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Highly Chemoselective One-Step Synthesis of Novel *N*-Substituted-Pyrrolo[3,4-b]quinoline-1,3-diones via Palladium-Catalyzed Aminocarbonylation/Carbonylative Cyclisation Sequence

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Novel *N*-substituted pyrrolo[3,4-b]quinoline-1,3-diones have been prepared via a highly chemoselective palladium-catalyzed carbonylative imidazation-cyclization reaction in a one-pot synthetic approach. This methodology, which has been applied for the first time to access such original scaffolds through two different protocols involving 3-bromo-2-iodoquinoline, as a typical partner, primary amines, and atmospheric or high carbon monoxide pressure (20 bar), has shown an excellent tolerance for many functional groups. The use of bidentate ligands such as XantPhos and dppp, either under atmospheric or high-pressure conditions, provides a wide range of carbonylated compounds in good to excellent yields (up to 82%). Furthermore, some new quinoline-2,3-dicarboxamides have been isolated as side products in very low yields and have been fully characterized. The solid state structures of three of the synthesized acridinimides have been unequivocally established by single-crystal XRD analysis.

Introduction

The broad spectrum of pharmacological as well as biological activities associated with quinoline ring provided an impetus to attach diverse pharmacophore units to this privileged scaffold.[1] Among various pioneering strategies that have been used to design innovative complex heterocyclic scaffolds, formal cycloadditions,[2] rearrangements,[3] epoxidation,[4] cascade reactions,[5] cross-couplings,[6] condensation reactions and annulations[7] have gained considerable attention as valuable building tools offering highly efficient and selective protocols to access multi-functionalized rings of biological relevance. Such alternative routes remain the most highly recommended synthetic pathways to furnish target fused-rings molecules bearing more than one pharmacophore.

Pyrroloquinolinediones and their related cyclic imide isomers are a very large class of original and exciting molecular architectures since they exhibit a wide range of bioactivities when well-decorated. Interestingly, a panoply of pyrrolodione-annulated quinolines have been described as effective antibacterial agents **I**,[8] and phosphodiesterase-4 inhibitors **II** that plays a crucial role in angiogenesis event in case of metastatic and solid tumor growth (Figure 1).[9] Moreover, an HIV-integrase inhibitor **III**[10] and an anti-HCV **IV**,[11] have been patented to treat and prevent human immunodeficiency virus and hepatitis C infection. Analogously, a survey of the literature revealed a myriad of pyrrolo[3,4-b]quinoline-1,3-diones that have previously served as antibacterial **V**,[12] matrix metalloproteinases (MMPs) inhibitors **VI**,[13] and antimicrobial **VII**[14] promising candidates.

On the other hand, cyclic imides such as succinimides, maleimides, phthalimides, naphthalimides, and pyrroloquinolinediones are, generally, accessible via conventional protocols involving the condensation of the corresponding cyclic anhydrides with primary amines under harsh conditions, mainly when sterically hindered amines are used.[15]

As befits their importance, many efforts have been made to develop new synthetic approaches for imidization reactions with the use of improved experimental conditions and efficient catalysts. For example, the Heck-style palladium-catalyzed amidation[16] has been applied to achieve *N*-substituted phthalimides, heteroarenedicarboximides, and 1,8- naphthalimides using different palladium catalysts, diverse reaction media, and a variety of carbon monoxide surrogates.[17] Howbeit, tremendous synthetic procedures have been reported for *N*-substi-

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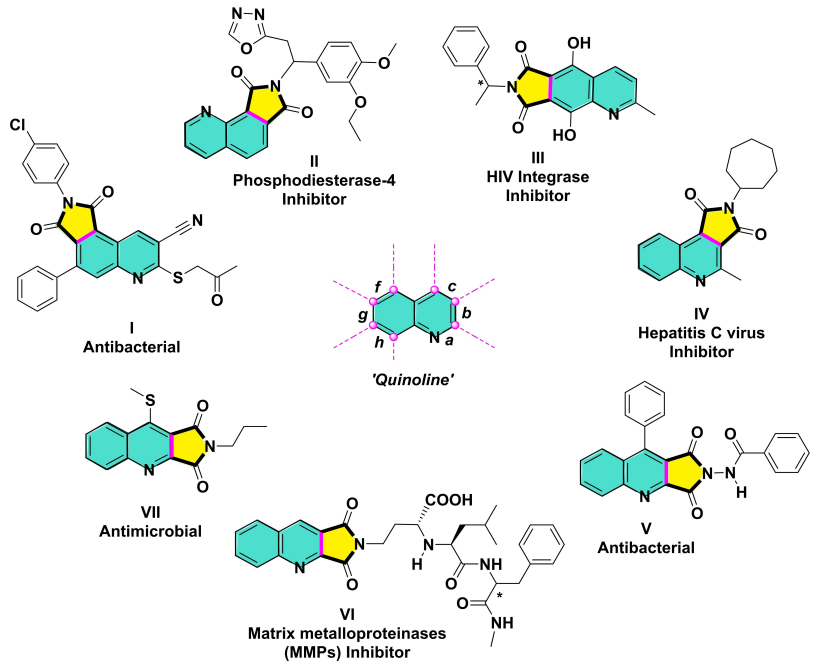


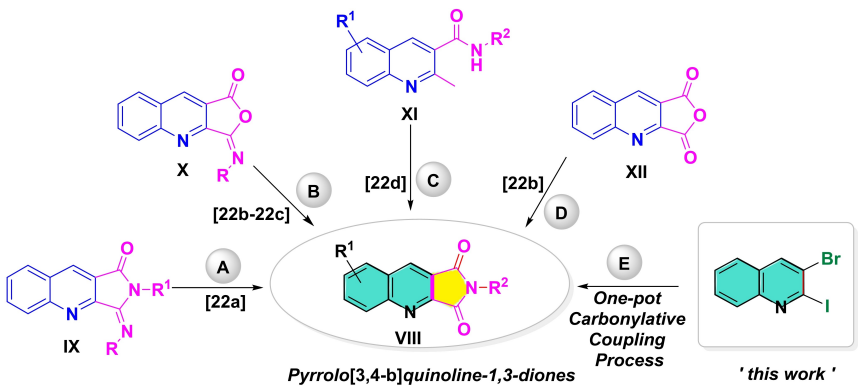
Figure 1. Selected biologically active isomers of pyrrolodione-annulated quinolines.

