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Palladium-Assisted Multicomponent Synthesis of 2-Aryl-4-aminoquinolines and 2-Aryl-4-amino[1,8]naphthyridines

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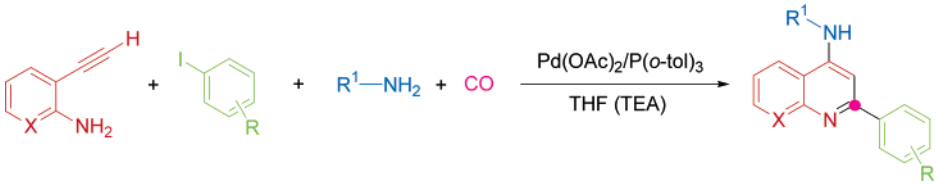

A palladium-mediated multicomponent domino reaction leading to 2-aryl-4-amino-quinolines and 2-aryl-4-amino[1,8]naphthyridines is reported. The scope of the reaction was examined using carbon monoxide, two 2-ethynyl-arylamines, four aryl iodides, and 10 primary amines as substrates. The selection of the appropriate catalytic system was achieved testing several palladium/phosphine systems and overrides previously reported drawbacks associated with the use of primary amines in related reactions. Moreover several features concerning the role of both palladium [(0) and (II)] and phosphines are reported.

Introduction

Multicomponent reactions allow the coupling of three or more simple and flexible building blocks in a one-pot operation, giving rise to complex structures by simultaneous formation of two or more bonds, according to the domino principle. Multicomponent reactions fulfill the requirements of an environmentally friendly process by reducing the number of synthetic steps, the energy consumption and the waste production.[1] Moreover, over the past 10 years industrial and academic researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis, as demonstrated by the increase in the literature devoted to this research field.[2] The success of palladium-catalyzed reactions for the development of multicomponent processes is based on the high levels of chemo-, regio-, and stereoselectivity achieved and the functional group tolerance observed.[3] In addition, these reactions accomplish a large chemical diversity in the new bonds formed.[4]

Our recent research efforts directed toward the synthesis of functionalized heterocycles through transition-metal-catalyzed[5] and uncatalyzed[6] domino processes led us to attain pyrroles, pyrrolo[3,2-c]pyrazolones, pyridines, quinolines, β-carbolines, naphthyridines, isoxazolo[4,5-c]quinolines, and pyrazino[1,2-a]indoles.

In particular, we recently reported[6a,d,7] a new synthetic approach to 2,4-disubstituted quinolines and [1,8]naphthyridines through conjugate stereoselective addition/cyclization domino reactions of nucleophiles with β-(2-aminoaryl)-α,β-ynones, which in turn can be easily prepared

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(1) Clark, J.; Macquarrie, D. In *Handbook of Green Chemistry & Technology*; Blackwell Science Ltd.: Oxford, 2002.

(2) For recent reviews, see: (a) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133−1144. (b) Bienaymé, H.; Hulme, C.; Tuch, A.; Walle, S. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH Verlag: Weinheim, 2002. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321−3329. (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210.

(3) (a) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201−216. (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101−4111.

(4) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: Hoboken, NJ, 2002.

(5) (a) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443−446. (b) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2715−2720. (c) Rossi, E.; Arcadi, A.; Abbiati, G.; Attanasi, O. A.; De Crescentini, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 1400−1402. (d) Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959−6966. (e) Abbiati, G.; Arcadi, A.; Bellinazzi, A.; Beccalli, E.; Rossi, E.; Zanzola, S. *J. Org. Chem.* **2005**, *70*, 4088−4095.

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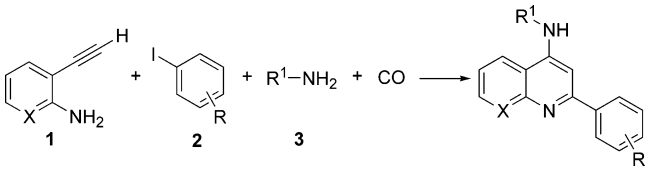
SCHEME 1



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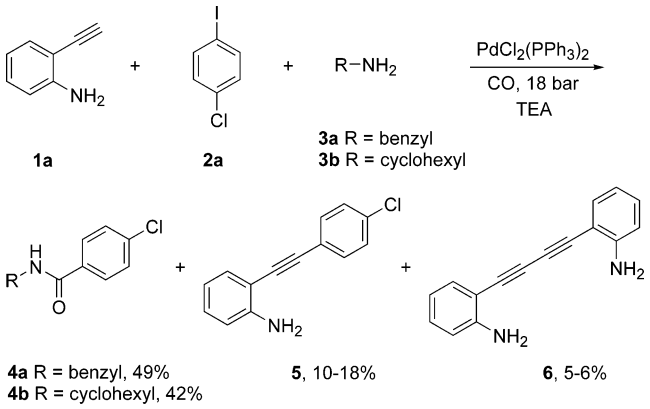


through a high yielding carbonylative coupling reaction of 2-trimethylsilylethynylarylamines with aryl iodides.[8]

In this work we show that palladium-assisted multicomponent reactions starting from 2-ethynylarylamines **1**, aryl iodides **2**, primary amines **3**, and carbon monoxide can lead to the same nucleus in a one-pot procedure, Scheme 1.

