* = 10.3 Hz, 1 H), 5.32 (d, *J* = 17.3 Hz, 1 H) 5.64–5.73 (m, 1 H), 6.03–6.13 (m, 1 H), 7.12 (d, *J* = 8.2 Hz, 1 H), 7.13 (d, *J* = 8.2 Hz, 1 H), 7.33 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.39 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.81 (d, *J* = 2.0 Hz, 1 H), 7.86 (d, *J* = 2.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1 (t), 24.6 (t), 29.3 (t), 30.3 (t), 30.4 (t), 31.3 (t), 32.2 (t), 32.4 (t), 44.5 (t), 48.9 (t), 57.1 (d), 61.0 (d), 93.1 (s), 93.5 (s), 116.7 (t), 117.2 (t), 127.8 (d), 128.5 (d), 128.7 (d), 129.0 (d), 135.0 (s), 135.1 (s), 135.0 (d), 135.1 (d), 138.7 (d), 139.1 (d), 142.2 (s), 142.1 (s), 169.9 (s), 170.4 (s) ppm. MS: *m*/*z* = 389 [M]$^+$. $C_{15}H_{17}ClINO$ (389.66): calcd. C 46.24, H 4.40, N 3.59; found C 46.31, H 4.28, N 3.42.

***N*-Allyl-4-chloro-2-iodo-*N*-phenylbenzamide (9cd):** Procedure B; yield 378 mg (95%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.53 (d, *J* = 6.2 Hz, 2 H), 5.21 (d, *J* = 7.5 Hz, 1 H), 5.24 (d, *J* = 15.6 Hz, 1 H), 5.62 (ddt, *J* = 15.6, 7.5, 6.2 Hz, 1 H), 6.94 (d, *J* = 8.2 Hz, 1 H), 7.09 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.13–7.45 (m, 5 H), 7.68 (d, *J* = 1.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (t), 94.4 (s), 118.9 (t), 127.4 (d), 128.0 (d), 128.3 (d), 129.4 (d), 129.5 (d), 132.8 (d), 134.9 (s), 139.0 (d), 141.2 (s), 142.0 (s), 169.3 (s) ppm. MS: *m*/*z* = 397 [M]$^+$. $C_{16}H_{13}ClINO$ (397.64): calcd. C 48.33, H 3.30, N 3.52; found C 48.42, H 3.19, N 3.68.

4-Chloro-*N*-ethyl-2-iodo-*N*-(2-methylallyl)benzamide (9cf): Procedure A; yield 1.078 g (89%) as a mixture of two conformer in a 1.5:1 ratio; colourless oil. IR (nujol): $\tilde{\nu}$ = 1651 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, major conformer): δ = 1.28 (t, *J* = 7.1 Hz, 3 H), 1.60 (s, 3 H), 3.04–3.16 (m, 2 H), 3.57–3.67 (m, 2 H), 4.90 (d, *J* = 22.8 Hz, 2 H), 7.15 (d, *J* = 8.2 Hz, 1 H), 7.35 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.83 (d, *J* = 1.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major conformer): δ = 12.3 (q), 20.5 (q), 39.7 (t), 49.2 (t), 60.8 (s), 93.4 (s), 113.4 (t), 128.3 (d), 128.9 (d), 139.2 (d), 140.8 (s), 141.1 (s), 170.2 (s) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, minor conformer): δ = 1.06 (t, *J* = 7.1 Hz, 3 H), 1.86 (s, 3 H), 3.95–4.07 (m, 3 H), 4.38–4.44 (m, 1 H), 5.01 (d, *J* = 11.4 Hz, 2 H), 7.15 (d, *J* = 8.2 Hz, 1 H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.87 (d, *J* = 1.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, minor conformer): δ = 13.7 (q), 21.1 (q), 42.6 (t), 54.1 (t), 59.8 (s), 93.1 (s), 114.0 (t), 128.4 (d), 129.0 (d), 138.9 (d), 140.4 (s), 141.8 (s), 170.0 (s) ppm. MS: *m*/*z* = 363 [M]$^+$. $C_{13}H_{15}ClINO$ (363.62): calcd. C 42.94, H 4.16, N 3.85; found C 42.71, H 4.24, N 3.70.