tuted-pyrroloquinolinediones. In this regard, sequential reactions based on Dieckman condensation,[18] oxidative annulation followed by dehydrogenation and *N*-demethylation,[19] oxidation in pyrroloacridone series,[20] and multicomponent aza-photocyclization reaction[21] are the notable examples. Peculiarly, pyrrolo[3,4-b]quinoline-1,3-diones (**VIII**), a very relevant subfamily of pyrrolodione-annulated quinolines, are prepared through common methods reported as multistep synthesis, and usually involving quinoline-based substrates (**IX–XII**) (Scheme 1).[22]

3-Bromo-2-iodoquinoline is a typical *ortho*-dihalosubstituted heteroarene synthon, which is a very useful coupling partner, tolerated in many palladium-catalyzed cross-couplings-type reactions for accessing benzoacridines (**XIII**) and benzophenanthridines (**XIV**),[23] triazapentacenes (**XV**),[24] indoloquinolines (**XVI**)[25] and related hybrid-quinoline skeletons (**XVII**) (Scheme 2).[26]

Surprisingly, as far as we could ascertain, no palladium-catalyzed aminocarbonylation reaction of quinoline-2,3-dihalide has been previously documented. Therefore, following our interest in such effective homogenous catalytic transformations during the last decades,[27] it seemed to be conceivable to provide novel *N*-substituted-pyrrolo[3,4-b]quinoline-1,3-diones, via palladium-catalyzed carbonylative coupling process of 3-bromo-2-iodoquinoline in the presence of various primary amines as *N*-nucleophiles. Furthermore, we presume that a subsequent intramolecular amidocarbonylation could occur in situ as a last stage of incorporation of the second CO leading to various pyrroloquinolinedione derivatives.

In this report, we gauge the viability of such an approach to a facile one-pot palladium-catalyzed double aminocarbonyla-



Scheme 1. Different synthetic pathways of pyrrolo[3,4-b]quinoline-1,3-diones starting from substituted quinoline derivatives.

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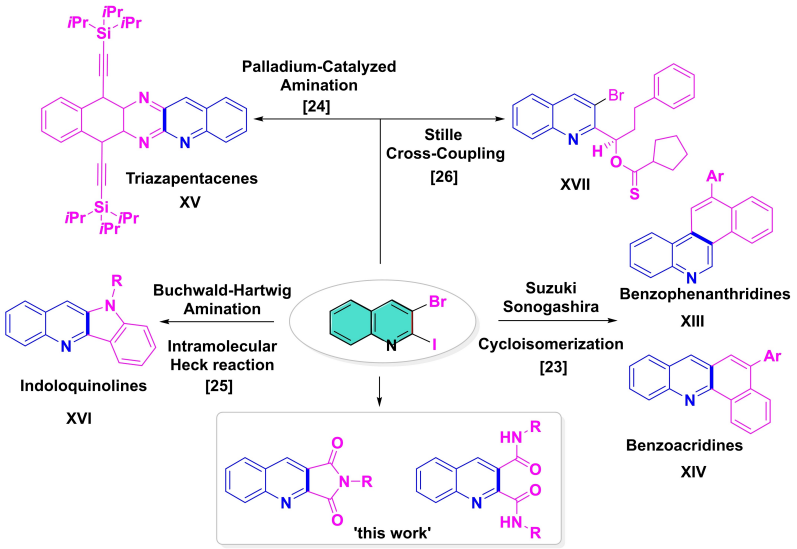


Scheme 2. Metal-catalyzed cross-couplings involving 3-bromo-2-iodoquinoline.

tion of 3-bromo-2-iodoquinoline resulting in various *N*-substituted tricyclic imides of auspicious biological relevance and with many potential applications in optical materials.[19,28]

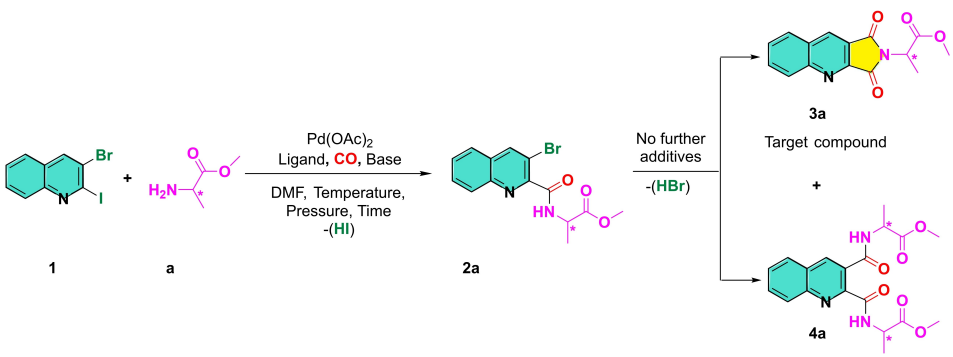
Results and Discussion

At the onset of our investigations, a set of experiments were carried out in order to establish the reaction conditions for the palladium-catalyzed ring-closing process of 3-bromo-2-iodo-quinoline (**1**) with L-alanine methyl ester (**a**), selected as model *N*-nucleophile, under a CO atmosphere leading to the target *N*-substituted pyrroloquinolinedione (**3a**) in good yields (Scheme 3). The effects of the ligand, the base, the temperature, the pressure, and the catalyst have been explored. The obtained results are summarized in Table 1.

Initially, the first reaction (Scheme 3) was carried out with 0.5 mmol of substrate (**1**), 0.55 mmol of L-alanine methyl ester hydrochloride, using 2.5 mol% of $Pd(OAc)_2$, 2.5 mol% of Xantphos, 0.25 mL of Et_3N in 5 mL of dry dimethylformamide, under 1 atm of carbon monoxide pressure at 50 °C (Table 1, Entry 1). Monitoring the reaction mixture by GC, it has been shown that only 5% of starting material has been converted into 3-bromo-quinoline-2-carboxamide product (**2a**) after 24 h.

To achieve higher conversion the reaction was performed at 80 °C under the same conditions. Our experience in similar systems suggests that the temperature (50 °C) was, probably, less than that required to reach the energetic barrier enabling aminocarbonylated product formation. The result was promising, 70% and total conversions were observed in 24 h and 48 h, respectively. The reaction gave carboxamide (**2a**) in 76% isolated yield (Table 1, entry 2).