Some years ago, Torii and co-workers[9] described a palladium-catalyzed multicomponent domino reaction giving rise to 2-aryl-4-dialkylaminoquinolines in moderate to good yields. The reaction was performed with 2-ethynylarylamines, aryl iodides, and dialkylamines or dialkylamines/triethylamine, at 70 °C under a carbon monoxide atmosphere (18 bar) in the presence of 5% $PdCl_2(PPh_3)_2$. However, as reported by Torii, this procedure is effective only with secondary amines and when we tried to perform the same reaction with 2-ethynylphenylamine **1a**, 1-chloro-4-iodobenzene **2a**, and carbon monoxide as substrates, in the presence of benzylamine **3a** or cyclohexylamine **3b**, the corresponding amides **4a,b** were isolated beside the Sonogashira cross-coupling product **5** and the dimer **6**, Scheme 2.

Thus, in the presence of primary amines, a palladium-catalyzed carbonylative amidation reaction, instead of a carbonylative cross-coupling reaction, takes place. The basicity of the amines employed was found to be influential in the carbonylative cross-coupling of terminal alkynes with aryl iodides and it has been reported that good results can be obtained using secondary amines both as a solvent and base.[10] Therefore, under Torii conditions, the nature of the amine employed could be the actual setback. Nevertheless, further than bases, the nature of solvent, catalyst, and carbon monoxide pressure, as well as the temperature, usually play a pivotal role on the reaction outcome of terminal alkynes with aryl iodides under carbonylative conditions.[11] So, we felt encouraged to explore the possibility to redirect the carbonylative palladium-catalyzed coupling of derivatives **1** with aryl iodides, in the presence of primary amino groups, toward the formation of the desired quinolines **7** through the appropriate choice of catalyst, ligand, solvent, and reaction temperature. In this work we wish to report the full details of our investigations.

Results and Discussion

Using 2-ethynylphenylamine **1a**, 1-chloro-4-iodobenzene **2a**, benzylamine **3a**, and carbon monoxide as model system, a comprehensive review of reaction conditions that we tested for the synthesis of quinoline **7a** is presented in Table 1. All reactions were performed in a stainless steel reactor at 100 °C for 24 h under a carbon monoxide atmosphere (6 bar), using the following molar ratios: **1a/2a/3a**/Pd catalyst/phosphine ligand = 1:1:3:0.05:0.07.

Palladium(0) complexes with strongly coordinated phosphines direct the reaction toward competitive formation of amide **4a**, and the quinoline **7a** was isolated in poor yield (entries 1 and 2). Ligandless palladium salt catalyst $Pd(OAc)_2$ gave rise to a satisfactory products ratio between **7a** and **4a**. However, a large amount of starting material was recovered alongside the required product (entry 3); very likely the precipitation of the catalyst occurs before the reaction is complete. Palladium acetate was thus tested in combination with several ligands and solvents. $Pd(OAc)_2$/phosphine catalytic systems were prepared in situ from $Pd(OAc)_2$ and the corresponding phosphine derivative in a 1:1.4 ratio. We have not investigated the effect of the Pd/P ratio on the reaction outcome. Bidentate phosphine ligands 1,1′-bis(diphenylphosphino)ferrocene (DPPF) and bis[(2-diphenylphosphino)phenyl]ether (DPPPE) (entries 4−7) yield almost equimolecular amount of amide **4a** and quinoline **7a**, and comparable results were obtained with the more basic bidentate 1,4-bis(diphenylphosphino)butane (DPPB) (entry 8), with poor total yield in the latter case. Besides, the reaction medium seems to have little influence on the reaction outcome (entries 4−6), and tetrahydrofuran was selected as solvent because it can be more easily removed from the reaction mixture with respect to DME or DMF. Thus, monodentate phosphine ligands were tested from the electrophilic tri(2-furyl)phosphine (TFP)

(6) (a) Arcadi, A.; Rossi, E.; Marinelli, F. *Tetrahedron* **1999**, *55*, 13233−13250. (b) Abbiati, G.; Beccalli, E.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, 2477−2483. (c) Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E. *Tetrahedron Lett.* **2001**, *42*, 3705−3708. (d) Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E. *Synthesis* **2002**, 1912−1916. (e) Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E. *Eur. J. Org. Chem.* **2003**, 1423−1427. (f) Abbiati, G.; Beccalli, E.; Arcadi, A.; Rossi, E. *Tetrahedron Lett.* **2003**, *44*, 5331−5334.

