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Studies on pyrrolidinones. On the application of copper-catalyzed arylation of methyl pyroglutamate to obtain a new benzo[*de*]quinoline scaffold

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ABSTRACT

Optimized conditions for copper-catalyzed *N*-arylation of methyl pyroglutamate are described. These studies permitted the synthesis of methyl *N*-naphthylpyroglutamate, which was then cyclized to a ketone. The known dehydration of amidoketones by PPA was extended to this new scaffold to lead to a novel condensed benzo[*de*]quinoline with potential antioxidative activity.

1. Introduction

Many chemical reactions occurring in vivo generate free radicals responsible of numerous cellular damages.[1] Certain mineral salts (selenium and zinc) and vitamins (C, E, and beta-carotenes) are known to contribute to free radicals neutralization.[2] We have already reported that heterocycles **1** react with oxygen di-radical from air.[3–6] Comparison of their scaffold with the structures of compounds exhibiting an antioxidant potency (such as flavonoids,[7] hexahydropyridoindoles[8] or curcumin[9] derivatives) led us to evaluate the anti-oxidant activity of lactam **2** (in which, by comparison with ketone **1**, there is no N–CH_2 bond). Because an extended conjugation can improve the potential activity, we wished also to test compounds **3**[4,10] and **4** (Fig. 1).

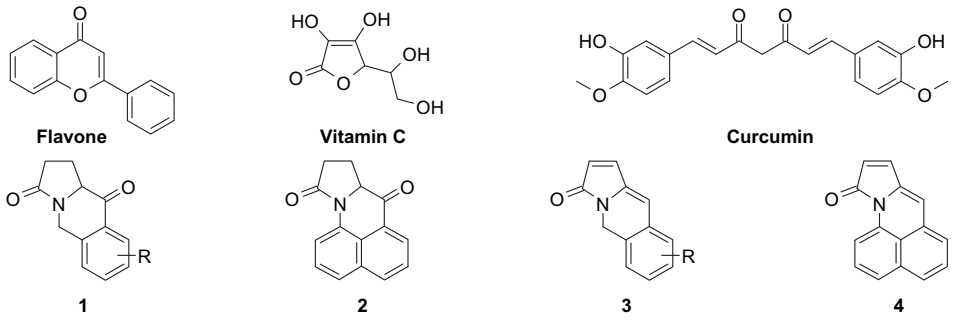

Figure 1. Structure of compounds with (potential) antioxidative activity.

Syntheses of lactams **1** and **3** have been already described from *N*-arylmethylpyroglutamic acids **5**.[3,10,11] (Scheme 1). In order to use the same reaction sequences for preparing naphthyl derivatives **2** and **4**, it was necessary to synthesize *N*-naphthylpyroglutamic acid (**6**).

Due to the low 20–30% yields generally obtained during the four-step malonic syntheses of *N*-arylpyroglutamic acids,[12] we decided to use an alternative route. In this paper, we described an optimization of the copper-catalyzed coupling of methyl pyroglutamate (**11**)[13] with different aryl bromides, in order to apply this method to the synthesis of lactams **2** and **4**.

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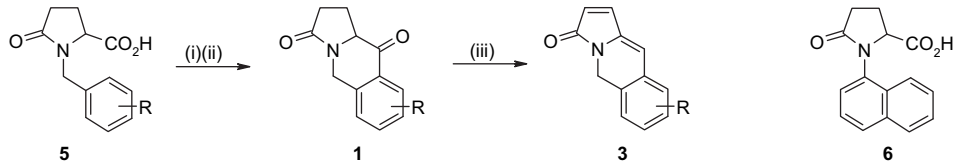


Scheme 1. Synthesis of lactams **1** and **3** (lit. 3, 10, and 11). Reaction conditions: (i) $SOCl_2$, CH_2Cl_2; (ii) $AlCl_3$, CH_2Cl_2; (iii) PPA, 140 °C.

2. Results and discussion

2.1. Copper-catalyzed reactions of pyroglutamic derivatives described in literature

Transition metal catalyzed C–N bond-formations represent, in pharmaceutical companies and academic laboratories, an useful method for introducing some groups: as for the nucleophilic aromatic substitution with aryl halides, mediated by palladium,[14] nickel[15] or copper[16,17] catalysts. Due to the high cost of palladium which invites to less expensive alternatives, and limitations which still remain in the palladium-catalyzed arylation of amides,[18] we chose to use the copper-catalyzed Ullmann–Goldberg arylation of amides.[17,19–21]

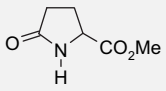
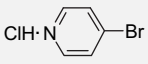
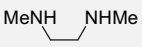
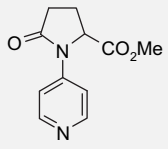
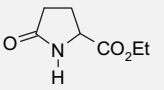
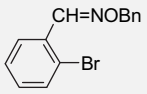
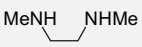
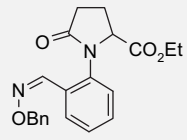
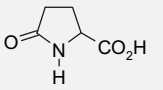
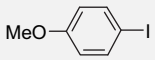
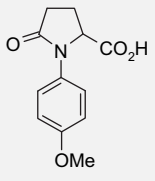
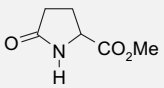
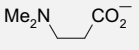
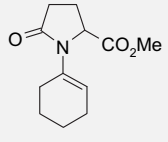
While the Ullmann reaction is sometimes performed with a ligand and additive free conditions,[22] success in arylation of amides and lactams is often highly dependent on the right combination of the ligand, the base, and the solvent used.[20] The copper-catalyzed coupling of pyroglutamic derivatives with aromatic halides is scarcely documented (Table 1).[23–28] Particularly, the solvent utilized was either dioxane or DMSO, the amount of CuI was varied from 0.05 to 0.5 equiv, and the temperature from 60 to 130 °C. Moreover, some data suggest that pyroglutamic derivatives could be used as reagent as well as ligand (Table 1 entry 3).[26] This led us to examine the different factors influencing the copper catalyzed N-arylation of methyl pyroglutamate (**11**) with aryl bromides.