Keeping in mind our main goal to establish the suitable experimental conditions for a one-pot carbonylative imidization-cyclisation reaction, we decided to examine the aminocarbonylation of **1** in the presence of carefully chosen phosphine-based ligands, introduced with $Pd(OAc)_2$, which are described as efficient catalysts for similar carbonylative cyclizations.[28] Unfortunately, no desired imide was obtained when the reaction was carried out in the presence of



Scheme 3. One-pot aminocarbonylation process of 3-bromo-2-iodo-quinoline (**1**) with L-alanine methyl ester (**a**).

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Table 1. Optimization study of the aminocarbonylation of 3-bromo-2-iodoquinoline (**1**) with L-alanine methyl ester (**a**) as nucleophile.[a]

Entry	Base	Ligand	Temp. [C°]	P_{CO} [bar]	Time [h]	Conv.[b]	Ratio of Products[b]		
							Amide (2a)	Imide (3a)	Diamide (4a)
1	Et_3N	XantPhos	50	1	24	6	100	0	0
2		XantPhos	80	1	48	100	100(76 %)[c]	0	0
3		PPh_3	80	1	72	92	100	0	0
4		PCy_3	80	1	72	5	100	0	0
5		dppp	80	1	48	92	100	0	0
6	K_2CO_3	**XantPhos**	**50**	**1**	**24**	**100**	**100**	**0**	**0**
7		XantPhos	80	1	24	100	85	15	0
8		**XantPhos**	**110**	**1**	**24**	**100**	**2**	**94**(40 %)[c]	**4**
9		dppp	110	1	24	100	49	51	0
10	Et_3N	PPh_3	80	20	72	100	33	67	0
11		PPh_3	80	40	72	100	64	36	0
12		PPh_3	100	20	24	100	25	75	0
13		PPh_3	120	20	24	100	14	78	8
14		XantPhos	120	20	24	100	7	71	22
15		**dppp**	**120**	**20**	**24**	**100**	**6**	**94**(53 %)[c]	**0**

[a] Reaction conditions: 0.5 mmol of 3-bromo-2-iodoquinoline (**1**), 0.55 mmol of L-alanine methyl ester hydrochloride (**a**), 0.0125 mmol of $Pd(OAc)_2$, 0.025 mmol of monodentate (PPh_3), (PCy_3) or 0.0125 mmol of bidentate (XantPhos, dppp) ligands, 0.25 mL of Et_3N or 1.5 mmol of K_2CO_3, 5 mL of DMF, at the mentioned temperature. The reactions were carried out under different carbon monoxide pressures. The complete conversion was detected in all cases after the given reaction time. [b] Determined by GC and GC-MS of the reaction mixture. [c] Isolated yield.

monodentate triphenylphosphine (PPh_3) or with more basic tricyclohexylphosphine (PCy_3), respecting the recommended ratio 1:2 of palladium catalyst to monophosphine ligand.[29]

Instead, the reactions performed with PPh_3 and PCy_3 led only to the corresponding monocarbonylated derivative **(2 a)** in 72 h with a maximum conversion of 92 % and 5 %, respectively (Table 1, entries 3 and 4). Similarly, the use of 1,3-bis(diphenylphosphino)propane (dppp) led to 92 % of conversion in reduced reaction time (48 h) (Table 1, entry 5).

Because the synthesis of the target pyrroloquinolinedione has not been accomplished under the above-mentioned conditions, we tried to change another parameter to produce the desired compound. As regards the effect of the base, the application of inorganic form such as potassium carbonate (K_2CO_3) instead of organic triethylamine (Et_3N), when the reaction is performed at 50 °C in the presence of XantPhos, selectively, provided amide **(2 a)** within 24 h, keeping the 1.5 excess of base (compare entries 1 and 6, Table 1). The use of K_2CO_3 proved to be very important for the aminocarbonylation reaction, as the introduced amount of starting material was totally converted to the corresponding carboxamide (**2 a**). Nevertheless, it can be seen that the 3-bromoarene functionality remained untouched under the circumstances given in entry 6.

With this result in our hand, the temperature was raised to activate the bromoarene functionality resulting in the target imide (**3 a**). The best amide/imide ratio was obtained when the reaction was carried out at 110 °C with a 1.5 excess of K_2CO_3 within 24 h (Table 1, entry 8). The aminocarbonylation-cyclization reaction showed high selectivity (94 %) toward the desired *N*-substituted pyrroloquinolinedione derivative (**3 a**), arising from two successive CO insertions, under the above-mentioned experimental conditions (compare entries 6, 7, and 8). The structure of (**3 a**), isolated in 40 % yield, was fully characterized by ^1H and ^{13}C NMR, and GC-MS.

We could also grow a crystal of compound **3 a** suitable for X-ray analysis which allowed us to establish unequivocally the structure elucidated using the above-mentioned characterization methods. The **3 a** crystallized in orthorhombic space group $P2_12_12_1$ with two rotamers found in the asymmetric unit. The absolute configuration of the asymmetric carbon could not be assigned as Mo radiation was applied for light atom structure. However, based on the specific rotation ($[\alpha]_D^{20} = 0°$ (c 1.2, $CHCl_3$)) measured for **3 a**, we could assume that a possible racemization could occur during the carbonylative cross-coupling process, even though, only the crystal corresponding to the (**R**)-enantiomer (for each rotamer), which could be shown in the ORTEP plot (Figure 2), has been analyzed from a racemic conglomerate presumably formed during the crystallization process. A similar racemization has been observed in case of **3 d**, starting from enantiopure L-phenylglycine methyl ester, as the optical rotation was canceled out ($[\alpha]_D^{20} = 0°$ (c 1, $CHCl_3$)),

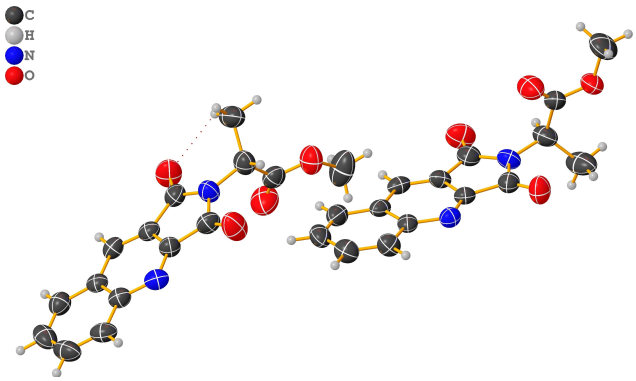

Figure 2. ORTEP style view of methyl (**R**)-2-(1,3-dioxo-1,3-dihydro-2H-pyrrolo[3,4-b]quinolin-2-yl)propanoate (**3 a**); showing thermal displacement ellipsoids, drawn at the 50 % probability level (Graphics were designed using **Olex2** program).