(7) Rossi, E.; Abbiati, G.; Canevari, V.; Nava, D.; Arcadi, A. *Tetrahedron* **2004**, *60*, 11391−11398.

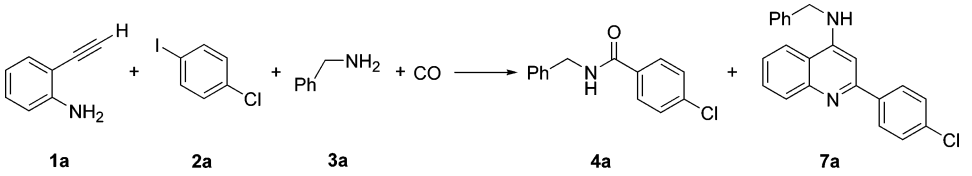
(8) Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **1999**, 401−404.

(9) Torii, S.; He Xu, L.; Sadakane, M.; Okumoto, H. *Synlett* **1992**, 513−514.

(10) (a) Torii, S.; Okumoto, H.; He Xu, L.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *49*, 6773−6784. (b) Kalinin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. *Tetrahedron Lett.* **1992**, *33*, 373−376. (c) Kalinin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. *Tetrahedron Lett.* **1990**, *31*, 4073−4076.

(11) (a) Arcadi, A.; Rossi, E. *Tetrahedron Lett.* **1996**, *37*, 6811−6814. (b) Delaude, L.; Masdeu, A. M.; Alper, H. *Synthesis* **1994**, 1149−1151. (c) Brocato, E.; Castagnoli, C.; Catellani, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1992**, *33*, 7433−7436. (d) An, Z.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1990**, *397*, C31−32. (e) Tamaru, Y.; Ochiai, H.; Yoshida, Z.-i. *Tetrahedron Lett.* **1984**, *25*, 3861−3864. (f) Kobayashi, T.; Tanaka, M. *J. Chem. Soc. Chem. Commun.* **1981**, 333−334.

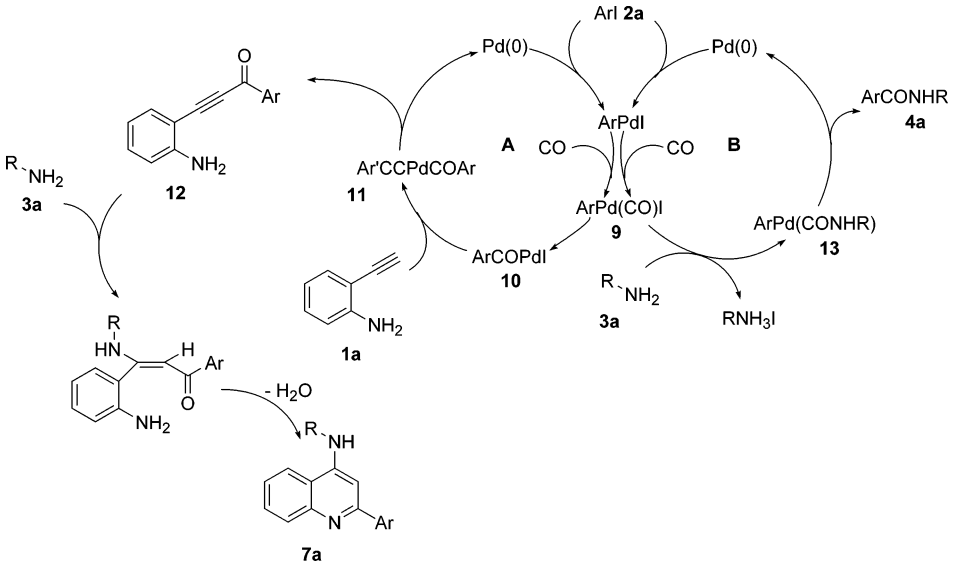
TABLE 1. Four-Component Synthesis of Quinoline 7a; Review of Conditions[a,b]



entry	catalytic system (palladium/ligand ratio)	solvent	temp (°C)	% yield 1a	% yield 4a	% yield 7a
1	$Pd(PPh_3)_4$	THF	100		61	30
2	$Pd_2(dba)_3$/TTP (1:1.4)	THF	100	32	35	10
3	$Pd(OAc)_2$	THF	100	34	7	43
4	$Pd(OAc)_2$/DPPF (1:0.7)	DMF	100		43	43
5	$Pd(OAc)_2$/DPPF (1:0.7)	DME	100		40	53
6	$Pd(OAc)_2$/DPPF (1:0.7)	THF	100		36	55
7	$Pd(OAc)_2$/DPPPE (1:0.7)	THF	100		35	29
8	$Pd(OAc)_2$/DPPB (1:0.7)	THF	100		20	15
9	$Pd(OAc)_2$/TFP (1:1.4)	THF	100	40	13	18
10	**$Pd(OAc)_2$/TTP (1:1.4)**	**THF**	**100**		**17**	**73**
11	$Pd(OAc)_2$/PPh_3 (1:1.4)	THF	100		38	56
12	$Pd(OAc)_2$/TBP (1:1.4)	THF	100	18	14	16
13	$PdCl_2$/TTP	THF	100		15	68

[a] Yields refer to single runs and are given for pure isolated products. [b] Sonogashira cross-coupling product **5** was detected in the crude by ^1H NMR in 5−10% yield.

