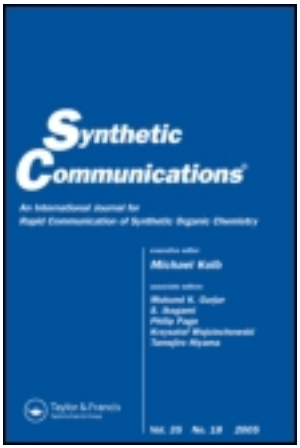

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Ortho-alkoxy-aryl Carboxamides via Palladium-Catalyzed Aminocarbonylation

Attila Takács [a], Artur R. Abreu [b], Andreia F. Peixoto [b], Mariette Pereira [b] & László Kollár [a]

[a] Department of Inorganic Chemistry, University of Pécs, Pécs, Hungary

[b] Departamento de Quimica, Universidade de Coimbra, Coimbra, Portugal

Published online: 02 Apr 2009.

To cite this article: Attila Takcs , Artur R. Abreu , Andreia F. Peixoto , Mariette Pereira & Lszl Kollr (2009) Synthesis of Ortho-alkoxy-aryl Carboxamides via Palladium-Catalyzed Aminocarbonylation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:9, 1534-1548, DOI: 10.1080/00397910802542028

To link to this article: http://dx.doi.org/10.1080/00397910802542028

Synthetic Communications®, 39: 1534–1548, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802542028

Taylor & Francis
Taylor & Francis Group

Synthesis of *Ortho*-alkoxy-aryl Carboxamides via Palladium-Catalyzed Aminocarbonylation

Attila Takács,[1] Artur R. Abreu,[2] Andreia F. Peixoto,[2] Mariette Pereira,[2] and László Kollár[1]
[1]Department of Inorganic Chemistry, University of Pécs, Pécs, Hungary
[2]Departamento de Quimica, Universidade de Coimbra, Coimbra, Portugal

Abstract: Various aryl carboxamides with alkoxy substituents at the *ortho*-position, applicable as direct intermediates toward novel ligands, were synthesised via aminocarbonylation of aryl-iodides (2-iodoanisole, 5-chloro-7-iodo-8-methoxy-quinoline, and 5-chloro-7-iodo-8-benzyloxy-quinoline) in the presence of in situ generated palladium(0) catalysts. Simple primary and secondary amines as well as aminoacid esters were used as *N*-nucleophiles. The optimization of the reaction conditions allowed the preferential formation of carboxamides or ketocarboxamides by simple or double carbon monoxide insertion, respectively. A strong dependence of the chemoselectivity on carbon monoxide pressure was observed.

Keywords: Aminocarbonylation, carbon monoxide, carbonylation, iodoaromatics, palladium, quinoline

INTRODUCTION

Palladium-catalyzed carbonylation reactions including aminocarbonylations are widely used in synthetic chemistry.[1] There are a number of applications concerning the synthesis of simple building blocks and the functionalization of biologically important skeletons.[2] Aminocarbonylation of iodoarenes and iodoalkenes (and that of the corresponding aryl- and enol-triflates) plays a special role among these reactions. Even

Received August 8, 2008.
Address correspondence to László Kollár, Department of Inorganic Chemistry, University of Pécs and MTA-PTE Research Group for Chemical Sensors, H-7624 Pécs, Ifjúság u. 6., Hungary. E-mail: kollar@ttk.pte.hu

carboxamides with bulky *N*-substituents are available via this methodology from easily available starting materials. The synthesis of aryl carboxamides and 2-oxo-carboxamides with various structures by using aryl triflates or aryl halides as model substrates was already published.[3] Many aspects of carbonylation reactions including aminocarbonylations have been published recently.[4] The potential of the aminocarbonylation of *ortho*-alkoxy-aryl-halides has been shown by several examples to result in compounds of biological importance. Various large-ring macrocycles[5] and O-, N-, or S-containing heterocycles[6] are available via intramolecular aminocarbonylations. The intermolecular version of this reaction allows the facile synthesis of tetracycline derivatives[7] C-11-labeled amides,[8] and Weinreb amides,[9] which are of high synthetic importance. Efforts were made to carbonylate amides on a polymer support.[10]

Although the *N*-acylation of amino acids is widely used in synthetic chemistry, there are just a few examples using homogeneous aminocarbonylation of aryl halides as a tool for the introduction of a carboxamide moiety.[11–13]

To the best of our knowledge, only sporadic results are available on catalytic coupling reactions using 2-iodoanisole or iodoquinolines. Palladium–Tol-BINAP systems were used in asymmetric amination of 2-iodoanisole with racemic amines.[14] Copper-catalyzed coupling of 2-iodoanisole with imidazole followed by methoxycarbonylation was carried out to synthesize an active site model compound of cytochrome-*c* oxidase.[15] However, the *para*-substituted analog, 4-iodoanisole, has been investigated in more detail. Its oxidative addition to palladium(0) species, formed via electroreduction, was found to be very efficient.[16] The Sonogashiracouplings of 4-iodoanisole with phenylacetylene[17] and with a diethynyl-benzothiadiazole derivative[18] were catalyzed by a catalyst formed from $PdCl_2(PPh_3)_2$, copper(I)-iodide, and aqueous ammonia and by a pincer-palladacycle catalyst, respectively. The kinetic investigation of the Heck reaction between 4-iodoanisole and styrene in the presence of a phosphorus-carbon-phosphorus (PCP)–pincer-palladium catalyst was carried out.[19] The double Suzuki reaction between pyridine-diboronic acid and 4-iodoanisole resulted in 2,6-bis(4-methoxyphenyl) pyridines, which can be used as synthetic building blocks.[20] Aminocarbonylation of 4-iodo-anisole[21] and, quite recently, its structural analog, 2,6-dimethoxy-iodobenzene,[8] was also carried out with in situ formed and "preformed" Pd(0) catalytic systems, respectively. Palladium-catalyzed cross-coupling reactions of iodoquinoline derivatives with alkynes were carried out to synthesise *tri*-substituted pyrroloquinolines[22] and 4-substituted quinolines.[23]