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and as both crystals (**R**)-**3 d** and (**S**)-**3 d** have been perceived in solid state (See Supporting Information data).

Based on our former results, in which several *N*-substituted imides have been synthesized at high carbon monoxide pressure using $Pd(OAc)_2/PPh_3$ catalyst,[17a,h] the aminocarbonylation of 3-bromo-2-iodoquinoline (**1**) with L-alanine methyl ester (**a**) under elevated CO atmosphere was further studied. A detailed examination of the effect of pressure on the reaction course was carried out, aiming to find suitable conditions that could be applicable to a wide range of *N*-nucleophiles, particularly, amines with lower boiling points.

For this, we opted for the use of the organic base Et_3N and different ligands, trying to find the best conditions, selectively, enabling the imidization reaction.

As reported in Table 1, firstly, $Pd(OAc)_2/PPh_3$ catalyst has been used at 20 and 40 bar of carbon monoxide pressure at 80 °C to activate the bromoarene moiety providing the pyrroloquinolinedione derivative (**3 a**) (Table 1, entries 10–11). While the target **3 a** product had been formed in 67% at 20 bar of CO, under higher carbon monoxide pressure (40 bar) the chemoselectivity has been shifted (64%) toward the monoamide (**2 a**). Performing the reaction at 100 °C and 20 bar of CO, the monodentate triphenylphosphine (PPh_3) gave a mixture of amide (**2 a**)/imide (**3 a**) type products in a ratio of 25:75 in 24 h (Table 1, entry 12). Furthermore, when PPh_3 or XantPhos were introduced at 120 °C, under 20 bar of CO, our results showed that a double-insertion of carbon monoxide both in position-2 and position-3, of quinolinedihalide (**1**) could, notably, occur leading to diamide (**4 a**) in 8% and 22% (Table 1, entries 13 and 14), respectively. The selectivity for the *N*-substituted pyrroloquinolinedione (**3 a**) was excellent (96% of imide) when the reaction was carried out in the presence of $Pd(OAc)_2$/dppp catalyst and Et_3N as a base under 20 bar of carbon monoxide at 120 °C yielding (**3 a**) in 53% (Table 1, entry 15).

In conclusion, the analysis of the results from Table 1 reveals that the synthesis of the *N*-substituted pyrroloquinolinedione (**3 a**), starting from 3-bromo-2-iodoquinoline (**1**), could proceed via a one-pot carbonylation process. This synthetic route may involve a palladium-catalyzed aminocarbonylation/intramolecular amidocarbonylation-cyclization cascade, employing two different experimental protocols that offer, selectively, the target acridine derivatives (**3 a**–**3 u**) in moderate to good yields under both atmospheric and high pressure carbon monoxide (Table 1, entries 8 and 15, and Table 2).

The screening of the α-amino acid esters (**a**-**f**) selected as *N*-nucleophiles in their enantiopure form, under the above-mentioned conditions, led selectively to the desired cyclic carbonylated products in moderate to good yields varying from 40% to 55% (Table 2, entries 1–6). Exceptionally, the use of a relatively hindered valine methyl ester bearing an isopropyl group gave a mixture of imide (**3 b**)/diamide (**4 b**) in a 3:1 ratio (Table 2, entry 2).

Interestingly, similar behavior has been noticed in the case of cyclohexylamine (**g**) which afforded both expected aminocarbonylated compounds in almost the same ratio (**3 g**/**4 g** = 65/35) as in the case of the L–ValOMe (**b**) (Table 2, entries 2 and 7). To our surprise, the chemoselectivity drastically shifted toward the dicarboxamide form when cyclopentylamine (**h**) was used giving 15% and 43% yields of imide (**3 h**) and diamide (**4 h**), respectively (Table 2, entry 8). The lower isolated yields of **3 i-j**

Table 2. One-pot synthesis of pyrroloquinolinediones **3** and quinoline-2,3-dicarboxamides **4**.

Entry	Amine	Time [h]	Imide(3a-u)/Dicarboxamide(4a-u) Ratio.[a] (3/4)	Yield[b] (3/4)	Experimental Method
1	L-Alanine methyl ester (**a**)	6	(94/6)	(40/–)	Atmospheric Pressure Protocol[c]
2	L–Valine methyl ester (**b**)	6	(77/23)	(52/–)	
3	L-Phenylalanine methyl ester (**c**)	6	(97/03)	(47/–)	
4	L-Phenylglycine methyl ester (**d**)	6	(100/00)	(40/–)	
5	L-Serine methyl ester (**e**)	6	(92/08)	(50/–)	
6	Glycine methyl ester (**f**)	6	(98/02)	(55/–)	
7	Cyclohexylamine (**g**)	8	(65/35)	(39/8)	
8	Cyclopentylamine (**h**)	6	(24/76)	(15/43)	
9	Decylamine (**i**)	6	(90/10)	(30/10)	
10	Furfurylamine (**j**)	6	(91/09)	(25/–)	
11	Butylamine (**k**)	11	(80/20)	(73/16)	High Pressure Protocol[d]
12	Benzylamine (**l**)	6	(90/10)	(43/10)	
13	α-Methylbenzylamine (**m**)	24	(85/15)	(64/–)	
14	(4-aminomethyl)pyridine (**n**)	6	(97/03)	(82/03)	
15	(3-aminomethyl)pyridine (**o**)	6	(94/06)	(82/–)	
16	Thiophenemethylamine (**p**)	24	(97/03)	(57/03)	
17	4-(2-Aminoethyl)morpholine (**q**)	9	(100/00)	(54/–)	
18	Piperonylamine (**r**)	9	(100/00)	(63/–)	
19	Tryptamine (**s**)	9	(100/00)	(73/–)	
20	Vanillylamine (**t**)	9	(100/00)	(65/–)	
21	2-Phenylethylamine (**u**)	9	(100/00)	(59/–)	

[a] Determined by GC and GC-MS of the reaction mixture. [b] Isolated yield based on the amount of starting material; (–) : not isolated. [c] Atmospheric pressure protocol: 0.5 mmol of 3-bromo-2-iodoquinoline (1), primary amine nucleophile: 0.55 mmol of solid amines (or 0.6 mmol of liquid amines), 0.0125 mmol of $Pd(OAc)_2$, 0.0125 mmol of XantPhos, 0.75 mmol of K_2CO_3, 5 mL of dry DMF, at 110 °C, under 1 bar of CO. The reaction was purged with argon and then replaced by carbon monoxide. The complete conversion was detected after the appropriate reaction time. [d] High pressure protocol: 0.5 mmol of 3-bromo-2-iodoquinoline (1), primary amine nucleophile: 0.55 mmol of solid amines (or 0.6 mmol of liquid amines), 0.0125 mmol of $Pd(OAc)_2$, 0.0125 mmol of dppp, 0.25 mL of Et_3N, 5 mL of dry DMF, at 120 °C, under 40 bar of carbon monoxide. The complete conversion was detected after the appropriate reaction time.