SCHEME 3



to the basic tributylphosphine (TBP), including the almost neutral tri(*o*-tolyl)phosphine (TTP) and the fairly basic PPh_3 (entries 9−12). As reported in entry 10, the use of 5% $Pd(OAc)_2$ and 7% TTP in THF at 100 °C allows the almost chemoselective synthesis of **7a** with complete consumption of 2-ethynylphenylamine **1a** and restraint of amide **4a** formation. High conversion yields but low chemoselectivity was observed with triphenylphosphine, whereas both the electrophilic and basic phosphines TFP and TBP show low selectivity and low conversion yield (entries 9 and 12). Finally, change from $Pd(OAc)_2$ to $PdCl_2$ has little effect on the reaction outcome (entry 13).

The proposed reaction mechanism for the formation of quinoline **7a** and amide **4a** is depicted in Scheme 3 and involves two catalytic cycles, cycle A giving rise to **7a** through the intermediacy of the ynone derivative **12** and cycle B giving rise to **4a**. Both catalytic cycles entail the oxidative addition of Pd(0) to the aryl iodide **2a** followed by coordination of carbon monoxide to give the aryl-carbonyl palladium species **9**.[12a] For ynone **12** formation from **9**, 1,2-aryl migration from palladium to coordinated CO generates the aroyl palladium complex **10** and subsequent addition of the incipient acetylide anion derived from **1a** gives rise to a *σ*-alkynyl-*σ*-acylorgano-palladium complex **11**, whereas reductive elimination is the final step.[12a,b] From **12** and benzylamine **3a**, a domino process of inter-/intramolecular nucleophilic attack, followed by elimination of water, leads to the formation of quinoline **7a**. The competitive formation of amide **4a** starting from complex **9** involves, as established by

(12) (a) Negishi, E.-i. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 2, Chapter VI.1, p 2309. (b) Tamaru, Y.; Kimura, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 2, Chapter VI.2.2, Section I, p 2447.

Yamamoto and co-workers,[13] nucleophilic attack of amine **3a** on the C=O ligand, yielding the arylcarbamoyl complex **13** that finally gives the corresponding amide **4a** by reductive elimination.

Thus, the influence of phoshine ligands on the reaction outcome should be rationalized in terms of speeding up cycle A with respect to cycle B and, in particular, starting from **9**, the 1,2-aryl migration versus nucleophilic attack of amine **3a**. In general, phosphines have different steric effects and electronic properties and often their role cannot be clearly understood or predictable. Recent investigations have indicated that more electrophilic palladium complexes containing less sterically hindered phosphines exhibit high reactivity toward the coordination of alkenes or alkynes to bring about efficient carbonylation reactions.[14] In our procedure the use of a palladium complex with weakly coordinated and neutral ligand such TTP looks to be effective for the selectivity of the reaction. It is clear from Table 1 that we need a ligand that is weak enough to favor the coordination of the acylpalladium complex **10** to the 2-aminophenylacetylene **1a** but strong enough to keep palladium in solution.[15] Moreover, the bulkiness of TTP favors the 1,2-aryl migration in complex **9**.[16]

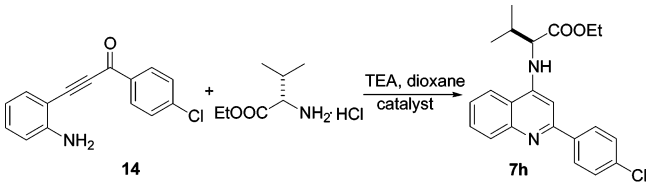
Also bidentate phosphine ligands such DPPF and DPPPE could accelerate the 1,2-aryl migration, forcing a *cis* relationship between coordinated carbon monoxide and aryl group in complex **9**.[17] However, the palladium complex containing bidentate phosphine ligands shows greater thermal stability and dissociates slowly compared to the palladium complex containing monodentate ligands, thus slowing down the migratory insertion step.[18] Probably for the same reason also monodentate basic phosphine ligands PPh_3 and TBP and the bidentate DPPB gave unsatisfactory results. On the contrary the palladium(0) complex with poorer σ-donor ligands TFP could speed up the conversion of **9** to **10** through the migratory insertion step; however, the same complex is found to be less reactive than neutral or basic complex in the oxidative addition with aryl iodides, and this effect appears to be overriding in our process, as demonstrated by the recovering of unreacted starting 2-ethynylphenylamine **1a** under these conditions.[19]

Starting from these results a series of 2-ethynylarylamines, primary amines, and aryl iodides was tested under our reaction conditions with carbon monoxide. Starting materials and obtained 2-aryl-4-aminoquinolines and 2-aryl-4-amino-6-methyl[1,8]naphtiridines **7a**−**q** are listed in Table 2.