General Procedure for the Pd-Catalyzed Carbonylative Cyclization: A mixture of 2-iodobenzamide **3** or **9** (1 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), Et_3N (0.28 mL, 2 mmol) and MeOH (0.16 mL, 4 mmol) in MeCN (20 mL) was placed in an autoclave. It was first purged 3 times with 20 atm of CO to remove residual air and then charged with 100 atm of CO. ***Caution:*** *Carbon monoxide is highly toxic!* The autoclave was heated at 80 °C for 24 h and then cooled to room temperature. After CO removal, the yellow solution was diluted with brine (20 mL), extracted with AcOEt (3 × 20 mL), and the organic phases were dried with Na_2SO_4. The solvent was evaporated. The products were purified by silica gel column chromatography with light petroleum/AcOEt (9:1) to AcOEt as the eluent to give **4** or **10**.

2-Allyl-4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-one (4a): Yield 153 mg (59%); pale yellow oil. IR (nujol): $\tilde{\nu}$ = 1663, 1709 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (dd, *J* = 16.0, 5.5 Hz, 1 H), 2.61 (dd, *J* = 16.0, 8.6 Hz, 1 H), 3.33–3.39 (m, 1 H), 3.36 (dd, *J* = 13.7, 3.2 Hz, 1 H), 3.61 (s, 3 H), 3.67 (dd, *J* = 13.7, 5.2 Hz, 1 H), 4.01 and 4.22 (AB part of ABX system, *J* = 14.8, 6.3 Hz, 2 H), 5.16 (d, *J* = 11.1 Hz, 1 H), 5.19 (d, *J* = 15.7 Hz, 1 H), 5.78 (ddt, *J* = 15.7, 11.1, 6.3 Hz, 1 H), 7.15 (d, *J* = 7.5 Hz, 1 H), 7.29 (dd, *J* = 7.5, 7.4 Hz, 1 H), 7.37 (dd, *J* = 7.7, 7.4 Hz, 1 H), 8.03 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6 (q), 38.1 (t), 49.2 (t), 50.0 (t), 52.1 (d), 118.8 (t), 126.8 (d), 127.9 (d), 128.9 (d), 129.0 (s), 132.4 (d), 133.1 (d), 140.9 (s), 164.0 (s), 172.3 (s) ppm. MS: *m*/*z* = 259 [M]$^+$. $C_{15}H_{17}NO_3$ (259.30): calcd. C 69.48, H 6.61, N 5.40; found C 69.70, H 6.33, N 5.36.

***N*,*N*-Diallyl-2-(methoxycarbonyl)benzamide (5a):** Yield 10 mg (4%); pale yellow oil. IR (nujol): $\tilde{\nu}$ = 1671, 1729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (d, *J* = 5.8 Hz, 2 H), 3.87 (s, 3 H), 4.10–4.24 (m, 2 H), 5.07 (d, *J* = 17.1 Hz, 1 H), 5.14 (d, *J* = 10.2 Hz, 1 H), 5.26 (d, *J* = 10.3 Hz, 1 H), 5.29 (d, *J* = 16.0 Hz, 1 H), 5.64 (ddt, *J* = 16.0, 10.3, 5.8 Hz, 1 H), 5.95 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 1 H), 7.43 (dd, *J* = 7.7, 7.6 Hz, 1 H), 7.54 (dd, *J* = 7.6, 7.5 Hz, 1 H), 8.01 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.8 (t), 50.9 (t), 52.7 (q), 118.3 (t),

118.5 (t), 127.3 (d), 127.7 (s), 129.1 (d), 131.0 (d), 133.0 (d), 133.2 (d), 133.3 (d), 139.0 (s), 166.5 (s), 171.2 (s) ppm. MS: *m/z* (%) = 259 $[M]^+$. $C_{15}H_{17}NO_3$ (259.30): calcd. C 69.48, H 6.61, N 5.40; found C 69.36, H 6.88, N 5.60.