2.2. Cu-catalyzed N-arylation of methyl pyroglutamate

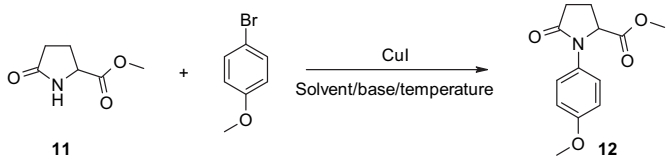
In the seminal report from Buchwald, aryl bromides reacted with lactams more slowly than aryl iodides and typically required heating at 110 °C for 24 h. The best conditions for most substrates utilized 5 mol % of CuI, K_2CO_3 or Cs_2CO_3 as base, toluene as solvent, and 10 mol % of *N*,*N*′-dimethylethylenediamine (DMEDA) as ligand.[20]

Our experiments were first conducted by coupling methyl pyroglutamate **11** and 1.1 mol equivalent of 4-bromoanisole (Scheme 2) catalyzed by 10 mol % of CuI, and 20 mol % of DMEDA (**L_1**) (Fig. 2). This reaction, proceeded at 110 °C in dioxane and in the presence of Cs_2CO_3, afforded methyl *N*-(4-methoxyphenyl)pyroglutamate (**12**) in 43% yield. In these conditions, no reaction occurred when using a triamine (**L_2** or **L_3**),[29] a tetramine (**L_4**)[30] or another known complexing agent like **L_5**[31] or **L_6** (Fig. 2). While realizing these coupling assays, we observed the formation and the persistence of a dark-blue gum, not soluble in the reaction

Table 1
Copper-catalyzed reactions of pyroglutamic derivatives described in literature

Entry (literature)	Pyroglutamic ester (mol %)	*R*-X (mol %)	CuI (mol %)	Ligand (mol %)	Base (mol %)	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)
1 (25)	 (100)	 (200)	(50)	 (ND)	Cs_2CO_3 (250)	Dioxane	100	23	 **7**	68
2 (24)	 (120)	 (100)	(5)	 (10)	K_2CO_3 (200)	Dioxane	130	5	 **8**	61
3 (26)	 (20)	 (100)	(10)	Pyroglutamic acid was the ligand tested in arylation of 1.2 equiv of indole	K_2CO_3 (250)	DMSO	80	63	 **9**	75
4 (27)	 (120)	 (100)	(10)	 (20)	Cs_2CO_3 (200)	Dioxane	60	12	 **10**	78

mixture: that suggested a too strong complexation of the copper and the catalytic cycle was blocked. No reaction also occurred without ligand, demonstrating that, contrarily to pyroglutamic acid,[26] methyl pyroglutamate does not possess suitable ligand properties.



Scheme 2. Reaction of methyl pyroglutamate with 4-bromoanisole.

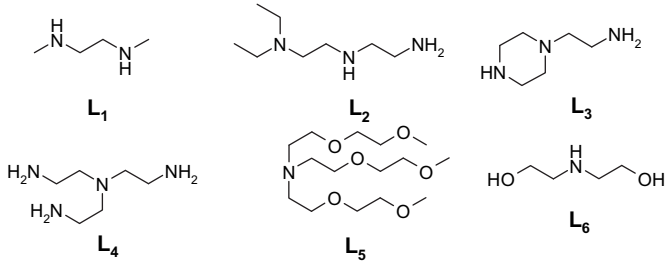


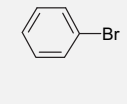
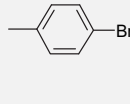
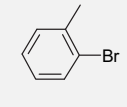
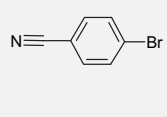
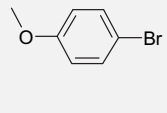
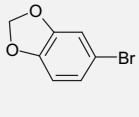
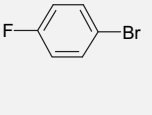
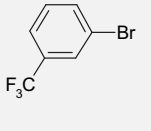
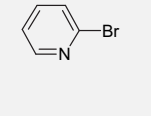
Figure 2. Ligands examined for the arylation of **11**.

Different solvents and bases were also tested. It was observed that dioxane gave the best result; DMF and toluene providing lower yields. Compared with Cs_2CO_3 (2 equiv), K_3PO_4 was a worse base, and K_2CO_3 led to a partial saponification of the ester group. Saponification also occurred when 4 equiv of Cs_2CO_3 were utilized and, in that case, 4-iodoanisole was obtained in 95% yield (according to NMR spectrum). Further exploration was then conducted in order to decrease the reaction temperature by using higher amount of CuI and ligand. It was found that, by employing the dioxane/Cs_2CO_3 combination, the reaction still worked well at 60 °C or even at room temperature. This led to a quantitative yield of **12** (according to NMR spectrum) when 50 mol % of CuI and 100 mol % of ligand were stirred with methyl pyroglutamate and 4-bromoanisole for 7 h at 60 °C or 12 h at room temperature.

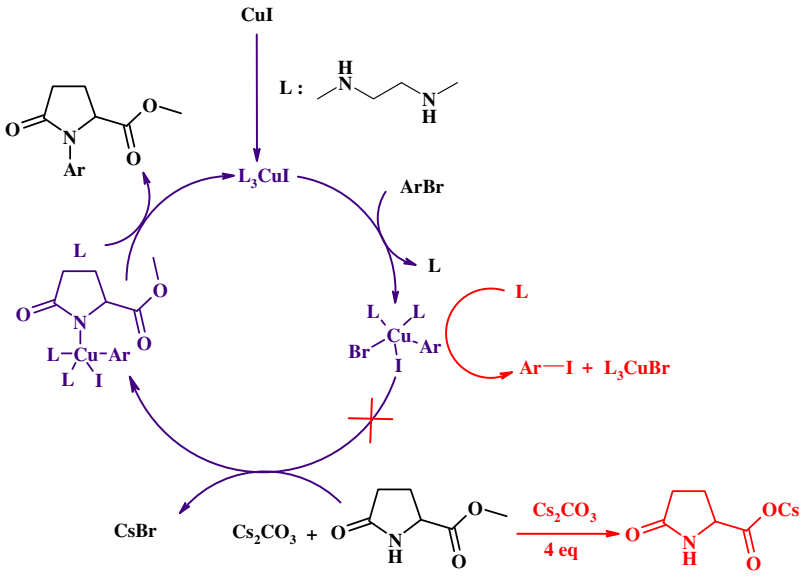
With the optimized conditions in hand, the scope of arylation of methyl pyroglutamate was explored with various aromatic bromides. Reactions were continued until total conversion (followed by NMR) of reagents, and results are listed in Table 2. It was found that bromobenzenes bearing both electron-donating (Table 2, entries 5 and 6) or electron-withdrawing groups (Table 2, entries 4, 7, and 8) were suitable for this reaction, and the expected methyl *N*-arylpyroglutamates were isolated in excellent yields. In the case of 2-bromopyridine, the reaction was slower: the final product was obtained only after 36 h (Table 2, entry 9). The reaction seemed not to be strongly sensitive to the sterical hindrance (Table 2, entry 3). It is to be noted that, upon entire consumption of methyl pyroglutamate, excesses of 4-bromoanisole or 4-bromocyanobenzene were converted to their iodo analogs. The best yields obtained by comparison to those reported in Table 1, were probably the result of the lower reaction temperature avoiding the saponification of the ester function and the interruption of the catalytic cycle.