The reactions with aliphatic primary amines **3b** and **3j** were performed as described for **3a**, whereas aniline derivatives **3c**−**d**, with pK_a values higher than those of **3a**, **3b**, and **3j**, gave better results when the reactions were performed in triethylamine instead of THF as solvent, the more basic medium probably affecting the migratory insertion step by activation of the terminal hydrogen atom of the alkyne moiety of **1**.[20] Moreover, the reactions employing amines **3e**−**i**, which were purchased as hydrochlorides, were run in the presence of an excess of triethylamine (15 equiv).

It is worth noting that we previously reported[7] that amines bearing an electron-withdrawing group in the α-position, such as **3e**−**i**, did not react with ynones to yield quinoline rings and the starting materials were recovered unreacted even after prolonged heating in toluene at reflux. Thus, in the one-pot reactions described here, a catalytic role must be attributed to the palladium/phosphine system also in the intermolecular nucleophilic attack of **3** on ynone **12** (Scheme 3). This hypothesis was confirmed by heating the β-(2-aminophenyl)-α,β-ynone **14**[8] and valine ethylester **3h** in dioxane at 100 °C with 15 equiv of triethylamine without catalyst or in the presence of our standard catalytic system ($Pd(OAc)_2$/TTP) (Scheme 4). Quinoline **7h** was isolated in 68% yield only in the catalyzed reaction.

SCHEME 4



Entry	Catalyst	Yield
1	-	0
2	$Pd(OAc)_2$ 5%/TTP 7%	68
3	$ZnCl_2$ 5%	73
4	$Pd[P(Ph)_3]_4$ 5%	75
5	$NaAuCl_4$ 5%	78

Thus, at a first glance the formation of **7h** is the result of a sequential palladium-catalyzed reaction involving carbonylative coupling followed by the aza-Michael addition of lysine ethyl ester **3h** to ynone **14**. The first part of the overall reaction thus requires palladium(0) as catalyst, while the second one needs palladium(II). Likely, some palladium species, present in the reaction mixture, give rise to palladium(II) catalyst. However, the multicomponent reactions described above and the domino reaction reported in Scheme 4 are both performed in a reducing medium, with respect to Pd(II) salt, due to the presence of an excess of amine and carbon monoxide in the first case and of amine in the latter, and under these conditions, Pd(II) species are easily reduced to Pd(0).[21] A reasonable pathway that could account for the forma-

(13) (a) Mori, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 2, Chapter VI.2, Section B, pp 2314−2322. (b) Huang, L.; Ozawa, F.; Yamamoto, A. *Organometallics* **1990**, *9*, 2603−2611. (c) Ozawa, F.; Soyama, H.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235−3245.

(14) Hu, Y.; Zhang, Y.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365−2368 and references therein.

(15) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2770.

(16) Ozawa, S.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1987**, *6*, 1640−1651.

(17) (a) Tsuji, J. Transition Metal Reagents and Catalysts. In *Innovation in Organic Synthesis*; Wiley: New York, 2000; Chapter 2.2.2, p 14. (b) Lee, J. S.; Lee, S. M.; Kim, K. D.; Cho, N. S.; Oh, J. S. *J. Mol. Catal.* **1993**, *81*, 17−25.

(18) Choueiry, D.; Negishi, E.-i. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, Chapter II.2, p 41.

(19) (a) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997−1030. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595. (c) Amatore, C.; Jutand, A.; Meyer, G.; Atmani, H.; Khalil, F.; Chahdi, F. O. *Organometallics* **1998**, *17*, 2958−2964.

(20) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, M. L. *Tetrahedron* **2003**, *59*, 4661−4671. (b) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403−6406.

TABLE 2. Prepared 2-Aryl-4-aminoquinolines and 2-Aryl-4-amino-6-methyl-1,8-naphthyridines 7a–q