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in the case of a long-chain aliphatic decylamine (**i**) and furfurylamine (**j**) (Table 2, entries 9 and 10) could be explained by the solubility problems during the work-up procedure.

Next, we decided to check the one-step approach to *N*-substituted pyrroloquinolinediones using the high-pressure protocol method to produce such carbonylated cyclic compounds. With the aim to expand the acridinimide series, we subjected 3-bromo-2-iodo-quinoline (**1**) to the carbonylative cyclization with dppp as the ligand of choice and new different primary amines (**k**-**u**). The reactions were carried out under the optimized conditions using $Pd(OAc)_2$/dppp catalyst, in the presence of Et_3N, under 20 bar of carbon monoxide pressure at 120 °C.

The expected acridines were obtained in high chemoselectivity in the case of most used amines following this second alternative experimental procedure. As can be seen from Table 2, no dicarboxamide form has been detected in the case of 2-morpholino-1-amine (**q**), piperonylamine (**r**), tryptamine (**s**), vanillylamine (**t**), and 2-phenylethylamine (**u**) (Table 2, entries 17–21). The corresponding cyclized products **3 q**–**u** were formed exclusively and isolated in moderate to good yields (54 % to 73 %).

As a first assumption, the use of flexible primary amines leads to the target pyrroloquinolinediones with excellent selectivity. The imidazation-cyclization process is favored when *N*-nucleophiles provide a spacer with one and two methylene groups. This could be crucial during the carbonylative cyclization step.

The pyrroloquinolinedione derivatives prepared in different yields are summarized in Table 3. The molecular structures of acridinimides **3 a**, **3 d**, and **3 g** have unambiguously been elucidated by single-crystal X-ray diffraction analysis.

Because the selectivity is shifted toward the imide form when butylamine (**k**), benzylamine (**l**), 4-picolylamine (**n**), and thiophenemethylamine (**p**) were used, very low yields of the corresponding dicarboxamides were obtained (Table 2, entries 11–12, 14, and 16). The use of picolylamine derivatives afforded imides **3 m** and **3 n** in excellent isolated yields of 82 %. The structures of different isolated quinoline-2,3-dicarboxamides are depicted in Table 4.

The proposed mechanism can be described in three concomitant catalytic cycles leading to the three types of aminocarbonylated products (Scheme 4). During the first catalytic cycle (cycle-1), after the regioselective oxidative addition of the carbon-iodine bond into low ligated palladium(0) complex (**A**), the coordination of carbon monoxide takes place giving a terminal carbonyl species (**B**). It is followed by the insertion of CO into the palladium-carbon bond at the C-2 position forming the acylpalladium(II) intermediate (**C**). This could be explained by the better leaving group ability of iodide as compared to bromine found in the C-3 position. Then, the coordination of the amine nucleophile to the newly formed acylpalladium(II) complex takes place, which is followed by the subsequent loss of hydrogen iodide giving the palladium(II)-acyl-amido intermediate (**E**). The 3-bromoquinoline-2-carboxamide (**F**), as a crucial reactive intermediate is formed in the reductive elimination step in cycle-1, which could be isolated in small traces at the end of the imidization reaction. This assumption has also been confirmed by monitoring the reaction by GC-MS analysis which reveals the presence of both monocarbonylated compound (**F**) and cyclic imide (**J**) in the reaction mixture.

Similarly, the formed monocarbonylated adduct (**F**) undergoes an intramolecular amidocarbonylation-cyclisation reaction after a similar carbonylative catalytic cycle in the presence of the regenerated active palladium(0) species (**cycle-2**), providing the final *N*-substituted-pyrrolo[3,4-b]quinoline-1,3-dione (**J**). Indeed, the 3-bromoquinoline-2-carboxamide intermediate (**F**) promotes a second catalytic cycle via oxidative addition of the 3-bromoarene moiety, followed by the coordination and incorporation of the second carbon monoxide providing the acyl-palladium(II) species bearing carboxamide moiety at position C-2 (**H**). The base-assisted HBr-elimination, the proximity of the 2-(CO)HNR, and the palladium(II) acyl functionality enable the nucleophile attack of the amide moiety resulting in the catalytic intermediate (**I**), which undergoes reductive elimination giving the target *N*-substituted-pyrrolo[3,4-b]quinoline-1,3-dione (**J**).

Expectedly, the formed diamide product (**M**), which was detected by GC-MS and isolated as the main product in very few cases, could be explained by a possible competitive aminocarbonylation that could occur during a concomitant catalytic cycle (cycle-3). As it has been mentioned above in the case of cycle-2, the oxidative addition of 3-bromoquinoline-2-carboxamide (**F**) and the subsequent CO coordination provide the (**H**) species, which could be considered as a branching key catalytic intermediate between the second and third cycle. The coordination of the second primary amine followed by HBr elimination provides the (**L**) intermediate, which could be involved in a reductive elimination giving the quinoline-2,3-dicarboxamide (**M**) as a side product. The same results have been recently published our group for some similar *ortho*-dihalogenated-(hetero)arene substrates.[17a,h]

The single crystal X-ray diffraction study in the case of **3 a** and **3 b**, and the measurements of the specific rotations for **3 a**–**3 e** derivatives revealed that an unexpected and interesting racemization has been perceived during the synthesis of pyrroloquinolinediones **3 a**–**3 e** even though enantiopure L-aminoacid methyl esters were used as *N*-nucleophiles (See Supporting data). Although in-depth investigations of the stereochemical and mechanistic features of the synthesis have not yet been carried out, these preliminary results indicate that a possible palladium-promoted-interconversion between enantiomers of the first-stage formed *N*-(3-*bromoquinoline*)-2-*acetyl*-α-amino acid methyl esters could happen, as it is described by Beller's group, for similar *N-acyl* α-amino acids.[30]

Moreover, a racemization step in the catalytic cycle leading to a racemic mixture of the final product is an assumption that could not be precluded. Further investigations regarding the racemization of the α-amino acid moiety (possibly followed by spontaneous resolution) during palladium-catalyzed imide (**3**) formation are in progress in our laboratory.