Although we have not carried out any mechanistic study, it is reasonable to postulate a mechanism similar to other Ullmann-type reactions[17,29] (Scheme 3). It explains the formation of aryl iodide when the nucleophile was entirely consumed (Table 2, entries 4 and 5) or removed from the catalytic cycle upon saponification of methyl pyroglutamate leading to insoluble cesium pyroglutamate (in red in Scheme 3). We have tested that the copper-catalyzed formation of aryl iodide—described in *i*-PrOH/diaminopropane[32]

Table 2
Copper-catalyzed N-arylation of DL-methyl pyroglutamate with functionalized aryl bromides[a]

Entry	Aryl bromide	Product	Temperature (°C)	Time (h)	Yield[b] (%)
1		**13**	rt	36	90
2		**14**	60	15	95
3		**15**	60	12	80
4		**16**	60	9	91[c]
5		**12**	rt	12	90[d]
6		**17**	60	6	85
7		**18**	60	8	81
8		**19**	60	16	91
9		**20**	rt–60	36	73

[a] Reaction conditions: aryl bromide (1.1 equiv), DL-methyl pyroglutamate (1 equiv), Cs_2CO_3 (2 equiv), $\mathbf{L_1}$ (1 equiv), dioxane, under inert atmosphere, CuI (0.5 equiv).
[b] Isolated yields after chromatography.
[c] 4-Cyanoiodobenzene was also isolated in 5% yield.
[d] 4-Methoxyiodobenzene was also isolated in 3% yield.

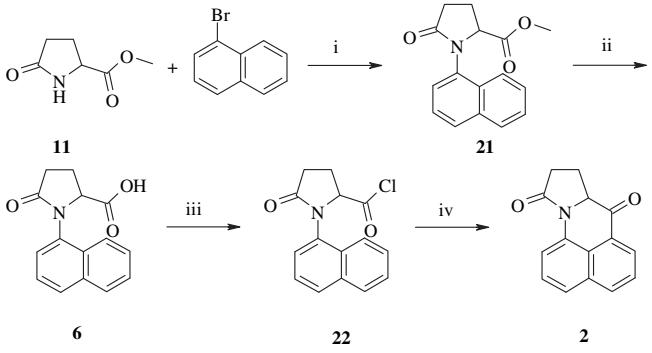


Scheme 3. Proposed mechanistic pathways for copper-catalyzed cross-coupling of methyl pyroglutamate with aryl bromides and for halogen exchange (in red) observed when using large excess of base.

or in the aromatic Finkelstein reaction in presence of dioxane/*N*,*N*′-dimethylcyclohexane-1,2-diamine[33]—gave a quantitative yield when 4-cyano(or 4-methoxy)bromobenzene was refluxed for 24 h with CuI/DMEDA in dioxane.

2.3. Synthesis of naphthyl derivatives 2 and 4

In the next part, synthesis of the expected lactam **2** and diene **4** was undertaken: methyl *N*-(1-naphthyl)pyroglutamate (**21**) was obtained in 73% yield by reacting methyl pyroglutamate **11** with 1-bromonaphthalene under the previous conditions. After saponification of its ester group, a Friedel–Crafts cyclization was realized as for ketones **1**[3] by treating acid chloride **22** with $AlCl_3$ in dichloromethane, to give ketone **2** in 76% yield (Scheme 4).



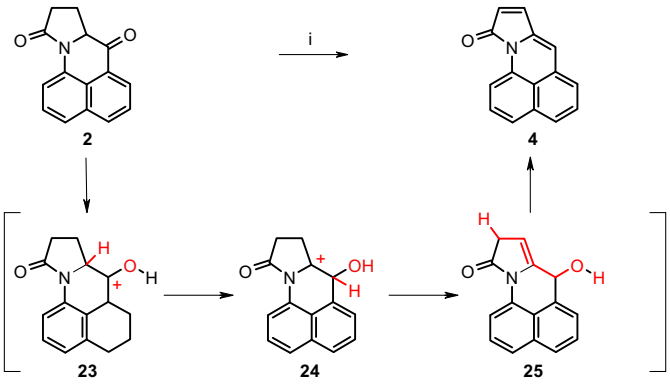
Scheme 4. Reagents and conditions: (i) α-bromonaphthalene (1.1 equiv), Cs_2CO_3 (2 equiv), CuI (0.5 equiv), *N*,*N*′-DMEDA (1 equiv), dioxane, 60 °C, 12 h, 73%; (ii) NaOH 2 N (2 equiv), rt, 2 h then HCl, 100%; (iii) $SOCl_2$, CH_2Cl_2, reflux, 2 h, 100%; (iv) $AlCl_3$ (3 equiv), CH_2Cl_2, rt, 12 h, 76%.

Ketones **1** led to dienes **3** when they were heated in polyphosphoric acid.[4,10] To the best of our knowledge, this type of dehydration reaction was not described in the literature with an *N*-naphthyl ketolactam scaffold like **2**. To our delight, stirring **2** in PPA at 120 °C for 6 h gave 32% of heterocycle **4** and the replacing of the dehydrating reagent by Eaton's reagent (P_2O_5/$MeSO_3H$)[34] improved the yield to 51%. It is to be noted that compound **4** presents a more aromatic character than dienes **3**.