As a main goal of our present reseach, encouraged by the increasing importance of the systematic investigation of ligand synthesis, we decided to extend the scope of aminocarbonylation to *ortho*-substituted iodoaryl

substrates, 2-iodoanisole and 7-iodo-8-alkoxy-quinoline derivatives. After deprotection of the methoxy moiety, the carboxamides/ketocarboxamides, available via aminocarbonylation of these types of substituted iodoarenes, could serve as challenging ligands in coordination chemistry of aluminum,[24] titanium,[25] molybdenum complexes.[26] Furthermore, the improvement of alternative synthetic methods for alkoxy-quinoline derivatives is of great interest because of their potential biological activity as PDE4 inhibitors[27] as well as for the preparation of electroluminescent materials for organic LEDs.[24]

Accordingly, the facile, high-yielding, palladium-catalyzed aminocarbonylation of 2-iodoanisole, 5-chloro-7-iodo-8-methoxy-quinoline, and 5-chloro-7-iodo-8-benzyloxy-quinoline with various *N*-nucleophiles is published in the present article. The *ortho*-carboxamido- or ketocarboxamido phenols, available by the convential organic transformation of the ether functionality to the corresponding phenol, could serve as novel sterically and electronically tuned ligands both in main-group metal and transition-metal coordination chemistry.

RESULTS AND DISCUSSION

Aminocarbonylation of 2-Iodo-anisole (1)

2-Iodo-anisole (**1**) was reacted with carbon monoxide and various primary or secondary amines such as *N*-nucleophiles [*tert*-butylamine (**a**), piperidine (**b**), morpholine (**c**), methyl glycinate (**d**), or benzyl prolinate (**e**)] in dimethylformamide (DMF) in the presence of palladium–phosphine catalysts (Fig. 1). The in situ formation of highly reactive, coordinatively unsaturated palladium(0) species from palladium(II) acetate has been investigated in details.[28,29]

Depending on the carbon monoxide pressure, the prevailing formation of carboxamides (**2a**–**e**) or ketocarboxamides (**3a**–**e**) can be achieved. In general, the simple or double carbon monoxide insertion is favored (vide infra) under atmospheric pressure or 40 bar, respectively (e.g., entry 1 and 2, Table 1). Both the corresponding carboxamido derivatives (**2a–d**) and ketocarboxamides (**3a**–**d**) were synthesized in moderate to good isolated yields, depending on the structure of the amine, under appropriate reaction conditions (Table 1). However, by using proline benzyl ester, the dicarbonylated derivative **3e** was formed as prevailing product and could be isolated preferentially (entry 10).

The aminocarbonylation reaction can be carried out even under atmospheric carbon monoxide. High reactivities were observed in all cases, and conversions higher than 95% have been obtained. As for the

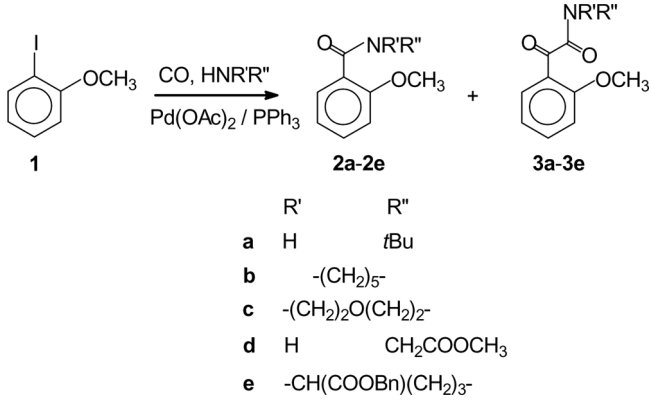

Figure 1. Aminocarbonylation of 2-iodoanisole.

chemoselectivity of aminocarbonylation, the carboxamides (**2**) formed via monocarbonylation prevail over ketocarboxamides (**3**), especially in case of methyl glycinate (**d**) where **2d** was exclusively formed.

Table 1. Aminocarbonylation of 2-iodo-anisole (**1**) with primary and secondary amines[a]

Entry	Amine	R time (h)	p(CO) (bar)	Conv. (%)	Ratio of the carbonylated products [b] to isolated yields [c] (%)	
					Carboxamide	Ketocarboxamide
1	*t*BuNH$_2$ (**a**)	91	1	>98	78 (**2a**): 60	22 (**3a**): n.d.
2	*t*BuNH$_2$ (**a**)	24	40	93	38 (**2a**): 57	62 (**3a**): 51
3	piperidine (**b**)	23	1	>98	92 (**2b**): 80	8 (**3b**): n.d.
4	piperidine (**b**)	23	40	>98	20 (**2b**): n.d.	80 (**3b**): 67
5	morpholine (**c**)	24	1	>98	83 (**2c**): 71	17 (**3c**): n.d.
6	morpholine (**c**)	24	40	>98	15 (**2c**): n.d.	85 (**3c**): 73
7	GlyOMe (**d**)	70	1	95	100 (**2d**): 80	0 (**3d**): 0
8	GlyOMe (**d**)	70	40	96	76 (**2d**): 60	24 (**3d**): 10
9	GlyOMe (**d**)	24	60	95	17 (**2d**): n.d.	83 (**3d**): 70
10	ProOBn (**e**)	24	40	95	5 (**2e**): n.d.[d]	95 (**3e**): 74[d]

[a]Reaction conditions: 0.025 mmol $Pd(OAc)_2$; 0.05 mmol PPh_3, 1 mmol **1**; 3 mmol unfunctionalized amine (or 1.1 mmol amino acid methylester hydrochloride), 0.5 ml triethylamine; 10 ml DMF, 50°C.

[b]Determined by GC-MS.

[c]Isolated yields are based on the amount of the starting material **1**.

[d]The ketocarboxamide derivative (**3e**) was isolated and characterized only.

The application of high carbon monoxide pressure (40 bar) resulted in the opposite chemoselectivity towards carboxamides except for **d**. In this specific case, the chemoselectivity toward double carbonylation could be shifted by using an increased carbon monoxide pressure (60 bar) (entry 9).