2-Cyclohexyl-4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-one (4b): Yield 175 mg (58%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1658, 1703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.61–1.01 (m, 1 H), 1.10–1.55 (m, 5 H), 1.59–1.91 (m, 4 H), 2.52 (dd, *J* = 16.4, 5.4 Hz, 1 H), 2.67 (dd, *J* = 16.4, 9.3 Hz, 1 H), 3.25–3.46 (m, 1 H), 3.51 and 3.58 (AB part of ABX system, *J* = 12.9, 3.3 Hz, 2 H), 3.70 (s, 3 H), 4.62–4.75 (m, 1 H), 7.21 (d, *J* = 7.3 Hz, 1 H), 7.36 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.43 (dd, *J* = 7.3 7.5 Hz, 1 H), 8.10 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (t), 26.1 (t), 26.3 (t), 30.2 (t), 30.4 (t), 34.7 (q), 37.5 (t), 43.9 (t), 51.3 (d), 51.9 (d), 126.7 (d), 127.9 (d), 129.6 (d), 130.6 (s), 131.7 (d), 141.0 (s) 163.1 (s), 172.0 (s) ppm. MS: *m/z* = 301 $[M]^+$. $C_{18}H_{23}NO_3$ (301.38): calcd. C 71.73, H 7.69, N 4.65; found C 71.52, H 7.97, N 4.86.

2-Cyclopentyl-4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-one (4c): Yield 158 mg (55%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1676, 1715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39–1.98 (m, 8 H), 2.52 (dd, *J* = 16.3, 5.0 Hz, 1 H), 2.66 (dd, *J* = 16.3, 9.4 Hz, 1 H), 3.35–3.48 (m, 2 H), 3.60 (dd, *J* = 12.9, 4.0 Hz, 1 H), 3.69 (s, 3 H), 4.48–4.60 (m, 1 H), 7.19 (d, *J* = 7.4 Hz, 1 H), 7.35 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.43 (dd, *J* = 7.4 7.5 Hz, 1 H), 8.09 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6 (t), 26.0 (t), 26.5 (t), 29.8 (t), 33.5 (q), 36.8 (t), 43.7 (t), 51.2 (d), 51.8 (d), 126.6 (d), 128.1 (d), 129.4 (d), 130.7 (s), 132.5 (d), 141.6 (s) 163.3 (s), 172.1 (s) ppm. MS: *m/z* = 287 $[M]^+$. $C_{17}H_{21}NO_3$ (287.35): calcd. C 71.06, H 7.37, N 4.87; found C 71.23, H 7.21, N 4.65.

4-[(Methoxycarbonyl)methyl]-2-phenyl-3,4-dihydroisoquinolin-1-one (4d): Yield 180 mg (61%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1691, 1707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.76 (dd, *J* = 16.1, 5.8 Hz, 1 H), 2.90 (dd, *J* = 16.1, 8.9 Hz, 1 H), 3.52–3.61 (m, 1 H), 3.69 (s, 3 H), 3.84 and 4.27 (AB part of ABX system, *J* = 12.6, 3.5 Hz, 2 H), 7.18–7.21 (m, 1 H), 7.22–7.33 (m, 2 H), 7.38–7.49 (m, 4 H), 7.59 (dd, *J* = 7.5, 7.5 Hz, 1 H), 8.19 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.2 (q), 38.2 (t), 52.3 (d), 53.6 (t), 126.0 (d), 126.9 (d), 127.0 (d), 128.2 (d), 129.3 (s), 129.5 (d), 129.6 (d), 132.9 (d), 141.1 (s), 143.3 (s), 163.1 (s), 172.0 (s) ppm. MS: *m/z* = 295 $[M]^+$. $C_{18}H_{17}NO_3$ (295.33): calcd. C 73.20, H 5.80, N 4.74; found C 73.10, H 6.06, N 4.62.