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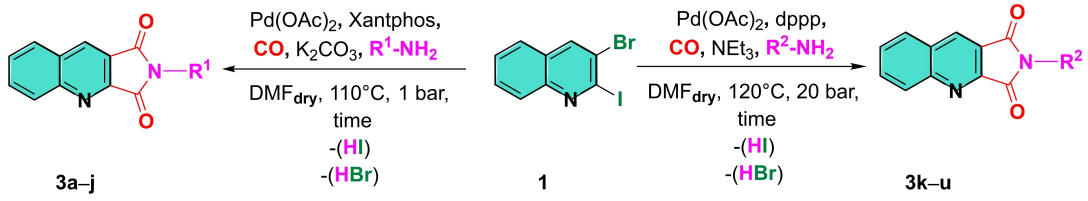
Table 3. Summary of designed *N*-substituted pyrroloquinolinediones **3** via one-pot processes.



3a–j **1** **3k–u**

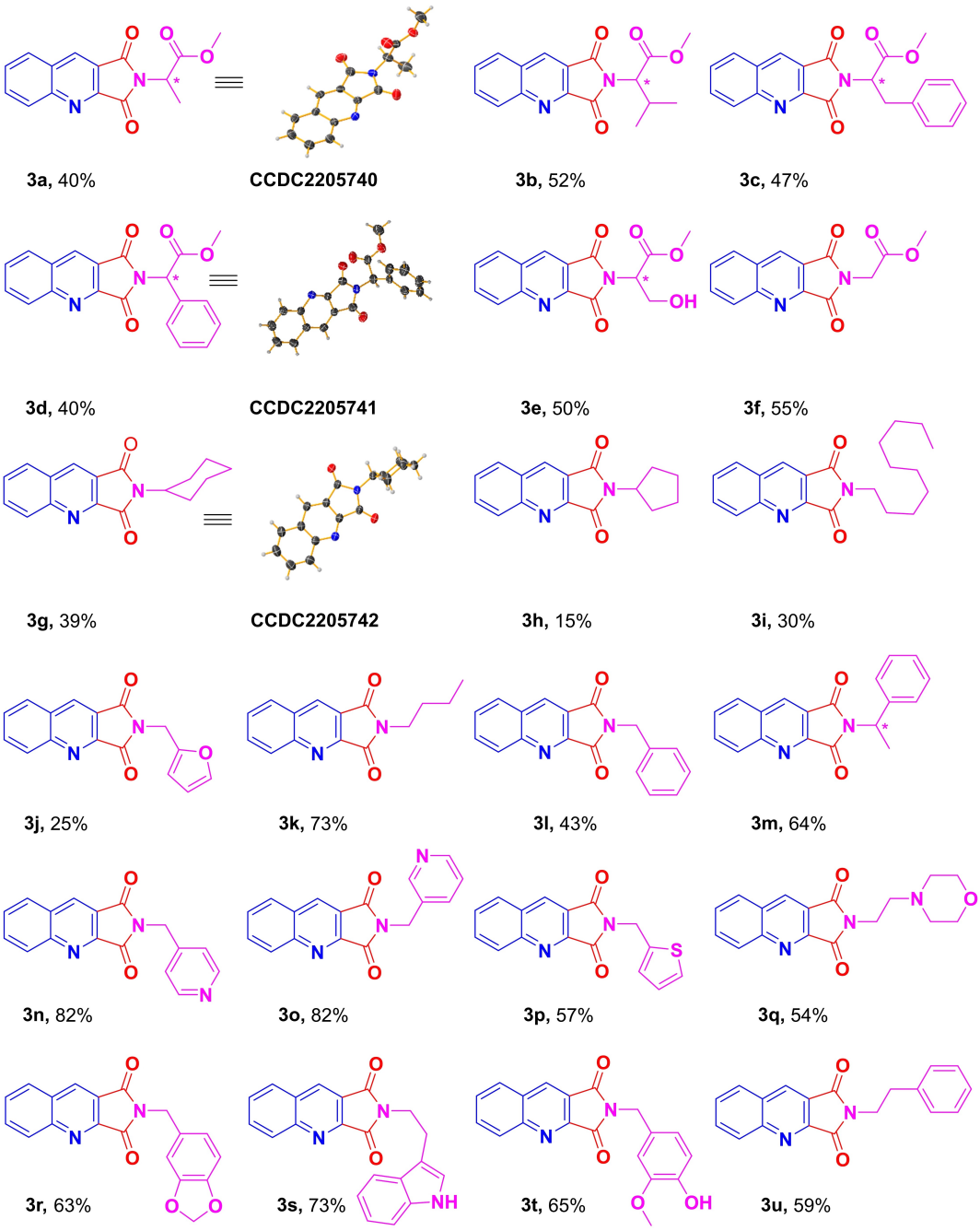


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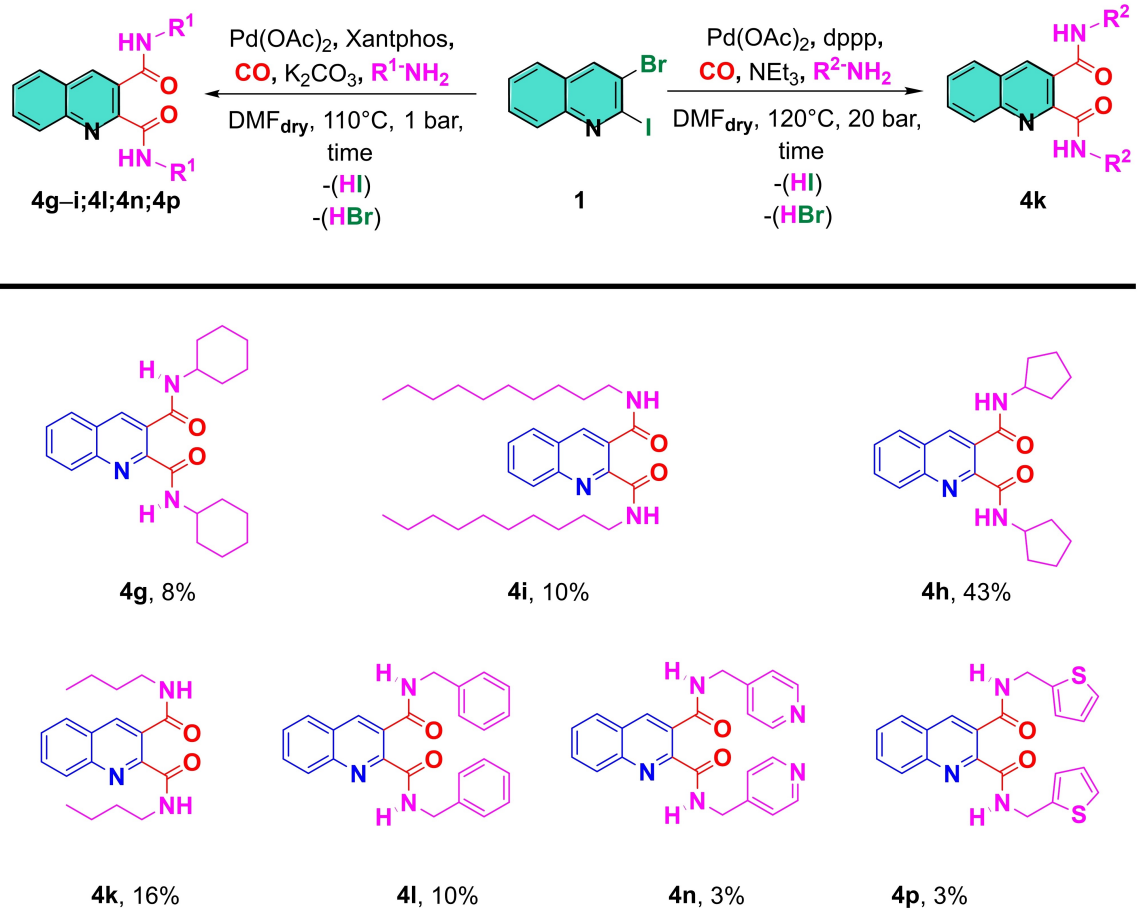
Table 4. Isolated quinolinedicarboxamides **4** as side-products via one-pot procedures.



Conclusion

In summary, a panoply of novel *N*-substituted pyrrolo[3,4-b]quinoline-1,3-diones has been synthesized by simple one-step palladium-catalyzed carbonylative cyclization of 3-bromo-2-iodoquinoline with a large variety of primary amines. A detailed optimization study revealed that the reaction conditions have a great influence on the selectivity toward the target pyrroloquinolinediones. Under atmospheric conditions, the $Pd(OAc)_2$/XantPhos catalyst has been the most effective using K_2CO_3 at 110 °C. Moreover, in the presence of $Pd(OAc)_2$/dppp catalyst, the reaction has selectively provided the target ring closed product under 20 bar of carbon monoxide pressure using Et_3N at 120 °C. It has to be mentioned, that in some cases the quinoline-2,3-dicarboxamide side products have also been isolated in low yields and fully characterized giving a new and non-described quinoline-2,3-dicarboxamide scaffold. The formation of the products has been explained by a proposed mechanism based on the well-known elementary steps of catalytic cycle of the aminocarbonylation.