Aminocarbonylation of 7-Iodo-Quinoline Derivatives (4, 5, and 8)

5-Chloro-7-iodo-8-hydroxy-quinoline (**4**) was reacted with various amines and carbon monoxide in the presence of the palladium(0) catalysts described previously (Fig. 2, Table 2). The carbon monoxide pressure was varied from 1 to 60 bar. The expected amides (5-chloro-7-carboxamido-8-hydroxy-quinoline derivatives) could not be detected even in traces by gas chromatography–mass spectrometry (GC-MS). However, selective dehydroiodination of the 7-iodo-aryl moiety resulted in known compound 5-chloro-8-hydroxy-quinoline (**4′**)[30,31] with wide application. It was isolated in nearly quantitative yields both in the presence of *tert*-butylamine and piperidine (entries 1–4). It has to be added that an oxidative addition—reductive elimination reaction sequence, including the formation of a palladium-hydride intermediate, might be operative. The same dehydroiodination was observed when attempts to protect the 8-hydroxyl group with iodomethane in the presence of NaH were carried out.

5-Chloro-7-iodo-8-methoxy-quinoline (**5**), prepared from 5-chloro-7-iodo-8-hydroxy-quinoline (**4**) with methyl iodide and sodium methylate,[25] was reacted with primary and secondary amines [*tert*-butyl-amine (**a**) and piperidine (**b**)] and carbon monoxide in the presence of the catalyst described previously (Fig. 3, Table 2). Monocarbonylation was observed as the prevailing reaction, resulting in the corresponding carboxamides (**6a, 6b**) in all cases. Double carbonylation took place only to a small extent. Less than 15% yields of ketocarboxamides (**7a, 7b**) have

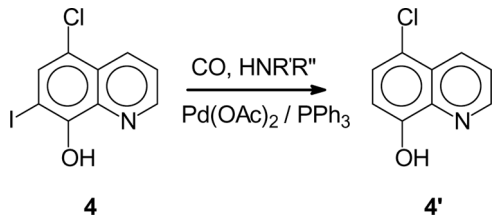

Figure 2. Dehydroiodination of 5-chloro-7-iodo-8-hydroxy-quinoline under carbonylation conditions.

Table 2. Aminocarbonylation of 5-chloro-7-iodo-8-hydroxyquinoline (**4**), 5-chloro-7-iodo-8-methoxyquinoline (**5**), and 5-chloro-7-iodo-8-benzyloxyquinoline (**8**) with *tert*-butylamine (**a**) and piperidine (**b**)[a]

Entry	Substrate	Amine	R time [h]	p(CO) (bar)	Conv. (%)	Ratio of carbonylated products[b] to isolated yields[c] (%) Carboxamide	Ketocarboxamide
1	**4**	**a**	24	1	>98[d]	0	0
2	**4**	**a**	24	60	>98[d]	0	0
3	**4**	**b**	24	1	>98[d]	0	0
4	**4**	**b**	24	60	>98[d]	0	0
5	**5**	**a**	24	1	0	0	0
6	**5**	**a**	24	20	5	>98 (**6a**): n.d	<2 (**7a**): n.d.
7	**5**	**a**	27	40	85	94 (**6a**): 67	6 (**7a**): n.d.
8	**5**	**a**	72	60	>98	92 (**6a**): 76	8 (**7a**): n.d.
9	**5**	**a**	24	60	97	85 (**6a**): 72	15 (**7a**): 9
10	**5**	**b**	24	60	50	>98 (**6b**): 41	<2 (**7b**): n.d.
11	**8**	**a**	24	60	70	>98 (**9a**): 62	<2 (**10a**): n.d.

[a]Reaction conditions: 0.025 mmol $Pd(OAc_2)$; 0.05 mmol PPh_3; 0.5 mmol substrate; 15 ml DMF; 0.5 ml Et_3N; and 1.5 mmol $tBuNH_2$ (or piperidine).

[b]Determined by GC-MS.

[c]Isolated yields (in brackets) are based on the amount of the starting material (**5** or **8**).

[d]The substrate (**4**) has been converted to 5-chloro-8-hydroxyquinoline (**4′**).

been obtained. Similarly, the *tert*-butylaminocarbonylation of 5-chloro-7-iodo-8-benzyloxy-quinoline (**8**) resulted mainly in the formation of the corresponding monocarboxamide, **9a** (Fig. 4, Table 2). It is worth noting that the reaction of simple iodoarenes such as iodobenzene and 2-iodo-naphthalene with carbon monoxide and amines provides

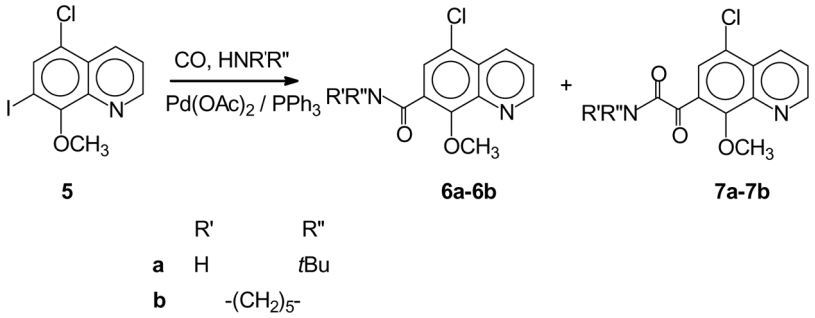

Figure 3. Aminocarbonylation of 5-chloro-7-iodo-8-methoxy-quinoline.