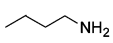
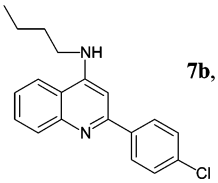
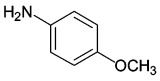
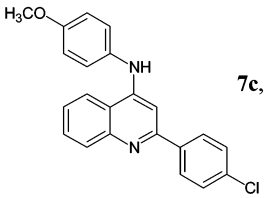
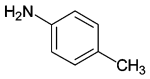
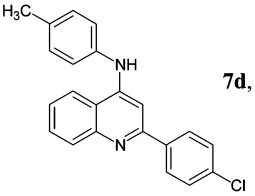
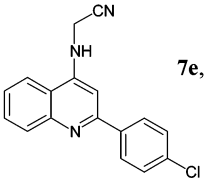
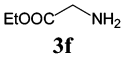
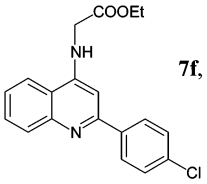
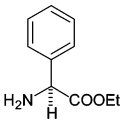
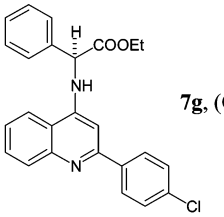
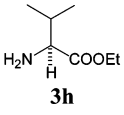
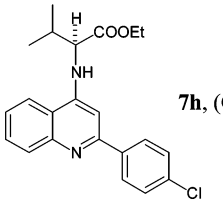
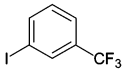
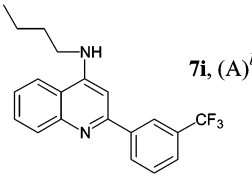
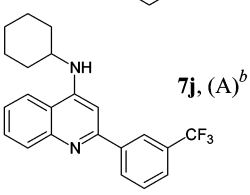
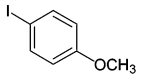
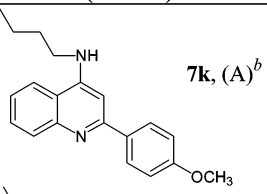
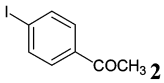
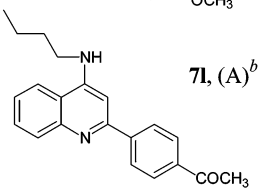
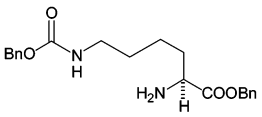
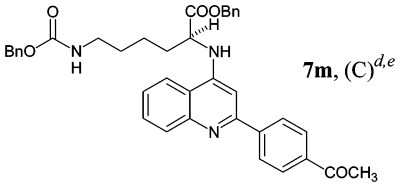
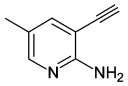
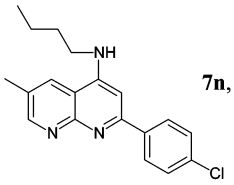
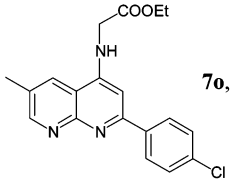
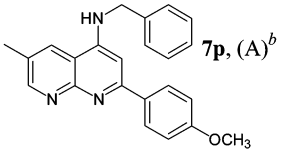
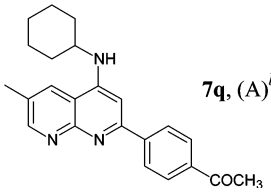
Ethynyl-arylamines 1	Aryl iodides 2	Amines 3	Quinolines and naphthyridines 7 (method)	Yield %[a]
1a	**2a**	 **3b**	 **7b**, (A)[b]	80
1a	**2a**	 **3c**	 **7c**, (B)[c]	47
1a	**2a**	 **3d**	 **7d**, (B)[c]	62
1a	**2a**	 **3e**	 **7e**, (C)[d]	45
1a	**2a**	 **3f**	 **7f**, (C)[d]	42
1a	**2a**	 **3g**	 **7g**, (C)[d,e]	59
1a	**2a**	 **3h**	 **7h**, (C)[d,e]	57
1a	 **2b**	**3b**	 **7i**, (A)[b]	99
1a	**2b**	 **3j**	 **7j**, (A)[b]	89

TABLE 2 (Continued)

Ethynyl-arylamines 1	Aryl iodides 2	Amines 3	Quinolines and naphthyridines 7 (method)	Yield %[a]
1a	 **2c**	**3b**	 **7k**, (A)[b]	50
1a	 **2d**	**3b**	 **7l**, (A)[b]	58
1a	**2d**	 **3i**	 **7m**, (C)[d,e]	48
 **1b**	**2a**	**3b**	 **7n**, (A)[b]	52
1b	**2a**	**3f**	 **7o**, (C)[d]	64
1b	**2c**	**3a**	 **7p**, (A)[b]	65
1b	**2d**	**3j**	 **7q**, (A)[b]	88

[a] Yields refer to pure isolated products after chromatographic purification. [b] Method A: reaction performed in THF (4 mL) using the following molar ratios: **1/2/3**/Pd catalyst/phosphine ligand = 1:1:3:0.05:0.07. [c] Method B: reaction performed in TEA (4 mL) using the following molar ratios: **1/2/3**/Pd catalyst/phosphine ligand = 1:1:3:0.05:0.07. [d] Method C: reaction performed in THF (4 mL) and in the presence of 15 equiv of triethylamine using the following molar ratios: **1/2/3**/Pd catalyst/phosphine ligand = 1:1:3:0.05:0.07. [e] The stereospecificity of the reactions performed with chiral amino acids **3g**−**i** was determined by enantioselective HPLC analysis of (*S*)-**7g** in comparison with the (*RS*) mixture and extended by analogy to the entire series.