2-Allyl-4-methylisoquinolin-1-one (6a): Yield 26 mg (13%) from the conditions of Entry 1 of Table 1; colourless oil. IR (nujol): $\tilde{\nu}$ = 1680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 4.62 (d, *J* = 5.7 Hz, 2 H), 5.20 (d, *J* = 15.7 Hz, 1 H), 5.27 (d, *J* = 12.6 Hz, 1 H), 5.78 (ddt, *J* = 15.7, 12.6, 5.7 Hz, 1 H), 6.86 (s, 1 H), 7.49 (dd, *J* = 7.7, 7.8 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.66 (dd, *J* = 8.0, 7.8 Hz, 1 H), 8.48 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 (q), 50.9 (t), 112.6 (s), 118.2 (t), 123. 4 (d), 126.4 (s), 127.0 (d), 128.7 (d), 129.2 (d), 132.4 (d), 133.7 (d), 137.7 (s), 162.0 (s) ppm. MS: *m/z* = 199 $[M]^+$. $C_{13}H_{13}NO$ (199.25): calcd. C 78.36, H 6.58, N 7.03; found C 78.28, H 6.76, N 6.88.

2-Allyl-8-fluoro-4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-one (10aa): Yield 238 mg (86%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1678, 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (dd, *J* = 16.4, 5.7 Hz, 1 H), 2.61 (dd, *J* = 16.4, 8.8 Hz, 1 H), 3.30–3.38 (m, 2 H), 3.62 (s, 3 H), 3.65 (dd, *J* = 12.8, 3.6 Hz, 1 H), 3.93 and 4.26 (AB part of ABX system, *J* = 14.7, 6.5 Hz, 2 H), 5.16 (d, *J* = 9.9 Hz, 1 H), 5.19 (d, *J* = 15.9 Hz, 1 H), 5.76 (ddt, *J* = 15.9, 9.9, 6.5 Hz, 1 H), 6.95–7.00 (m, 2 H), 7.30–7.36 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.2 (d), 37.6 (t), 48.8 (t), 49.7 (t), 52.1 (q), 116.7 (dd, $J_{C,F}$ = 22.4 Hz), 117.4 (d, $J_{C,F}$ = 5.4 Hz), 119.1 (t), 122.7 (dd, $J_{C,F}$ = 3.4 Hz), 133.0 (d), 133.6 (dd, $J_{C,F}$ = 9.6 Hz), 143.8 (s), 161.0 (s), 162.6 (d, $J_{C,F}$ = 261.0 Hz), 172.0 (s) ppm. MS: *m/z* = 277 $[M]^+$. $C_{15}H_{16}FNO_3$ (277.29): calcd. C 64.97, H 5.82, N 5.05; found C 64.88, H 5.96, N 5.18.

8-Fluoro-2-methyl-4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-one (10ae): Yield 168 mg (67%); pale yellow oil. IR (nujol): $\tilde{\nu}$ = 1693, 1711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.59 (dd, *J* = 16.1, 5.6 Hz, 1 H), 2.90 (dd, *J* = 16.1, 8.9 Hz, 1 H), 3.14 (s, 3 H), 3.35–3.43 (m, 2 H), 3.69 (s, 3 H), 3.82 (dd, *J* = 12.9, 3.8 Hz, 1 H), 7.02 (dd, *J* = 8.2, 7.5 Hz, 1 H), 7.06 (d, *J* = 8.2 Hz, 1 H), 7.36–7.41 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.4 (q), 35.7 (q), 37.7 (t), 51.8 (t), 52.3 (d), 116.8 (dd, $J_{C,F}$ = 22.3 Hz), 117.5 (d, $J_{C,F}$ = 5.3 Hz), 133.5 (dd, $J_{C,F}$ = 3.1 Hz), 133.6 (dd, $J_{C,F}$ = 9.7 Hz), 143.8 (s), 161.2 (s), 162.7 (d, $J_{C,F}$ = 222.9 Hz), 172.2 (s) ppm. MS: *m/z* = 251 $[M]^+$. $C_{13}H_{14}FNO_3$ (251.25): calcd. C 62.14, H 5.62, N 5.57; found C 62.25, H 5.43, N 5.42.