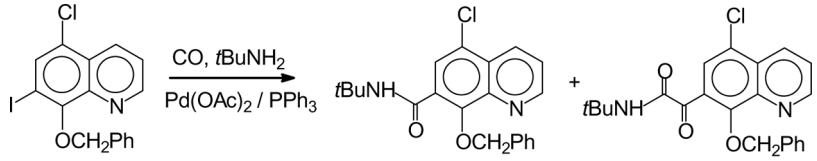

Figure 4. Aminocarbonylation of 5-chloro-7-iodo-8-benzyloxy-quinoline.

the mixture of the corresponding carboxamides and 2-ketocarboxamides with the prevailing formation of the latter product under similar reaction conditions.[11,12]

Furthermore, the reaction with **5** goes much more slowly than with simple monofunctionalized iodo-arenes. As a result of that, nearly complete conversion to carbonylated products has been observed only with *tert*-butylamine (entry 8 and 9). Using piperidine as nucleophile, we obtained 50% conversion of carboxamide **6b** (entry 10). The yield of the aminocarbonylation was influenced substantially by the carbon monoxide pressure. Nearly complete conversion to **6a** and **7a** could be obtained under more severe conditions [60 bar carbon monoxide pressure and elevated reaction time (entry 8 only)]. The low reactivity of this substrate can be also illustrated by the fact that no reaction occurs at atmospheric carbon monoxide pressure (entry 5). It has to be noted that the aminocarbonylation at high carbon monoxide pressure is accompanied by the formation of some 2-ketocarboxamides (up to 15% and 2% for *tert*-butyl-amine and piperidine, respectively) (entries 7–10).

CONCLUSION

The palladium-catalyzed aminocarbonylation of *ortho*-alkoxy-iodoarenes can be carried out, and the corresponding carboxamides and 2-ketocarboxamides were isolated in moderate to high isolated yields. The chemoselectivity is dependent on the carbon monoxide pressure; that is, at low pressure the formation of monocarboxamides is observed. However, at high pressure the formation of ketocarboxamides is favored. The products are potential intermediates of ligands (e.g., the quinoline derivatives may form oxine-type ligands after deprotection) or are of direct practical importance (e.g. the acylated amino acid derivatives).

The high yields related to those obtained with conventional procedures and the high functional group tolerance of homogeneous catalytic aminocarbonylation make these reactions of great synthetic relevance.

EXPERIMENTAL

General Procedures

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. Chemical shifts δ are reported in parts per million (ppm) relative to $CHCl_3$ (7.26 and 77.00 ppm for ^1H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. Samples of the catalytic reactions were analyzed with a Hewlett Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1.

5-Chloro-7-iodo-8-methoxy-quinoline and 5-chloro-7-iodo-8-benzyloxy-quinoline were synthesized as described previously.[32] 2-Iodo-anisole and 5-chloro-7-iodo-8-hydroxy-quinoline, as well as the amines, were purchased from Aldrich and were used without any further purification. Solvents were dried and purified by generally used procedures.

Aminocarbonylation Reaction at High Pressure

In a typical reaction, 5.6 mg (0.025 mmol) of $Pd(OAc)_2$ and 13.0 mg (0.05 mmol) of PPh_3 together with 1 mmol of substrate (**1**, **4**, **5**, or **6**) were placed into a 100-ml autoclave equipped with a magnetic stirring bar. The atmosphere was changed to argon, and all the solid substances were dissolved in 15 ml dimethylformamide (DMF), and then 0.5 ml triethylamine and 1.5 mmol of the appropriate amine were added. The atmosphere was changed to carbon monoxide, the autoclave was pressurized by carbon monoxide to the given pressure, and the reaction mixture was kept at 50°C for 24 h. After cooling and venting the autoclave, the reaction mixture was analyzed immediately by GC-MS.

The solvent was evaporated to dryness, and the residue was dissolved in chloroform. It was washed three times with water and brine. The organic phase was dried over Na_2SO_4 and evaporated. The carboxamides were isolated by column chromatography (silica gel, EtOAc/CH_2Cl_2, or EtOAc/$CHCl_3$ eluent mixtures; exact composition and physical state of compounds vide infra).

Analytical and Spectroscopic Data of Compounds

(2-Methoxyphenyl)-*tert*-butylamino-methanone (**2a**)

δ_H (400 MHz, $CDCl_3$) 8.06 (ddt, 7.7 Hz, 1.8 Hz, 0.7 Hz, 1H, Ar); 7.72 (br s, 1H, NH); 7.28 (dtt, 8.3 Hz, 1.9 Hz, 0.8 Hz, 1H, Ar); 6.95 (dt, 7.7 Hz,

0.7 Hz, 1H, Ar); 6.82 (d, 8.3 Hz, 1H, Ar); 3.80 (s, 3H, OCH_3); 1.35 (s, 9H, *t*Bu). δ_C (100.6 MHz, $CDCl_3$) 164.1, 157.2, 132.3, 131.7, 122.7, 121.1, 111.4, 55.8, 50.9, 28.9. IR (KBr, cm^{-1}): 3397 (NH); 1660 (CON). MS m/z (rel. int., %): 207 (11), 192 (12), 135 (100), 105 (8), 77 (15). Analysis calculated for $C_{12}H_{17}NO_2$ (207.27): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.45; H, 8.42; N, 6.60, R_f (5% EtOAc/CH_2Cl_2) 0.65; R_f (20% EtOAc/petroleum ether) 0.81; highly viscous material.

(2-Methoxyphenyl)-*tert*-butylamino-ethandione (**3a**)

δ_H (400 MHz, $CDCl_3$) 7.61 (d, 7.6 Hz, 1H, Ar); 7.47 (t, 8.5 Hz, 1H, Ar); 7.01 (t, 7.6 Hz, 1H, Ar); 6.96 (d, 8.5 Hz, 1H, Ar); 6.45 (br s, 1H, NH); 3.83 (s, 3H, OCH_3); 1.46 (s, 9H, *t*Bu). δ_C (100.6 MHz, $CDCl_3$) 192.4, 162.5, 159.5, 134.3, 131.0, 124.8, 120.7, 112.0, 56.0, 51.5, 28.4. IR (KBr, cm^{-1}): 3268 (NH); 1668 (CO); 1638 (CON). MS m/z (rel. int., %): 235 (5), 135 (100), 92 (8), 77 (15). Analysis calculated for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.17; H, 7.52; N, 5.69. R_f (3% EtOAc/CH_2Cl_2) 0.54; mp 87–90°C; white crystalline material.