tion of a palladium(II) complex involves nuclephilic attack of amines or amine activation by oxidative addition of a N−H bond to the metal followed by hydrometalation of alkyne.[22] Nevertheless, as demonstrated by the result obtained in the experiments performed in the presence either of Pd(0) derivatives or zinc(II) and Au(III) derivatives, the sequential aza-Michael/cyclization reaction of α,*β*-ynones with α-amino esters occurs in the presence of all of these catalysts (Scheme 4). Several transition metal salts have been reported to efficiently catalyze aza-Michael reaction of enones by acting as powerful Lewis acids.[23] Au(I)-catalyzed highly efficient intermolecular

(21) Negishi, E.-i. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, Chapter I.2, Section C, p 31.

(22) (a) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104−114. (b) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12670−12671. (c) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−704.

hydroamination reactions have also been described.[24] So, an alternative mechanism that leads to the quinoline derivative **7** involving a palladium catalyst that acts simultaneously[25] both as transition metal in the Pd(0) oxidation state and as Lewis acid in the Pd(II) oxidation state cannot be ruled out.

Conclusion

In conclusion, we reported a multicomponent domino reaction leading to 2-aryl-4-amino-quinolines and -[1,8]-naphthyridines starting from carbon monoxide, 2-ethynyl-arylamines, aryl iodides, and primary amines. The palladium-mediated process involves a triple domino sequence, e.g., carbonylative coupling between 2-ethynyl-arylamines and aryl iodides followed by inter- and intramolecular nucleophilic addition to a carbon−carbon triple bond and carbon−oxygen double bond, respectively. The reaction, performed for the first time with primary amine, overrides the drawback reported for the procedure developed by Torii, which was effective only with secondary amines. The success of the synthetic cycle is related to the correct selection of the appropriate catalytic system that suppresses the competitive palladium-catalyzed carbonylative amidation reaction, thus demonstrating that chemoselectivity in multicomponent palladium mediated process can be improved by a careful tuning of the reaction parameters.

Finally, some insights about the reaction mechanism are reported, the influence of phosphine ligands on the first step of the domino sequence (carbonylative coupling versus carbonylative amidation reaction) has been elucidated, and the observed catalytic effect of the palladium(0) and palladium(II) on the aza-Michael addition has been highlighted also by comparison with other transition metal derivatives.

These latter results also overcome the negative aspect envisaged in the multistep domino reaction previously reported[7] by our research group for the synthesis of 2-aryl-4-aminoquinolines and open up new prospects in the use of transition metals in these and related reactions.

Experimental Section

2-Aryl-4-aminoquinolines and 2-Aryl-4-amino-6-methyl-[1,8]naphthyridines, 7a−q. Method A. A nitrogen-flushed glass vessel was equipped with a stirring bar and charged with 2-ethynyl-arylamine **1** (1 mmol), aryl iodide **2** (1 mmol), amine **3** (3 mmol), and dry THF (4 mL). $Pd(OAc)_2$ (0.011 g, 5% mol) and TTP (0.021 g, 7% mol) were added, and the vessel was placed in a stainless steel reactor equipped with safety valve, manometer, and carbon monoxide inlet. Carbon monoxide was then charged up to 6 bar at room temperature, and the mixture was stirred overnight at 100 °C in an oil bath. After cooling, the gas was vented, the solvent was removed from the reaction mixture in a vacuum, and crude product was purified by flash chromatography over silica gel column (PE/EtOAc mixture).

Cyclohexyl-[2-(3-trifluoromethyl-phenyl)-quinolin-4-yl]-amine, 7j. Eluent for chromathography: PE/EtOAc (9:1). Yield: 0.330 g, 89%. Amorphous yellow solid. IR (KBr) ν 3437, 2933, 2856, 1587, 1534−1438, 1126, cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84−2.21 (m, 10H, CH_2), 3.62 (m, 1H, -HN-C*H*),4.98 (bm, 1H, NH, exchange with D_2O), 6.85 (s, 1H, H-3 quinoline), 7.38−7.48 (m, 1H, arom), 7.60−7.76 (m, 4H, arom), 8.05 (d, J = 8.8 Hz, 1H, arom), 8.25 (d, J = 7.3 Hz, 1H, arom), 8.27 (s, 1H, arom) ppm. ^{13}C NMR: δ 25.3, 26.1, 33.0, 51.8, 96.5, 116−132.6 (dq, $J_{1,2}$ = 272, 32 Hz), 117.9, 119.5, 124.7 (m), 125.1, 125.9, 129.1, 129.3, 129.9, 131.2, 138.6, 141.0, 147.5, 150.8, 151.3, 156.8 ppm. ESI-MS *m/z* (%): 371 [M^+ + 1] (100). $C_{22}H_{21}F_3N_2$ (370.42): calcd C 71.34, H 5.71, N 7.56; found C 71.52, H 5.72, N 7.70.