A reasonable mechanism for this dehydration is similar to the one postulated for the formation of products **3**[4,10]: protonation of ketone **2** leading to **23**, followed by a retro-pinacol reaction. This intramolecular hydride shift yielded the *N*-acyliminium salt **24**,[35] more stable than cation **23**, which evolved to enamide **25** in the anhydrous conditions of PPA.[36] Then, an allylic dehydration was able to give diene **4**.

3. Conclusion

In this paper, we have described optimized conditions for copper-catalyzed N-arylation of methyl pyroglutamate. That permitted the synthesis of methyl *N*-naphthylpyroglutamate that was cyclized to a ketone. The known PPA dehydration of amidoketones was extended to this new scaffold leading to a new condensed benzo[*de*]-quinoline. The antioxidative properties of products **2**, **3**, and **4** are currently evaluated, and the results will be presented in due course.



Scheme 5. Reagents and conditions: (i) PPA (4 equiv), 140 °C, 6 h, 32% or Eaton's reagent (P_2O_5/$MeSO_3H$ 1/10) (5 equiv), 90 °C, 12 h, 51%.

4. Experimental section

Starting materials were commercially available (DL-methyl pyroglutamate was prepared in kilo-scale quantities in our laboratory).[13] Melting points were measured on a Electrothermal® apparatus and are uncorrected. The infrared spectra were recorded on a FTIR Brücker TENSOR 27 in ATR with a DTGS (Deuterated Tri-Glycine Sulfate) detector. NMR spectra were acquired at 200 MHz for ^1H NMR and 50 MHz for ^{13}C NMR on a Varian Gemini 2000®

spectrometer and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Thin layer chromatographies were realized on Macherey Nagel silica gel plates with a fluorescent indicator and were visualized with UV-lamp at 254 nm and 366 nm. Column chromatographies were performed with silica gel (40–60 μm). Elemental analyses (C, H, N) of new compounds were determined by Service de Microanalyses, Faculté de Sciences Mirande, Université de Bourgogne, France.

4.1. General procedure for the synthesis of *N*-arylpyroglutamic derivatives by cross-coupling of DL-methyl pyroglutamate with aromatic bromides (Table 2)

A suspension of coupling substrate (DL-methyl pyroglutamate) (1 equiv), 0.5 equiv of copper (I) iodide, 2 equiv of mineral basis (Cs_2CO_3), and corresponding aryl bromide (1.1–1.2 equiv) in dioxane was placed under nitrogen (inert atmosphere). The coupling ligand (*N*,*N*'-dimethylethylenediamine) (1 equiv) was added dropwise with a syringe. The mixture was then stirred at room temperature or at 60 °C for various periods of time (7–48 h). The mixture got blue very quickly (this color corresponds to the complex copper–ligand formation) and the catalytic cycle started. All insoluble salts deposited after cooling at room temperature were collected by filtration then washed with dichloromethane. The resulting filtrate was concentrated in vacuo and the residue was partitioned between water and dichloromethane. The organic layer was dried on $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica gel (EtOAc/*n*-heptane) to afford pure compounds (Table 2 compounds **12**–**20** and Scheme 4 compound **21**).

*4.1.1. Methyl N-phenylpyroglutamate (**13**).* The general procedure was followed using DL-methyl pyroglutamate (3.0 g, 21 mmol), bromobenzene (2.4 mL, 23 mmol), cesium carbonate (13.7 g, 42 mmol), copper (I) iodide (2.0 g, 10 mmol), and DMEDA (2.3 mL, 21 mmol) in dioxane (50 mL). The mixture was stirred under nitrogen atmosphere at room temperature for 36 h. The residue obtained after treatment was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 5/5 to generate pure product **13** as a white solid in 90% yield; mp 72 °C, TLC R_f (EtOAc/*n*-heptane 8/2)=0.25; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.11–2.25 (m, 1H, CH_2CH_2CH), 2.39–2.83 (m, 3H, CH_2CH_2CH), 3.71 (s, 3H, CO_2CH_3), 4.69–4.77 (m, 1H, CH_2CH_2CH), 7.12–7.22 (m, 1H, Ar*H*), 7.30–7.48 (m, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.0 (CH_2), 30.6 (CH_2), 52.3 and 52.6 (2 rotamers, CH_3), 61.0 and 61.9 (2 rotamers, CH), 121.2 and 121.8 (2 rotamers, 2CH), 125.1 and 125.7 (2 rotamers, CH), 128.6 and 129.2 (2 rotamers, 2CH), 137.9 (C), 172.1 (C), 174.1 (C). Anal. Calcd for $C_{12}H_{13}O_3N$: C 65.74, H 5.98, N 6.39; found: C 65.47, H 6.03, N, 6.55.

*4.1.2. Methyl N-(4-methylphenyl)pyroglutamate (**14**)*[37]. The general procedure was followed using DL-methyl pyroglutamate (3.0 g, 21 mmol), 4-methylbromobenzene (3.5 mL, 23 mmol), cesium carbonate (13.7 g, 42 mmol), copper (I) iodide (2.0 g, 10 mmol), and DMEDA (2.3 mL, 21 mmol) in dioxane (50 mL). The mixture was stirred under nitrogen atmosphere at 60 °C for 15 h. The residue was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 5/5 to generate pure product **14** as a brilliant white powder in 95% yield; mp 91 °C, TLC R_f (EtOAc/*n*-heptane 5/5)=0.21; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.09–2.26 (m, 1H, CH_2CH_2CH), 2.32 (s, 3H, $ArCH_3$), 2.38–2.84 (m, 3H, CH_2CH_2CH), 3.72 (s, 3H, CO_2CH_3), 4.70 (dd, *J*=8.8, 3.4 Hz, 1H, CH_2CH_2CH), 7.16 (d, *J*=8.5 Hz, 2H, Ar*H*), 7.32 (d, *J*=8.5 Hz, 2H, Ar*H*). Anal. Calcd for $C_{13}H_{15}O_3N$: C 66.94, H 6.48, N 6.00; found: C 66.64, H 6.63, N, 6.05.