(2-Methoxyphenyl)piperidin-1-yl-methanone (**2b**)

δ_H (400 MHz, $CDCl_3$) 7.28 (dt, 7.7 Hz, 1.6 Hz, 1H, Ar); 7.17 (d, 8.3 Hz, 1H, Ar); 6.92 (dt, 7.7 Hz, 1.6 Hz, 1H, Ar); 6.83 (d, 8.3 Hz, 1H, Ar); 3.76 (s, 3H, OCH_3); 3.60–3.80 (m, 2H, NCH_2); 3.12 (br s, 2H, NCH_2); 1.35–1.63 (m, 6H, $3 \times CH_2$). δ_C (100.6 MHz, $CDCl_3$) 167.6, 155.3, 130.0, 127.6, 126.5, 120.8, 110.9, 55.5, 47.9, 42.5, 26.3, 25.6, 24.6. IR (KBr, cm^{-1}): 1635 (CON). MS m/z (rel. int., %): 219 (23), 218 (84), 135 (100), 77 (22). Analysis calculated for $C_{13}H_{17}NO_2$ (219.28): C, 71.21; H, 7.81; N, 6.39. Found: C, 71.05; H, 8.02; N, 6.20; R_f (20% EtOAc/CH_2Cl_2) 0.51; highly viscous material.

(2-Methoxyphenyl)piperidin-1-yl-ethandione (**3b**)

δ_H (400 MHz, $CDCl_3$) 7.87 (dd, 7.6 Hz, 1.7 Hz, 1H, Ar); 7.49 (dt, 8.4 Hz, 1.7 Hz, 1H, Ar); 7.01 (t, 7.6 Hz, 1H, Ar); 6.93 (d, 8.4 Hz, 1H, Ar); 3.82 (s, 3H, OCH_3); 3.6 (m, 2H, NCH_2); 3.26 (m, 2H, NCH_2); 1.48–1.50 (m, 6H, $3 \times CH_2$). δ_C (100.6 MHz, $CDCl_3$) 190.7, 167.1, 160.2, 135.9, 131.0, 123.6, 121.2, 112.3, 56.1, 46.6, 41.9, 25.5, 25.3, 24.5. IR (KBr, cm^{-1}): 1668 (CO); 1647 (CON). MS m/z (rel. int., %): 247 (4), 135 (100), 77 (12). Analysis calculated for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 67.85, H, 7.12; N, 5.60. R_f (10% EtOAc/CH_2Cl_2) 0.54; highly viscous material.

(2-Methoxyphenyl)morpholin-4-yl-methanone (**2c**)

δ_H (400 MHz, $CDCl_3$) 7.33 (dt, 7.6 Hz, 1.7 Hz, 1H, Ar); 7.20 (d, 8.4 Hz, 1H, Ar); 6.95 (dt, 7.6 Hz, 1.7 Hz, 1H, Ar); 6.87 (d, 8.4 Hz, 1H, Ar); 3.80 (s, 3H, OCH_3); 3.70–3.80 (m, 4H, $2 \times CH_2$); 3.50–3.65 (m, 2H, CH_2); 3.15–3.30 (m, 2H, CH_2). δ_C (100.6 MHz, $CDCl_3$) 167.9, 155.3, 130.6, 128.1, 125.4, 121.0, 111.0, 67.0, 66.8, 55.5, 47.3, 42.1. IR (KBr, cm^{-1}): 1638 (CON). MS m/z (rel. int., %): 221 (7), 220 (18), 135 (100), 77 (15). Analysis calculated for $C_{12}H_{15}NO_3$ (221.26): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.01, H, 6.89; N, 6.10. R_f (35% EtOAc/CH_2Cl_2) 0.40; highly viscous material.

(2-Methoxyphenyl)morpholin-4-yndione (**3c**)

δ_H (400 MHz, $CDCl_3$) 7.87 (d, 7.8 Hz, 1H, Ar); 7.52 (dt, 8.2 Hz, 1.6 Hz, 1H, Ar); 7.04 (t, 7.8 Hz, 1H, Ar); 6.95 (d, 8.2 Hz, 1H, Ar); 3.86(s, 3H, OCH_3); 3.60–3.74 (m, 6H, $3 \times CH_2$); 3.35 (t, 5 Hz, 2H, CH_2). δ_C (100.6 MHz, $CDCl_3$) 190.2, 167.3, 160.2, 136.2, 131.0, 123.6, 121.4, 112.3, 66.5, 66.3, 56.2, 45.9, 41.4. IR (KBr, cm^{-1}): 1667 (CO); 1635 (CON). MS m/z (rel. int., %): 249 (3), 135 (100), 77 (15). Analysis calculated for $C_{13}H_{15}NO_4$ (249.27): C, 62.64; H, 6.07; N, 5.62. Found: C, 62.44; H, 6.26; N, 5.39. R_f (35% EtOAc/CH_2Cl_2) 0.54; mp 142–145°C, white crystalline material.

(2-Methoxyphenyl)(methoxycarbonyl-methylamino)-methanone (**2d**)

δ_H (400 MHz, $CDCl_3$) 8.42 (br s, 1H, NH); 8.16 (dt, 7.7 Hz, 1.6 Hz, 1H, Ar); 7.41 (dt, 8.2 Hz, 1.8 Hz, 1H, Ar); 7.02 (dt, 7.7 Hz, 1.8 Hz, 1H, Ar); 6.93 (d, 8.2 Hz, 1H, Ar); 4.23 (d, 6.8 Hz, 2H, CH_2); 3.94 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3). δ_C (100.6 MHz, $CDCl_3$) 170.7, 165.3, 157.8, 133.1, 132.3, 121.2, 120.8, 111.4, 56.0, 52.2, 41.8. IR (KBr, cm^{-1}): 3383 (NH); 1744 (COO); 1659 (CON). MS m/z (rel. int., %): 223 (3), 164 (5), 135 (100), 105 (4), 77 (20). Analysis calculated for $C_{11}H_{13}NO_4$ (223.23): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.03; H, 5.98; N, 6.01. R_f (20% EtOAc/CH_2Cl_2) 0.64; highly viscous material.