Method B. A nitrogen-flushed glass vessel was equipped with a stirring bar and charged with 2-ethynyl-arylamine **1** (1 mmol), aryl iodide **2** (1 mmol), amine **3** (3 mmol), and dry TEA (4 mL). $Pd(OAc)_2$ (0.011 g, 5% mol) and TTP (0.021 g, 7% mol) were added, and the vessel was placed in a stainless steel reactor equipped with safety valve, manometer, and carbon monoxide inlet. Carbon monoxide was then charged up to 6 bar at room temperature, and the mixture was stirred overnight at 100 °C in an oil bath. After cooling, the gas was vented, the solvent was removed from the reaction mixture in a vacuum, and crude product was purified by flash chromatography over silica gel column (PE/EtOAc mixture).

[2-(4-Chloro-phenyl)-quinolin-4-yl-amino]-acetonitrile, 7e. Eluent for chromathography: PE/EtOAc (from 95:5 to 85:15). Yield: 0.132 g, 45%. Brown dense oil. IR (KBr) ν 3401, 2925, 2852, 2220, 1593, 1537−1433 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.35 (m, 2H, CH_2), 5.91 (bs, 1H, NH, exchange with D_2O), 6.90 (s, 1H, H-3 quinoline), 7.30−7.50 (m, 3H, arom), 7.60−7.74 (m, 2H, arom), 8.00−8.11 (m, 3H, arom) ppm. ^{13}C NMR: δ 31.9, 97.6, 115.9, 118.2, 119.7, 125.7, 129.2 (two peaks overlapped), 130.3, 132.3, 135.7, 138.7, 143.6, 148.7, 157.2 ppm. ESI-MS *m/z* (%): 294 [M^+ +1] (100), 296 [M^+ + 3] (35). $C_{17}H_{12}ClN_3$ (293.76): calcd C 69.51, H 4.12, N 14.30; found C 70.12, H 4.37, N 14.61.

Method C. A nitrogen-flushed glass vessel was equipped with a stirring bar and charged with 2-ethynyl-arylamine **1** (1 mmol), aryl iodide **2** (1 mmol), amine hydrochloride **3** (3 mmol), TEA (1.51 g, 15 mmol), and dry THF (4 mL). $Pd(OAc)_2$ (0.011 g, 5% mol) and TTP (0.021 g, 7% mol) were added, and the vessel was placed in a stainless steel reactor equipped with safety valve, manometer, and carbon monoxide inlet. Carbon monoxide was then charged up to 6 bar at room temperature, and the mixture was stirred overnight at 100 °C in an oil bath. After cooling, the gas was vented, the solvent was removed from the reaction mixture in a vacuum, and crude product was purified by flash chromatography over silica gel column (PE/EtOAc mixture).

[2-(4-Chloro-phenyl)-quinolin-4-yl]-(4-methoxy-phenyl)-amine, 7c. Eluent for chromathography: PE/EtOAc (from 95:5 to 85:15). Yield: 0.170 g, 47%. Yellow solid. Mp: 156 °C. IR (KBr) ν 3435, 2998, 2929, 1587, 1529−1441 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.88 (s, 3H, OCH_3), 6.58 (bs, 1H, NH, exchange with D_2O), 7.01 (d, J = 8.8 Hz, 2H, arom), 7.13 (s, 1H, H-3 quinoline), 7.28 (d, J = 9.1 Hz, 2H, arom), 7.40 (m, 2H, arom), 7.48 (m, 1H, arom), 7.70 (dt, J = 1.1, 6.6 Hz, 1H, arom), 7.92 (m, 3H, arom), 8.09 (dd, J = 0.7, 8.4 Hz, 1H, arom) ppm. ^{13}C NMR: δ 55.8, 98.8, 115.3, 118.5, 119.7, 125.3, 126.2, 129.9, 130.4, 132.4, 135.3, 139.1, 149.3, 149.7, 157.2, 157.6 ppm. ESI-MS *m/z* (%): 361 [M^+ + 1] (100), 363 [M^+ + 3] (35). $C_{22}H_{17}ClN_2O$ (360.85): calcd C 73.23, H 4.75, N 7.76; found C 73.48, H 4.81, N 7.78.

Acknowledgment. Financial support from MURST is gratefully acknowledged.

Supporting Information Available: General experimental details and characterization data for compounds **7a−q**. This material is available free of charge via the Internet at http://pubs.acs.org. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050882Q

(23) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319−1322.
(24) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349−3352.
(25) Asao, N.; Nogami, T.; Takanashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764−765.