*4.1.3. Methyl N-(2-methylphenyl)pyroglutamate (**15**).* The general procedure was followed using DL-methyl pyroglutamate (2.8 g, 20 mmol), 2-methylbromobenzene (2.3 mL, 20 mmol), cesium carbonate (12.7 g, 39 mmol), copper (I) iodide (1.9 g, 9.7 mmol), and DMEDA (2.1 mL, 20 mmol) in dioxane (50 mL). The mixture was stirred under nitrogen atmosphere at 60 °C for 12 h. The residue obtained after treatment was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 8/2 to generate pure product **15** as a colorless oil in 80% yield; TLC R_f (EtOAc/*n*-heptane 8/2)=0.33; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.16–2.32 (m, 1H, CH_2CH_2CH), 2.27 (s, 3H, $ArCH_3$), 2.45–2.87 (m, 3H, CH_2CH_2CH), 3.69 (s, 3H, CO_2CH_3), 4.56 (dd, *J*=8.3, 3.2 Hz, 1H, CH_2CH_2CH), 7.18–7.26 (m, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.6 (CH_3), 23.8 (CH_2), 29.6 (CH_2), 52.1 and 52.5 (2 rotamers, CH_3), 62.2 and 62.7 (2 rotamers, CH), 126.3 and 126.9 (2 rotamers, CH), 127.9 and 128.5 (2 rotamers, CH), 130.9 (CH), 131.4 (CH), 135.8 (C), 136.0 (C), 172.0 (C), 174.4 (C). IR: ν cm^{-1}: 1741, 1700, 1515, 1394. Anal. Calcd for $C_{13}H_{15}O_3N$: C 66.94, H 6.48, N 6.00; found: C 66.57, H 6.68, N, 5.94.

*4.1.4. Methyl N-(4-cyanophenyl)pyroglutamate (**16**).* The general procedure was followed using DL-methyl pyroglutamate (3.0 g, 21 mmol), 4-cyanobromobenzene (6.2 g, 23 mmol), cesium carbonate (13.7 g, 42 mmol), copper (I) iodide (2.0 g, 10 mmol), and DMEDA (2.3 mL, 21 mmol) in dioxane (40 mL). The mixture was stirred under nitrogen atmosphere at 60 °C for 9 h. The residue was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 5/5 to generate pure product **16** as a white solid in 91% yield and 4-cyano-iodobenzene in 5% yield (white powder) as by-product; TLC R_f (EtOAc/*n*-heptane 5/5)=0.17; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.15–2.32 (m, 1H, CH_2CH_2CH), 2.43–2.90 (m, 3H, CH_2CH_2CH), 3.77 (s, 3H, CO_2CH_3), 4.80 (dd, *J*=8.3, 2.9 Hz, 1H, CH_2CH_2CH), 7.65 (s, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.7 (CH_2), 30.7 (CH_2), 52.6 and 52.9 (2 rotamers, CH_3), 60.1 and 60.9 (2 rotamers, CH), 107.7 (C), 118.4 (C), 119.7 and 120.7 (2 rotamers, 2CH), 132.6 and 133.2 (2 rotamers, 2CH), 142.0 (C), 171.4 (C), 174.3 (C). IR: ν cm^{-1}: 2246, 1770, 1685, 1520, 1376, 1339, 1300. Anal. Calcd for $C_{13}H_{12}O_3N_2$: C 63.93, H 4.95, N 11.47; found: C 63.57, H 5.02, N, 11.40.

*4.1.5. Methyl N-(4-methoxyphenyl)pyroglutamate (**12**)*[38]. The general procedure was followed using DL-methyl pyroglutamate (10 g, 70 mmol), 4-bromoanisole (13.1 mL, 105 mmol), cesium carbonate (56.9 g, 175 mmol), copper (I) iodide (6.6 g, 35 mmol), and DMEDA (7.5 mL, 70 mmol) in dioxane (100 mL). The mixture was stirred under nitrogen atmosphere at room temperature for 12 h. The residue was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 75/25 to generate pure product **12** as a white powder in 90% yield and 4-methoxy-iodobenzene in 3% yield (white solid) as by-product; mp similar to the literature[38]; TLC R_f (EtOAc/*n*-heptane 75/25)=0.39; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.08–2.25 (m, 1H, CH_2CH_2CH), 2.41–2.82 (m, 3H, CH_2CH_2CH), 3.72 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 4.68 (dd, *J*=8.6, 2.1 Hz, 1H, CH_2CH_2CH), 6.89 (d, *J*=9.1 Hz, 2H, Ar*H*), 7.34 (d, *J*=9.1 Hz, 2H, Ar*H*). Anal. Calcd for $C_{13}H_{15}O_4N$: C 62.64, H 6.07, N 5.62; found: C 62.28, H 5.79, N, 5.29.

*4.1.6. Methyl N-(benzo[1,3]dioxol-5-yl)pyroglutamate (**17**).* The general procedure was followed using DL-methyl pyroglutamate (2.0 g, 14 mmol), 5-bromo-1,3-benzodioxole (2.5 mL, 21 mmol), cesium carbonate (9.1 g, 28 mmol), copper (I) iodide (1.3 g, 7 mmol), and DMEDA (1.5 mL, 14 mmol) in dioxane (40 mL). The mixture was stirred under nitrogen atmosphere at 60 °C for 12 h. The residue was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 6/4 to generate pure product **17** as a white powder in 85% yield; mp 142 °C; TLC R_f (EtOAc/*n*-heptane 6/4)=0.39; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.03–2.27 (m, 1H, CH_2CH_2CH), 2.39–2.89 (m, 3H, CH_2CH_2CH), 3.73 (s, 3H, CO_2CH_3), 4.59–4.66 (m, 1H, CH_2CH_2CH), 5.96 (s, 2H, OCH_2O), 6.72 (d, *J*=8.3 Hz, 1H, Ar*H*), 6.78 (d, *J*=8.3 Hz, 1H, Ar*H*), 7.07 (s, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$,

50 MHz) δ 23.1 (CH_2), 30.3 (CH_2), 52.4 (CH_3), 101.3 (CH_2), 105.2 (CH), 108.0 (CH), 116.0 (CH), 131.9 (C), 145.6 (C), 147.9 (C), 172.1 (C), 174.2 (C). IR: ν cm^{-1}: 1740, 1695, 1509, 1489, 1433, 1390, 1201. Anal. Calcd for $C_{13}H_{13}O_5N$: C 59.31, H 4.98, N 5.32; found: C 59.31, H 4.95, N, 5.53. This product has been reported in a patent written in Japanese.[39]