(2-Methoxyphenyl)(methoxycarbonyl-methylamino)-ethandione (**3d**)

δ_H (400 MHz, $CDCl_3$) 7.65 (dd, 7.6 Hz, 1.8 Hz, 1H, Ar); 7.48 (dt, 8.4 Hz, 1.8 Hz, 1H, Ar); 7.15 (br s, 1H, NH); 7.00 (t, 7.6 Hz, 1H, Ar); 6.88

(d, 8.4 Hz, 1H, Ar); 4.14 (d, 6.6 Hz, 2H, CH_2); 3.83 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3). δ_C (100.6 MHz, $CDCl_3$) 190.4, 169.5, 163.4, 159.7, 134.8, 131.1, 124.3, 120.7, 112.1, 56.1, 52.4, 41.0. IR (KBr, cm^{-1}): 3355 (NH); 1754 (COO); 1673 (vs, CO + CON). MS m/z (rel. int., %): 251 (6), 135 (100), 92 (10), 77 (24). Analysis calculated for $C_{12}H_{13}NO_5$ (251.24): C, 57.37; H, 5.22; N, 5.58. Found: C, 57.19, H, 5.03; N, 5.33. R_f (30% EtOAc/CH_2Cl_2) 0.70; highly viscous material.

(2-Methoxyphenyl)(2-benzyloxycarbonyl-pyrrolidin-1-yl)-ethandione (**3e**)

δ_H (400 MHz, $CDCl_3$) (two conformational isomers due to C(O)-N hindered rotation) 7.83/7.78 (dd, 7.5 Hz, 1.8 Hz, 1H, Ar); 7.50/7.46 (dt, 8.4 Hz, 1.8 Hz, 1H, Ar); 7.2–7.4 (m, 5H, Ph); 6.90–7.02 (m, 2H, Ar); 5.19/5.02 (AB-quartet/AB-quartet, 8.0 Hz, 11.0 Hz/8.0 Hz, 12.5 Hz, 2H, C*H*$_2$Ph); 4.58–4.63 (m, 1H, CHCOO); 3.82/3.78 (s, 3H, OCH_3); 3.50–3.80 (m, 2H, NCH_2); 1.90–2.30 (m, 4H, 2 × CH_2). δ_C (100.6 MHz, $CDCl_3$) (two conformational isomers due to C(O)-N hindered rotation) 190.6/190.5, 171.5/171.4, 166.4/165.9, 160.4/160.1, 135.9/135.7, 135.5/135.4, 128.6, 128.5, 128.2, 128.0, 124.0/123.5, 121.1/121.0, 112.2/112.1, 66.9/66.8, 59.3/58.3, 56.3/56.1, 46.9/46.1, 31.1/29.3, 24.7/22.4. IR (KBr, cm^{-1}): 1747 (COO); 1648 (vs, CO + CON). Analysis calculated for $C_{21}H_{21}NO_5$ (367.40): C, 68.65; H, 5.76; N, 3.81. Found: C, 68.49; H, 5.52; N, 3.63. R_f (10% EtOAc/CH_2Cl_2) 0.75; highly viscous material.

5-Chloro-7-(N-tert-butylcarboxamido)-8-methoxy-quinoline (**6a**)

^{1}H NMR($CDCl_3$) δ: 8.95 (d, 2.8 Hz, 1H, H-2); 8.55 (d, 7 Hz, 1H, H-4); 8.30 (s, 1H, H-6); 8.16 (brs, 1H, N-H); 7.58 (dd, 2.8 Hz, 7 Hz, 1H, H-3); 4.20 (s, 3H, OCH_3); 1.51 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR ($CDCl_3$) δ: 162.7, 153.4, 150.4, 143.2, 133.3, 129.0, 127.3, 126.7, 126.5, 123.1, 63.2, 51.3, 28.8. IR (KBr, cm^{-1}): 3375 (NH); 1665 (CON). MS m/z (rel. int., %): 292/294 (27/9) (M^+), 235/233 (41/14), 220/222 (100/34), 205/207 (40/13), 191/193 (26/9), 179/181 (31/10). Analysis calculated for $C_{15}H_{17}N_2O_2Cl$ (292.77): C, 61.54; H, 5.85; N, 9.57. Found: C, 61.41; H, 5.59; N, 9.44. R_f (10% EtOAc/CH_2Cl_2) 0.44; highly viscous yellow material.

5-Chloro-7-(N-tert-butylglyoxylamido)-8-methoxy-quinoline (**7a**)

^{1}H NMR($CDCl_3$) δ: 8.93 (d, 2.8 Hz, 1H, H-2); 8.55 (d, 7 Hz, 1H, H-4); 7.75 (s, 1H, H-6); 7.57 (dd, 2.8 Hz, 7 Hz, 1H, H-3); 6.40 (brs, 1H, NH);

4.36 (s, 3H, OCH_3); 1.53 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR ($CDCl_3$) δ: 191.8, 162.0, 156.6, 149.8, 143.1, 133.4, 130.1, 127.4, 126.8, 125.8, 123.4, 64.0, 51.7, 28.5. IR (KBr, cm^{-1}): 3378 (NH); 1653 (shoulder at *ca*. 1665) (CO + CON). MS m/z (rel. int., %): 320/322 (9/3) (M^+), 220/222 (100/33), 193 (18), 164 (17), 57 (20). Analysis calculated for $C_{16}H_{17}N_2O_3Cl$ (320.78): C, 59.91; H, 5.34; N, 8.73. Found: C, 59.80; H, 5.49; N, 8.66. R_f (10% EtOAc/CH_2Cl_2) 0.55; mp 127–130 °C, white crystalline material.