2-Allyl-4-[(methoxycarbonyl)methyl]-5-methyl-3,4-dihydroisoquinolin-1-one (10ba): Yield 142 mg (52%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1669, 1723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 2.03 (dd, *J* = 16.3, 2.1 Hz, 1 H), 2.49 (dd, *J* = 16.3, 11.3 Hz, 1 H), 3.13 (dd, *J* = 13.2, 9.2 Hz, 1 H), 3.23–3.28 (m, 2 H), 3.36 (s, 3 H), 3.72 and 4.29 (AB part of ABX system, *J* = 14.7, 6.5 Hz, 2 H), 5.02 (d, *J* = 18.3 Hz, 1 H), 5.04 (d, *J* = 10.1 Hz, 1 H), 5.78 (ddt, *J* = 18.3, 10.1, 6.5 Hz, 1 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 7.08 (dd, *J* = 7.6, 7.7 Hz, 1 H), 8.32 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3 (q), 31.3 (d), 35.1 (t), 48.0 (t), 50.4 (t), 51.4 (q), 118.9 (t), 127.3 (d), 127.9 (d), 128.9 (s), 132.6 (d), 134.2 (s), 134.7 (d), 139.3 (s), 165.8 (s), 171.9 (s) ppm. MS: *m/z* = 273 $[M]^+$. $C_{16}H_{19}NO_3$ (273.33): calcd. C 70.31, H 7.01, N 5.12; found C 70.08, H 7.13, N 5.33.

2-Allyl-6-chloro-4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-one (10ca): Yield 256 mg (87%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1685, 1704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.52 (dd, *J* = 16.2, 5.5 Hz, 1 H), 2.63 (dd, *J* = 16.2, 8.5 Hz, 1 H), 3.34–3.38 (m, 2 H), 3.65 (s, 3 H), 3.69 (AB system, *J* = 5.1 Hz, 1 H), 3.95 and 4.28 (AB part of ABX system, *J* = 14.8, 5.9 Hz, 2 H), 5.19 (d, *J* = 9.1 Hz, 1 H), 5.21 (d, *J* = 12.0 Hz, 1 H), 5.77 (ddt, *J* = 12.0, 9.1, 5.9 Hz, 1 H), 7.19 (d, *J* = 2.0 Hz, 1 H), 7.29 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.98 (d, *J* = 8.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.4 (q), 37.9 (t), 49.1 (t), 50.0 (t), 52.2 (d), 119.1 (t), 126.9 (d), 127.6 (s), 128.3 (d), 130.7 (d), 132.9 (d), 138.4 (s), 142.6 (s), 163.3 (s), 172.0 (s) ppm. MS: *m/z* = 293 $[M]^+$. $C_{15}H_{16}ClNO_3$ (293.75): calcd. C 61.33, H 5.49, N 4.77; found C 61.54, H 5.23, N 4.89.

6-Chloro-2-cyclohexyl-4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-one (10cb): Yield 238 mg (71%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1672, 1721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91–1.83 (m, 10 H), 2.52 (dd, *J* = 16.5, 5.4 Hz, 1 H), 2.66 (dd, *J* = 16.5, 9.2 Hz, 1 H), 3.35–3.39 (m, 1 H), 3.53 (AB system, *J* = 13.0 Hz, 2 H), 3.71 (s, 3 H), 4.58–4.67 (m, 1 H), 7.21 (d, *J* = 2.0 Hz, 1 H), 7.32 (dd, *J* = 8.3, 2.0 Hz, 1 H), 8.02 (d, *J* = 8.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8 (t), 26.0 (t), 30.2 (q), 30.3 (t), 34.3 (d), 37.3 (t), 44.0 (t), 52.3 (d), 126.7 (d), 128.2 (s), 128.3 (d), 130.9 (d), 138.2 (s), 142.3 (s), 162.9 (s), 172.3 (s) ppm. MS: *m/z* = 335 $[M]^+$. $C_{18}H_{22}ClNO_3$ (335.83): calcd. C 64.38, H 6.60, N 4.17; found C 64.51, H 6.42, N 4.43.