It can be stated that the designed synthetic pathway, applying the two different experimental procedures, provides a very useful and convenient aminocarbonylative transformation to rarely described and valuable acridinimides by using a wide variety of *N*-nucleophiles. The high efficiency, the broad scope of amines with various structures, and the good to excellent isolated yields (up to 82 %) make this synthetic route as one of the prominent alternative routes to pyrroloquinolinediones.

Additionally, the molecular structures of three new pyrrolo[3,4-b]quinoline-1,3-dione derivatives have been established by means of single crystal XRD analysis.

Experimental Section

General Procedures: The GC measurements have been performed with a Shimadzu GC-2030 gas-chromatograph (Shimadzu, Tokyo, Japan) fitted with a capillary column coated with OV-1 (injector temp. 250 °C; oven: starting temp. 50 °C (hold-time 1 min), heating rate 15 °C min^{-1}, final temp. 320 °C (hold-time 11 min); detector temp. 280 °C; carrier gas: helium (rate: 1 mL min^{-1})). Mass spectrometry data were recorded using a GC-MS-2020 system (Shimadzu, Tokyo, Japan) operated in EI mode (70 eV). High-resolution mass spectra were acquired on a 6530 Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS system (Agilent Technologies, Singapore) equipped with an Agilent Jet Stream electrospray ionization (ESI) source. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance III 500 spectrometer (Bruker BioSpin Corp., Karlsruhe, Germany) at 500 and 125.7 MHz, respectively. Chemical shifts δ are reported in ppm relative to $CDCl_3$ (7.26 and 77.00 ppm