5-Chloro-7-(N,N-(1′,5′-pentadiyl)carboxamido)-8-methoxy-quinoline (**6b**)

^{1}HNMR($CDCl_3$) δ: 8.98 (d, 2.8 Hz, 1H, H-2); 8.56 (d, 7 Hz, 1H, H-4); 7.58 (dd, 2.8 Hz, 7 Hz, 1H, H-3); 7.50 (s, 1H, H-6); 4.18 (s, 3H, OCH_3); 3.7–3.9 (m, 2H, NCH_2); 3.1–3.3 (m, 2H, NCH_2); 1.58–1.75 [m, 6H, $(CH_2)_3$]. ^{13}C NMR ($CDCl_3$) (two conformational isomers due to C(O)-N hindered rotation) δ: 165.9, 150.6, 143.0, 133.3, 132.1, 132.0, 128.5, 128.4, 125.3, 122.5, 63.2, 48.3/47.1, 42.8/41.7, 26.4/25.6, 25.3/24.7, 24.4. IR (KBr, cm^{-1}): 1639 (CON). MS m/z (rel. int., %): 304/306 (40/14) (M^+), 220/222 (100/34), 191/193 (50/13), 128 (31). Analysis calculated for $C_{16}H_{17}N_2O_2Cl$ (304.78): C, 63.05; H, 5.62; N, 9.19. Found: C, 63.15; H, 5.50; N, 8.97. R_f (50% EtOAc/CH_2Cl_2) 0.39; highly viscous material.

5-Chloro-7-(N-tert-butylcarboxamido)-8-benzyloxy-quinoline (**9a**)

^{1}HNMR($CDCl_3$) δ: 9.03 (d, 2.6 Hz, 1H, H-2); 8.58 (d, 7.2 Hz, 1H, H-4); 8.33 (s, 1H, H-6); 8.08 (brs, 1H, N-H); 7.60 (dd, 2.6 Hz, 7.2 Hz, 1H, H-3); 7.30–7.42 (m, 5H, Ph); 5.55 (s, 2H, CH_2Ph); 1.22 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR ($CDCl_3$) δ: 162.8, 159.6, 152.6, 150.0, 143.3, 136.4, 133.3, 129.0, 128.9, 128.6, 128.5, 127.5, 126.5, 123.0, 78.8, 51.3, 28.5. IR (KBr, cm^{-1}): 3376 (NH), 1663 (CON). Analysis calculated for $C_{21}H_{21}N_2O_2Cl$ (368.86): C, 68.38; H, 5.74; N, 7.59. Found: C, 68.29; H, 5.56; N, 7.43. R_f (10% EtOAc/$CHCl_3$) 0.83; mp 165–168°C, yellow crystalline material.

ACKNOWLEDGMENT

The authors thank the Hungarian Research Fund (OTKA NI61591), the Portuguese FCT project (PTDC/QUI/66015/2006), and the Joint Project of the European Union–Hungarian National Development Program (GVOP-3.2.1-2004-04-0168/3) for the financial support and Johnson Matthey for the generous gift of palladium(II) acetate. A. F. Peixoto

(SFRH/BD/29681/2006) and A. R. Abreu (SFRH/BD/21314/2005) are thankful for their PhD grants.

REFERENCES

1. Skoda-Földes, R.; Kollár, L. Synthetic applications of palladium catalysed carbonylation of organic halides. *Curr. Org. Chem.* **2002**, *6*, 1097–1119.
2. Cornils, B.; Herrmann, W. A. (Eds.). *Applied Homogeneous Catalysis with Organometallic Compounds*; Wiley-VCH: Weinheim, 1996; Beller, M.; Bolm, C. (Eds.). *Transition Metals for Organic Synthesis*, vols. 1 and 2; Wiley-VCH: Weinheim, 1998.
3. Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991.
4. Kollár, L. (Ed). *Modern Carbonylation Methods*; Wiley-VCH: Weinheim, 2008.
5. Lu, S.-M.; Alper, H. Synthesis of large ring macrocycles (12–18) by recyclable palladium-complexed dendrimers on silica gel catalyzed intramolecular cyclocarbonylation reactions. *Chem. Eur. J.* **2007**, *13*, 5908–5916.
6. Lu, S.-M.; Alper, H. Intramolecular carbonylation reactions with recyclable palladium-complexed dendrimers on silica: Synthesis of oxygen, nitrogen, or sulfur-containing medium ring fused heterocycles. *J. Am. Chem. Soc.* **2005**, *127*, 14776–14784.
7. Nelson, M. L.; Ismail, M. Y.; McIntyre, L.; Bhatta, B.; Viski, P.; Hawkins, P.; Rennie, G.; Andorsky, D.; Messerschmith, D.; Stapleton, K.; Dumornay, J.; Sheahan, P.; Verma, A. K.; Warchol, T.; Levy, S. B. Versatile and facile synthesis of diverse semisynthetic tetracycline derivatives via Pd-catalyzed reactions. *J. Org. Chem.* **2003**, *68*, 5838–5851.
8. Karimi, F.; Langstrom, B. Synthesis of ^{11}C-labelled amides by palladium-mediated carboxamination using [^{11}C]carbon monoxide, in situ activated amines and 1,2,2,6,6-pentamethylpiperidine. *Eur. J. Org. Chem.* **2003**, 2132–2137.
9. Martinelli, J. R.; Freckmann, D. M. M.; Buchwald, S. L. Intramolecular formal *oxa*-[3 + 3] cycloaddition approach to the ABD system of phomactin. *Org. Lett.* **2006**, 4843–4846.
10. Yamazaki, K.; Kondo, Y. Carbonylation reaction of aryl halides on a polymer support using in situ–generated carbon monoxide without the assistance of microwaves. *J. Comb. Chem.* **2004**, *6*, 121–125.
11. Müller, E.; Péczely, G.; Skoda-Földes, R.; Takács, E.; Kokotos, G.; Bellis, E.; Kollár, L. Homogeneous catalytic aminocarbonylation of iodoalkenes and iodobenzene with amino acid esters under conventional conditions and in ionic liquids. *Tetrahedron* **2005**, *61*, 797–802.
12. Takács, E.; Skoda-Földes, R.; Ács, P.; Müller, E.; Kokotos, G.; Kollár, L. Prolinates as secondary amines in aminocarbonylation reactions: Synthesis of *N*-acylated prolinates via homogeneous catalysis in conventional solvents and in ionic liquid. *Lett. Org. Chem.* **2006**, *3*, 62–67.