6-Chloro-2-cyclopentyl-4-[(methoxycarbonyl)methyl]-3,4-dihydroisoquinolin-1-one (10cc): Yield 219 mg (68%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1659, 1718 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.95 (m, 8 H), 2.54 (dd, *J* = 16.6, 5.3 Hz, 1 H), 2.67 (dd, *J* = 16.6, 9.1 Hz, 1 H), 3.36–3.45 (m, 2 H), 3.60 (AB system, *J* = 9.0 Hz, 1 H), 3.72 (s, 3 H), 5.13–5.21 (m, 1 H), 7.22 (d, *J* = 2.1 Hz, 1 H),

7.34 (dd, J = 8.3, 2.1 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (t), 24.6 (t), 28.3 (t), 29.1 (t), 34.4 (q), 37.2 (t), 44.0 (t), 52.3 (d), 54.2 (d), 126.7 (d), 128.1 (s), 128.4 (d), 130.9 (d), 138.3 (s), 142.3 (s), 163.5 (s), 172.3 (s) ppm. MS: m/z = 321 $[M]^+$. $C_{17}H_{20}ClNO_3$ (321.80): calcd. C 63.45, H 6.26, N 4.35; found C 63.22, H 6.35, N 4.53.

6-Chloro-4-[(methoxycarbonyl)methyl]-2-phenyl-3,4-dihydroisoquinolin-1-one (10cd): Yield 274 mg (83%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1672, 1714 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74 (dd, J = 16.2, 5.8 Hz, 1 H), 2.88 (dd, J = 16.2, 8.7 Hz, 1 H), 3.50–3.58 (m, 1 H), 3.69 (s, 3 H), 3.82 (dd, J = 12.7, 3.2 Hz, 1 H), 4.26 (dd, J = 12.7, 3.9 Hz, 1 H), 7.06–7.46 (m, 7 H), 8.11 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.0 (q), 37.9 (t), 52.4 (d), 53.5 (t), 118.6 (s), 125.9 (d), 127.0 (d), 127.1 (d), 127.9 (s), 128.6 (d), 129.6 (d), 131.2 (d), 138.9 (s), 142.8 (s), 163.4 (s), 172.0 (s) ppm. MS: m/z = 329 $[M]^+$. $C_{18}H_{16}ClNO_3$ (329.78): calcd. C 65.56, H 4.89, N 4.25; found C 65.44, H 4.96, N 4.41.

6-Chloro-2-ethyl-4-[(methoxycarbonyl)methyl]-4-methyl-3,4-dihydroisoquinolin-1-one (10cf): Yield 163 mg (55%); colourless oil. IR (nujol): $\tilde{\nu}$ = 1649, 1723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 3 H), 1.47 (s, 2 H), 2.59 (AB system, J = 14.6 Hz, 2 H), 3.48 (d, J = 12.7 Hz, 1 H), 3.56–3.71 (m, 7 H), 7.27 (d, J = 1.9 Hz, 1 H), 7.34 (dd, J = 8.3, 1.9 Hz, 1 H), 8.07 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9 (q), 22.8 (q), 36.8 (s), 42.5 (t), 42.7 (t), 52.0 (q), 54.9 (t), 124.5 (d), 128.0 (s), 128.8 (d), 130.8 (d), 138.6 (s), 146.6 (s), 163.3 (s), 171.4 (s) ppm. MS: m/z = 295 $[M]^+$. $C_{15}H_{18}ClNO_3$ (295.76): calcd. C 60.91, H 6.13, N 4.74; found C 61.08, H 5.98, N 4.82.

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