*4.1.7. Methyl N-(4-fluorophenyl)pyroglutamate (**18**)*[37,40]. The general procedure was followed using DL-methyl pyroglutamate (2.0 g, 14 mmol), 4-fluorobromobenzene (2.9 g, 17 mmol), cesium carbonate (9.1 g, 28 mmol), copper (I) iodide (1.3 g, 7 mmol), and DMEDA (1.5 mL, 14 mmol) in dioxane (30 mL). The mixture was stirred under nitrogen atmosphere at 60 °C for 8 h. The residue was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 5/5 to generate pure product **18** as a white powder in 81% yield; TLC R_f (EtOAc/*n*-heptane 5/5)=0.18; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.11–2.29 (m, 1H, CH_2CH_2CH), 2.40–2.87 (m, 3H, CH_2CH_2CH), 3.73 (s, 3H, CO_2CH_3), 4.69 (dd, J=9.1, 3.2 Hz, 1H, CH_2CH_2CH), 7.01–7.10 (m, 2H, ArH), 7.37–7.46 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.1 (CH_2), 30.4 (CH_2), 52.5 (CH_3), 61.8 (CH), 115.5 (CH), 116.0 (CH), 123.9 (CH), 124.1 (CH), 157.8 (C), 162.7 (C), 172.1 (C), 174.1 (C). IR: ν cm^{-1}: 1746, 1685, 1518, 1380, 537. Anal. Calcd for $C_{12}H_{12}O_3NF$: C 60.76, H 5.10, N 5.90; found: C 60.79, H 5.21, N, 6.02.

*4.1.8. Methyl N-(3-trifluoromethylphenyl)pyroglutamate (**19**)*[37,41]. The general procedure was followed using DL-methyl pyroglutamate (3.0 g, 21 mmol), 3-trifluoromethylphenyl-bromobenzene (3.2 mL, 23 mmol), cesium carbonate (13.7 g, 42 mmol), copper (I) iodide (2.0 g, 10 mmol), and DMEDA (2.3 mL, 21 mmol) in dioxane (40 mL). The mixture was stirred under nitrogen atmosphere at 60 °C for 16 h. The residue was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 5/5 to generate pure product **19** as a white powder in 91% yield; TLC R_f (EtOAc/*n*-heptane 5/5)=0.34; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.13–2.32 (m, 1H, CH_2CH_2CH), 2.42–2.93 (m, 3H, CH_2CH_2CH), 3.75 (s, 3H, CO_2CH_3), 4.78 (dd, J=8.7, 2.6 Hz, 1H, CH_2CH_2CH), 7.47 (dd, J=15.7, 7.8 Hz, 2H, ArH), 7.68 (d, J=7.5 Hz, 1H, ArH), 7.79 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.0 (CH_2), 30.6 (CH_2), 52.6 (CH_3), 61.1 (CH), 117.9 (q, J=8.1, 4.2 Hz, CH), 121.8 (q, J=7.8, 3.8 Hz, CH), 124.2 (q, J=3.2, 1.7 Hz, CH), 124.3 (C), 129.4 (CH), 131.2 (q, J=65.2, 33.0 Hz, C), 138.6 (C), 171.7 (C), 174.2 (C). IR: ν cm^{-1}: 1743, 1698, 1455, 1394, 1333, 1299, 690, 550, 497. Anal. Calcd for $C_{13}H_{12}O_3NF_3$: C 54.36, H 4.21, N 4.88; found: C 54.21, H 4.38, N, 5.12.

*4.1.9. Methyl N-(pyridin-2-yl)pyroglutamate (**20**).* The general procedure was followed using DL-methyl pyroglutamate (2.0 g, 14 mmol), 2-bromopyridine (1.6 mL, 17 mmol), cesium carbonate (9.1 g, 28 mmol), copper (I) iodide (1.3 g, 7 mmol), and DMEDA (1.5 mL, 14 mmol) in dioxane (20 mL). The mixture was stirred under nitrogen atmosphere at 60 °C for 16 h. The residue was separated by chromatography on silica gel, eluting EtOAc to generate pure product **20** as a brown oil in 73% yield; TLC R_f (EtOAc)=0.22; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.09–2.20 (m, 1H, CH_2CH_2CH), 2.31–2.98 (m, 3H, CH_2CH_2CH), 3.71 (s, 3H, CO_2CH_3), 4.68 (dd, J=8.7, 2.4 Hz, 1H, CH_2CH_2CH), 7.40–8.32 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.0 (CH_2), 31.3 (CH_2), 53.2 (CH_3), 60.1 (CH), 113.1 (CH), 144.2 (CH), 150.6 (CH), 171.7 (C), 174.6 (C). IR: ν cm^{-1}: 1720, 1698, 1455, 1394, 1333, 1299. Anal. Calcd for $C_{11}H_{12}O_3N_2$: C 59.99, H 5.49, N 12.72; found: C 59.47, H 5.60, N, 12.83.

*4.1.10. Methyl N-(α-naphthyl)pyroglutamate (**21**).* The general procedure was followed using DL-methyl pyroglutamate (7.0 g, 49 mmol), α-bromonaphthalene (6.1 mL, 49 mmol), cesium carbonate (31.9 g, 98 mmol), copper (I) iodide (4.7 g, 24.5 mmol), and DMEDA (5.3 mL, 49 mmol) in dioxane (70 mL). The mixture was stirred under nitrogen atmosphere at 60 °C for 12 h. The residue was separated by chromatography on silica gel, eluting EtOAc/*n*-heptane 6/4 to generate pure product **21** as a white powder in 73% yield; TLC R_f (EtOAc/*n*-heptane 6/4)=0.28; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.20–2.36 (m, 1H, CH_2CH_2CH), 2.44–2.88 (m, 3H, CH_2CH_2CH), 3.72 (s, 3H, CO_2CH_3), 4.71 (dd, J=9.2, 3.0 Hz, 1H, CH_2CH_2CH), 6.73–7.21 (m, 7H, ArH). IR: ν cm^{-1}: 1746, 1691, 1456, 1392, 1321, 1290. Anal. Calcd for $C_{16}H_{15}O_3N$: C 71.36, H 5.61, N 5.20; found: C 71.22, H 5.46, N, 5.09.