13. Wannberg, J.; Larhed, M. Increasing rates and scope of reactions: Sluggish amines in microwave-heated aminocarbonylation reaction under air. *J. Org. Chem.* **2003**, *68*, 5750–5753.
14. Tagashira, J.; Imao, D.; Yamamoto, T.; Ohta, T.; Furukawa, I.; Ito, Y. Optically active palladium-catalyzed asymmetric amination of aryl halide. *Tetrahedron: Asymm etns* **2005**, *16*, 2307–2314.
15. Collman, J. P.; Wang, Z.; Zhong, M.; Zeng, I. Syntheses and pKa determination of 1-(o-hydroxyphenyl)imidazole carboxylic esters. *J. Chem. Soc., Perkin Trans. 1* **2000**, *8*, 1217–1221.
16. Chiarotto, I.; Carelli, I.; Carnicelli, V.; Marinelli, F.; Arcadi, A. Electrochemical behaviour of $PdII(PPh_3)_2Cl_2$ in the presence of carbon monoxide and its use in the palladium-catalyzed electrochemical formylation of iodoanisole. *Electrochim. Acta* **1996**, *41*, 2503–2509.
17. Mori, A.; Ahmed, M. S. M.; Sekiguchi, A.; Masui, K.; Kolke, T. Sonogashira coupling with aqueous ammonia. *Chem. Lett.* **2002**, 756–757.
18. Neto, B. A. D.; Lopes, A. S. A.; Ebeling, G.; Goncalves, R. S.; Costa, V. E. U.; Quina, F. H.; Dupont, J. Sonogashira coupling: Photophysical and electrochemical properties of π-extended molecular 2,1,3-benzothiadiazoles. *Tetrahedron* **2005**, *61*, 10975–10982.
19. Nilsson, P.; Wendt, O. F. Kinetic investigation of a $PC(sp^3)P$ pincer palladium (II) complex in the Heck reaction. *J. Organomet. Chem.* **2005**, *690*, 4197–4202.
20. Mandolesi, S. D.; Vaillard, S. E.; Podesta, J. C.; Rossi, R. A. Synthesis of benzene- and pyridinediboronic acids via organotin compounds. *Organometallics* **2002**, *21*, 4886–4888.
21. Takács, E.; Varga, C.; Skoda-Földes, R.; Kollár, L. Facile synthesis of primary amides and ketoamides via a palladium-catalysed carbonylation–deprotection reaction sequence. *Tetrahedron Lett.* **2007**, *48*, 2453–2456.
22. Kang, S. K.; Park, S. S.; Kim, S. S.; Choi, J.-K.; Yum, E. K. Synthesis of 1,2,3-trisubstituted pyrrolo[3,2-c]quinolines via palladium-catalyzed heteroannulation with internal alkynes. *Tetrahedron Lett.* **1999**, *40*, 4379–4382.
23. Comins, D. L.; Nolan, J. M.; Bori, I. D. Regioselective lithium–halogen exchange and palladium-catalyzed cross-coupling reactions of 2,4-dihaloquinolines. *Tetrahedron Lett.* **2005**, *46*, 6697–6699.
24. Hopkins, T. A.; Meerholz, K.; Shaheen, S.; Anderson, M. L.; Schmidt, A.; Kippelen, B.; Padias, A. B.; Hall, H. K. Jr.; Peyghambarian, N.; Armstrong, N. R. Substituted aluminum and zinc quinolates with blue-shifted absorbance/luminescence bands: synthesis and spectroscopic, photoluminescence, and electroluminescence characterization. *Chem Mater.* **1996**, *8*, 344–351.
25. Forrat, V. J.; Prieto, O.; Ramón, D. J.; Yus, M. *trans*-1-Sulfonylamino-2-isoborneolsulfonylaminocyclohexane derivatives: Excellent chiral ligands for the catalytic enantioselective addition of organozinc reagents to ketones. *Chem. Eur. J.* **2006**, *12*, 4431–4445.
26. Kühn, F. E.; Lopes, A. D.; Santos, A. M.; Herdtweck, E.; Haider, J. J.; Romão, C. C.; Santos, A. G. Lewis base adducts of bis-(halogeno)dioxomolybdenum(VI): Syntheses, structures, and catalytic applications. *J. Mol. Cat. A: Chem.* **2000**, *151*, 147–160.

27. Billah, M.; Buckley, G. M.; Cooper, N.; Dyke, H. J.; Egan, R.; Ganguly, A.; Gowers, L.; Haughan, A. F.; Kendall, H. J.; Lowe, C.; Minnicozzi, M.; Montana, J. G.; Oxford, J.; Peake, J. C.; Picken, C. L.; Piwinski, J. J.; Naylor, R.; Sabin, V.; Shih, N.-Y.; Warneck, J. B. H. 8-Methoxyquinolines as PDE4 inhibitors. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1617–1619.
28. Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. Evidence for the ligation of palladium(0) complexes by acetate ions: Consequences on the mechanism of their oxidative addition with phenyl Iodide and PhPd(OAc)$(PPh_3)_2$ as intermediate in the Heck reaction. *Organometallics* **1995**, *14*, 5605–5614.
29. Csákai, Z.; Skoda-Földes, R.; Kollár, L. NMR investigation of Pd(II)—Pd(0) reduction in the presence of mono- and ditertiary phosphines. *Inorg. Chim. Acta* **1999**, *286*, 93–97, and references cited therein.
30. Ruehl, K.; Rappen, L. 5-Chloro-8-hydroxy-quinoline or -quinaldine preparation by chlorinating 8-hydroxy-quinoline or -quinaldine in hydrochloric acid. Ruetgerswerke AG, DE1770018-B.1972.
31. Kuroda, Y.; Ohguchi, Y.; Kobayashi, K. Detection of neuro toxicities of clioquinol by in vitro brain slices and cultured nerve cells. *Jap. J. Pharm.* **1983**, *33*, 89.
32. Gershon, H.; McNeil, M. W. Electrophilic halogenation of 8-methoxyquinoline. *J. Org. Chem.* **1972**, *37*, 4078–4082.