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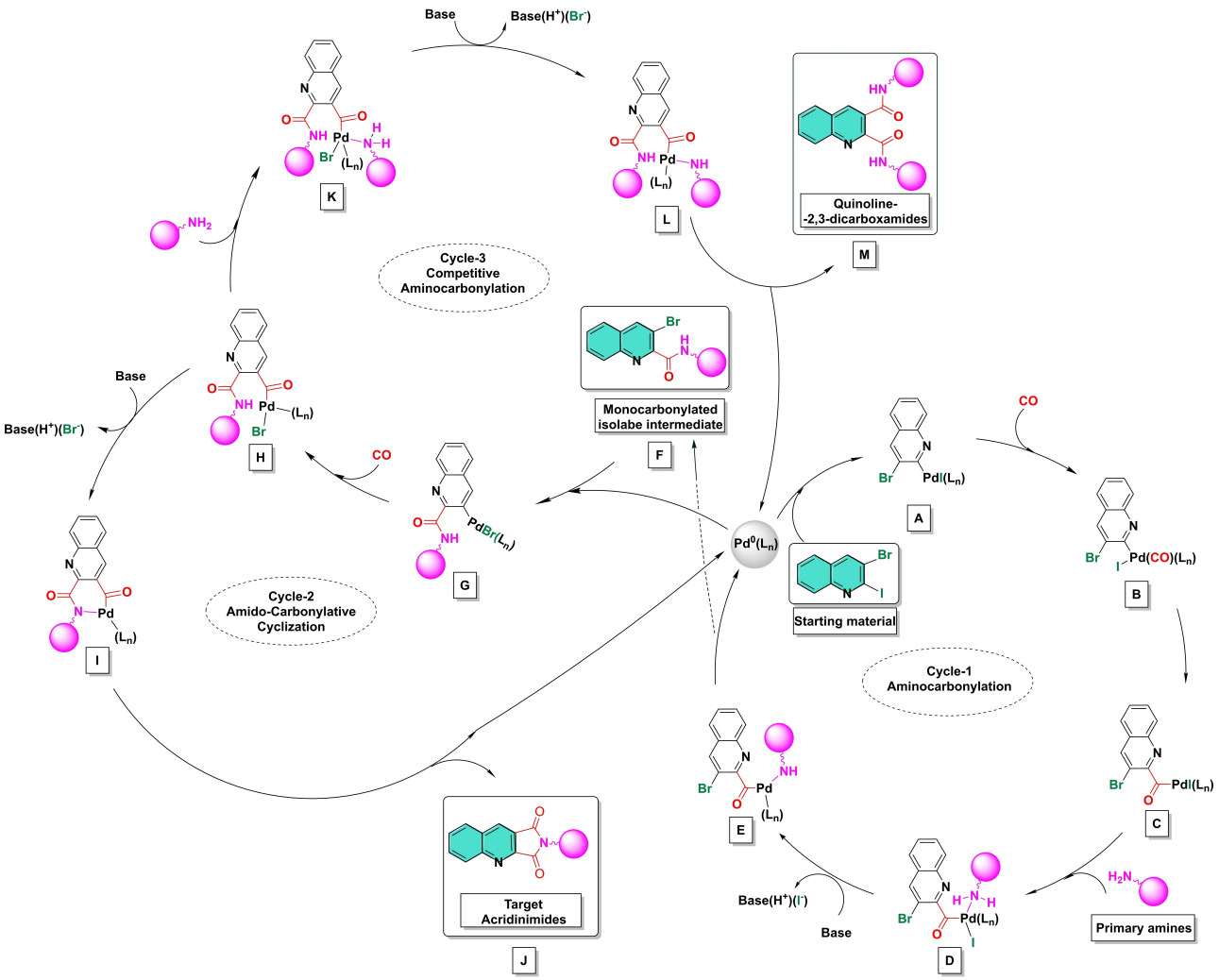

Scheme 4. Plausible mechanism of aminocarbonylation of 3-bromo-2-iodoquinoline with primary amines.

for ^{1}H and ^{13}C, respectively) or DMSO-d_6 (2.50 and 39.50 ppm for ^{1}H and ^{13}C, respectively). The FTIR spectra were taken in KBr pellets using a Nicolet IMPACT 400 spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) applying a DTGS detector in the region of 400–4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was ca. 0.5 mg. Optical rotations were measured with a circular polarimeter (PL-1) using 1 mL of cuvette with 10 cm length.

TLC plates (silica gel on TLC Al foils with fluorescence indicator 254 nm) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The eluents used in thin-layer chromatography are specified below. The $Pd(OAc)_2$, the ligands (PPh_3, PCy_3, dppp and Xantphos), the bases (Et_3N, K_2CO_3), the solvents, the 3-bromo-2-iodoquinoline (**1**) and the amine nucleophiles (**a**–**u**) were purchased from Sigma-Aldrich and were used without any further purification. The compounds **3 g**, **3 k**, **3 l** have been described in the literature. In the case of **3 g** and **3 l** the spectral data were in accordance with the literature data.[31] In the case of **3 k**, the characterization was not complete and the ^{1}H or ^{13}C NMR data for these compound are provided here for the sake of completeness.[32]

Aminocarbonylation of 3-Bromo-2-iodoquinoline (1) in the Presence of Various Amine Nucleophiles (a–u) under Atmospheric Carbon Monoxide Pressure: In a typical experiment $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), triphenylphosphine (6.6 mg, 0.025 mmol) or XantPhos (7.2 mg, 0.0125 mmol) or dppp (5.2 mg, 0.0125 mmol), 3-bromo-2-iodoquinoline (**1**) substrate (0.5 mmol), amine nucleophiles ((**a**–**u**), amount of the amines are given in Tables 1 and 2) and triethylamine (0.25 mL, 1.79 mmol) or potassium carbonate (103.7 mg, 0.75 mmol) were dissolved in DMF (5 mL) under argon in a 100 mL three-necked flask equipped with reflux condenser connected to a balloon filled with argon. The atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50–120 °C (see in Tables 1 and 2) and analyzed by GC and GC-MS. The cooled reaction mixture was then concentrated and evaporated to dryness under reduced pressure. The residue was dissolved in chloroform (20 mL) and washed twice with water (20 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to a solid material. All compounds were subjected to column chromatography (Silicagel 60 (Sigma), 0.063–0.200 mm), using different eluent mixtures (the exact eluents (content, ratio) are specified in *Characterization* part found in the Supporting file).

Aminocarbonylation of 3-Bromo2-iodoquinoline (1) in the Presence of Various Amine Nucleophiles (a–u) under High Carbon Monoxide Pressure: In a typical experiment $Pd(OAc)_2$, ligands (triphenylphosphine, XantPhos or dppp), 3-bromo-2-iodoquinoline (**1**) substrate and amine nucleophiles (**a**–**w**) were used in the same

amount as above and were dissolved in 5 mL of DMF under argon in a 100 mL stainless steel autoclave. The atmosphere was changed to carbon monoxide and the autoclave was pressurized to the given pressure with carbon monoxide. (Caution: High pressure carbon monoxide should only be used with adequate ventilation (hood) using CO sensors as well.) The reaction was conducted for the given reaction time upon stirring at 80–120 °C. After the given reaction time the reaction mixture was cooled to room temperature and the autoclave was carefully depressurized in a well-ventilated hood. The product mixture was analyzed by GC and GC-MS. The work-up of the reaction mixture was identical to that discussed for the atmospheric experiments.

Deposition Number(s) 2205740 (for 3a), 2205741 (for 3d), 2205742 (for 3 g) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

A more detailed crystallographic study can be found in the Supporting file.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: aminocarbonylation · carbon monoxide · cyclization · palladium · heterocycles

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