*4.1.11. N-(α-Naphthyl)pyroglutamic acid (**6**).* A stirred mixture of ester **21** (Scheme 4) (3.2 g, 12 mmol) and sodium hydroxide (0.7 g, 17.5 mmol) in distilled water (9.0 mL) was refluxed for 2 h (till complete solubilisation of starting ester which is equivalent to sodium carboxylate formation). After cooling at room temperature, the solution was stirred by using a magnetic bar, and then acidified to pH=5–6 by adding slowly concentrated HCl. The solid obtained by filtration was washed with distilled water and dried to give acid **6** as white solid in quantitative yield; mp 185 °C; TLC R_f (dichloromethane/methanol 95/5)=0.29; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.20–2.36 (m, 1H, CH_2CH_2CH), 2.44–2.88 (m, 3H, CH_2CH_2CH), 4.63 (m, 1H, CH_2CH_2CH), 7.40–7.67 (m, 4H, ArH), 7.80–7.91 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.1 (CH_2), 29.7 (CH_2), 63.2 (CH), 125.5 (CH), 126.3 (2CH), 126.8 (CH), 128.5 (C), 128.6 (C), 128.9 (2CH), 129.5 (C), 134.4 (C), 171.2 (C), 174.6 (C). IR: ν cm^{-1}: 3070, 1733, 1636, 1510, 1412, 1250, 1143. Anal. Calcd for $C_{15}H_{13}O_3N$: C 70.58, H 5.13, N 5.49; found: C 70.34, H 5.28, N, 5.65.

*4.1.12. N-(α-Naphthyl)-5-oxoprolyl chloride (**22**).* A mixture of acid **6** (Scheme 4) (2.2 g, 8.6 mmol) and thionyl chloride (1.9 mL, 25.8 mmol) in dichloromethane (15 mL) was refluxed for 3 h. The pale yellow solution was concentrated in vacuo to give the crude acid chloride **22** (Scheme 4) as a yellow pale solid in a quantitative yield. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.52–2.68 (m, 1H, CH_2CH_2CH), 2.71–3.00 (m, 3H, CH_2CH_2CH), 4.92–5.07 (m, 1H, CH_2CH_2CH), 7.47–7.61 (m, 4H, ArH), 7.75–7.96 (m, 3H, ArH).

*4.1.13. 8,9-Dihydro-7H-benzo[de]pyrrolo[1,2-a]quinoline-7,10(7aH)-dione (**2**).* The above acid chloride **22** (2.3 g, 8.4 mmol) was dissolved in 15 mL dichloromethane. Aluminium trichloride (3.4 g, 25.5 mmol) was then added as a catalyst. The resulting mixture was stirred at room temperature for 12 h. After hydrolysis, extraction, and evaporation, the residue was recrystallized from acetone to give ketone **2** as brown solid in 76% yield; TLC R_f (dichloromethane/methanol 95/5)=0.21; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.47–2.64 (m, 2H, CH_2CH_2CH), 2.68–2.89 (m, 2H, CH_2CH_2CH), 4.71 (t, J=8.1 Hz, 1H, CH_2CH_2CH), 7.62 (t, J=7.3 Hz, 1H, ArH), 7.67 (t, J=7.3 Hz, 1H, ArH), 7.76 (dd, J=8.3, 1.3 Hz, 1H, ArH), 8.17 (dd, J=8.2, 1.4 Hz, 1H, ArH), 8.29 (dd, J=7.3, 1.4 Hz, 1H, ArH), 8.55 (dd, J=7.7, 1.3 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.1 (CH_2), 31.3 (CH_2), 63.3 (CH), 118.2 (CH), 124.2 (CH), 124.6 (C), 125.5 (CH), 125.9 (CH), 126.1 (C), 126.9 (CH), 131.3 (C), 133.2 (C), 134.9 (CH), 173.7 (C), 192.8 (C). IR: ν cm^{-1}: 1696, 1653, 1508, 1464, 1405, 1375, 1351, 1335, 1267, 1148. Anal. Calcd for $C_{15}H_{11}O_2N$: C 75.94, H 4.67, N 5.90; found: C 75.58, H 4.88, N, 5.80.

*4.1.14. 10H-Benzo[de]pyrrolo[1,2-a]quinolin-10-one (**4**).* A stirred mixture of ketone **2** (Scheme 4) (0.15 g, 0.632 mmol) in polyphosphoric acid (8 mL) was heated at 140 °C for 6 h. The hot mixture was decanted over crushed ice. The aqueous solution was extracted with dichloromethane. The organic phase was washed with distilled water, dried (magnesium sulfate), filtered, and concentrated in vacuo to give a brown oil which was treated at room temperature overnight in dichloromethane with activated carbon and filtered to give ethylenic compound **4** (Scheme 5) as brown solid in 32% yield; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 6.31 (s, 1H, CH), 6.41 (d, J=5.6 Hz, 1H, CH=CH), 7.25 (d, J=5.6 Hz, 1H, CH=CH), 7.76–8.60 (m, 6H, ArH).[13]C NMR ($CDCl_3$, 50 MHz) δ 105.1 (CH), 127.4

(CH), 129.9 (CH), 130.2 (CH), 131.2 (CH), 133.4 (CH), 133.6 (C), 135.5 (C), 136.9 (C), 142.2 (CH), 142.4 (C), 143.3 (CH), 144.9 (C), 156.1 (CH), 169.7 (C). IR: ν cm^{-1}: 1660, 1645, 1529, 1432, 1401, 1380, 1351, 1335, 1125. Anal. Calcd for $C_{15}H_9ON$: C 82.18, H 4.14, N 6.39; found: C 82.57, H 4.32, N, 6.49.

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References and notes

1. Miquel, J.; Economos, A. C.; Fleming, J. E.; Johnson, J. E. *Exp. Gerontol.* **1980**, *15*, 575; Harman, D. *Age* **1995**, *18*, 51.
2. De la Fuente, M.; Ferrández, M. D.; Burgos, M. S.; Soler, A.; Prieto, A.; Miquel, J. *Can. J. Physiol. Pharmacol.* **1998**, *76*, 373.
3. Rigo, B.; Kolocouris, N. *J. Heterocycl. Chem.* **1983**, *20*, 893.
4. Akué-Gédu, R.; Bourry, A.; Camus, F.; Norberg, B.; Durant, F.; Couturier, D.; Debacker, M.; Rigo, B. *Heterocycles* **2004**, *63*, 1855.
5. Bourry, A.; Couturier, D.; Sanz, G.; Van Hijfte, L.; Hénichart, J.-P.; Rigo, B. *Tetrahedron* **2006**, *62*, 4400.
6. Rigo, B.; Akué-Gédu, R. *Targets Heterocycl. Syst.* **2006**, *10*, 232.
7. Rackova, L.; Firakova, S.; Kostalova, D.; Stefek, M.; Sturdik, E.; Majekova, M. *Bioorg. Med. Chem.* **2005**, *13*, 6477.
8. Rackova, L.; Snirc, V.; Majekova, M.; Majek, P.; Stefek, M. *J. Med. Chem.* **2006**, *49*, 2543.
9. Dutta, S.; Padhye, S.; Priyadarsini, K. I.; Newton, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2738.
10. Rigo, B.; Tulier, E.; Barbry, D.; Couturier, D.; Warin, V.; Lamiot, J.; Baert, F. *J. Heterocycl. Chem.* **1990**, *27*, 1383.
11. Bourry, A.; Akué-Gédu, R.; Rigo, B.; Hénichart, J.-P.; Sanz, G.; Couturier, D. *J. Heterocycl. Chem.* **2003**, *40*, 989.
12. Rigo, B.; Gautret, P. *Tetrahedron Lett.* **2006**, *47*, 295; Artico, M.; Nacci, V.; De MartinoC. *Ann. Chim.* **1967**, *57*, 1115; Nacci, V.; Campiani, G.; Garofalo, A. J. *Heterocycl. Chem.* **1990**, *27*, 1329.
13. Cauliez, P.; Rigo, B.; Fasseur, D.; Couturier, D. *J. Heterocycl. Chem.* **1991**, *28*, 1143.
14. Muci, A. R.; Buchwald, S. L. Practical palladium catalysts for C–N and C–O bond formation. In *Topics in Current Chemistry*; Miyaura, N., Ed.; Springer: Berlin, 2002; Vol. 219, p 133; Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041.
15. Desmarets, C.; Schneider, C.; Fort, Y. *J. Organomet. Chem.* **2002**, *67*, 3029; Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003**, *68*, 1190.
16. Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269.
17. Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607.
18. Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035; Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539; Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381.
19. Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.
20. Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.
21. Browning, R. G.; Badarinarayaha, V.; Mahmud, H.; Lovely, C. J. *Tetrahedron* **2004**, *60*, 359.
22. Chang, J. W. W.; Xu, X.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 245; Sperotto, E.; De Vries, J. G.; Van Klink, G. P. M.; Van Koten, G. *Tetrahedron Lett.* **2007**, *48*, 7366.
23. However $Pd_2(dba)_3$/Xantphos coupling of ethyl pyroglutamate with 2-bromobenzaldoxime benzylether was reported to give a quantitative yield of *N*-aryl pyroglutamic ester.[24]
24. Miyata, O.; Shirai, A.; Yoshino, S.; Takeda, Y.; Sugiura, M.; Naito, T. *Synlett* **2006**, 0893; Shirai, A.; Miyata, O.; Tohnai, N.; Miyata, M.; Procter, D. J.; Sucunza, D.; Naito, T. *J. Org. Chem.* **2008**, *73*, 4464.
25. Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Schedel, H. *J. Am. Chem. Soc.* **2007**, *129*, 12890.
26. Ma, D.; Cai, Q. *Synlett* **2004**, 0128.
27. Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809.
28. Benzylation of pyroglutamic acid mediated by $[Cu(OH)\cdot TMEDA]_2Cl_2$ was also described: Kumaraswamy, G.; Pitchaiah, A.; Ramakrishna, G.; Ramakrishna, D. S.; Sadaiah, K. *Tetrahedron Lett.* **2006**, *47*, 2013.
29. A triamine was tested without results in the copper-catalyzed nitration 4-iodoanisole: Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715.
30. The N-donor tripod ligand **L_4** was recently used for a copper-catalyzed Ullmann diaryl ether synthesis: Jogdand, N. R.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2009**, *50*, 4019; these authors have also described the thioetherification of thiols with aryl halides in presence of the same **L_4** ligand: Jogdand, N. R.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2009**, *50*, 6092.
31. The choice of testing trident tris(3,6-dioxaheptyl)amine **L_5** was based on its confirmed importance in a copper-catalyzed diaryl ether synthesis from inactivated aryl halides: Soula, G. *J. Org. Chem.* **1985**, *50*, 3717.
32. Goodbrand, H. B.; Bender, T. P.; Gaynor, R. E.; Murphy, L. U.S. 2005/0234272; *Chem. Abstr.* **2005**, *143*, 386760.
33. Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.
34. Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Organomet. Chem.* **1973**, *38*, 4071; Boger, D. L. *J. Org. Chem.* **1978**, 2296.
35. For some reactions of *N*-acyliminium salts analog to **12**, see: Ref. 6 and references cited therein.
36. In non-anhydrous conditions, lactam ring opening followed by another type of allylic dehydration could lead to benzoquinoline.[4]
37. Giang, L.; Fetter, J.; Kajtár-Peredy, M.; Lempert, K.; Bertha, F.; Keseru, G. M.; Czira, G. *J. Chem. Res., Synop.* **2000**, *5*, 0601.
38. Giang, L.; Fetter, J.; Lempert, K.; Kajtár-Peredy, M.; Gömöry, A. *Tetrahedron* **1996**, *52*, 10169.
39. Jpn. Kokai Tokkyo Koho JP 59065071; *Chem. Abstr.* **1984**, *101*, 110897.
40. Bertha, F.; Giang, L.; Fetter, J.; Kajtár-Peredy, M.; Lempert, K.; Czira, G. *J. Chem. Res., Synop.* **2003**, *12*, 759 M1224.
41. Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Bellus, D. *Tetrahedron* **1985**, *41*, 4057.