JOC Article

Versatile Synthesis of Quinoline-3-Carboxylic Esters and Indol-2-Acetic Esters by Palladium-Catalyzed Carbonylation of 1-(2-Aminoaryl)-2-Yn-1-Ols

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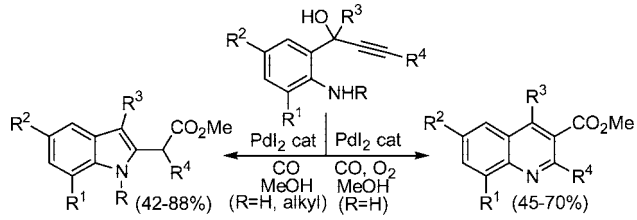

1-(2-Aminoaryl)-2-yn-1-ols, easily obtained by the Grignard reaction between 1-(2-aminoaryl)ketones and alkynylmagnesium bromides, were subjected to carbonylative conditions in the presence of the PdI_2−KI catalytic system, in the presence and in the absence of an external oxidant. Under oxidative conditions (80 atm of a 4:1 mixture of CO−air, in MeOH as the solvent at 100 °C and in the presence of 2 mol % of PdI_2 and 20 mol % of KI), 1-(2-aminoaryl)-2-yn-1-ols bearing a primary amino group were selectively converted into quinoline-3-carboxylic esters in fair to good yields [45−70%, based on starting 1-(2-aminoaryl)ketones], ensuing from 6-*endo-dig* cyclization followed by dehydration and oxidative methoxycarbonylation. On the other hand, indol-2-acetic esters, deriving from 5-*exo-dig* cyclization followed by dehydrating methoxycarbonylation, were selectively obtained in moderate to good yields [42−88%, based on starting 1-(2-aminoaryl)ketones] under nonoxidative conditions (90 atm of CO, in MeOH as the solvent at 100 °C and in the presence of 2 mol % of PdI_2 and 20 mol % of KI), in the case of 1-(2-aminoaryl)-2-yn-1-ols bearing either a primary or secondary amino group and substituted with a bulky group on the triple bond.

Introduction

During the last years, the intramolecular nucleophilic attack to a triple bond coordinated to Pd(II) followed by alkoxycarbonylation has proved to be one of the most important and powerful methodologies for the direct synthesis of carbonylated heterocycles starting from acyclic precursors.[1] In this area, we have shown that PdI_2 in conjunction with an excess of KI is a very useful and versatile catalyst for achieving several convenient syntheses of carbonylated heterocycles starting from suitably functionalized alkynes, under oxidative as well as nonoxidative conditions.[1a,b,k–m,2]

In this work, we have investigated the reactivity of 1-(2-aminoaryl)-2-yn-1-ols under carbonylative conditions in the presence of the PdI_2−KI catalytic system to develop new and selective synthetic approaches to carbonylated nitrogen heterocycles.

Results and Discussion

1-(2-Aminoaryl)ketones **1**−**5** were reacted with an excess of alkynylmagnesium bromides to give the corresponding (2-aminoaryl)-2-yn-1-ols, according to Scheme 1. The crude products **6**−**19** thus obtained could be used as substrates for the subsequent carbonylation reactions without further purification (see the Experimental Section for details).

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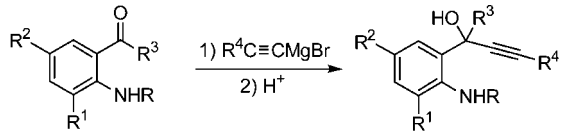
SCHEME 1



1 R=R^1=R^2=H, R^3=Me
2 R=R^2=H, R^1=OMe, R^3=Me
3 R=R^1=H, R^2=Cl, R^3=Me
4 R=R^1=R^2=H, R^3=Ph
5 R=R^3=Me, R^1=R^2=H
6 R=R^1=R^2=H, R^3=Me, R^4=Bu
7 R=R^2=H, R^1=OMe, R^3=Me, R^4=Bu
8 R=R^1=H, R^2=Cl, R^3=Me, R^4=Bu
9 R=R^1=R^2=H, R^3=Me, R^4=Ph
10 R=R^2=H, R^1=OMe, R^3=Me, R^4=Ph
11 R=R^1=H, R^2=Cl, R^3=Me, R^4=Ph
12 R=R^1=R^2=H, R^3=Me, R^4=*t*-Bu
13 R=R^2=H, R^1=OMe, R^3=Me, R^4=*t*-Bu
14 R=R^1=H, R^2=Cl, R^3=Me, R^4=*t*-Bu
15 R=R^1=R^2=H, R^3=Ph, R^4=*t*-Bu
16 R=R^1=R^2=H, R^3=Me, R^4=TMS
17 R=R^2=H, R^1=OMe, R^3=Me, R^4=TMS
18 R=R^1=R^2=H, R^3=Ph, R^4=TMS
19 R=R^3=Me, R^1=R^2=H, R^4=*t*-Bu

In principle, different reaction pathways can be followed when 1-(2-aminoaryl)-2-yn-1-ols bearing a primary amino group (R = H) are reacted in the presence of the PdI_2/KI catalytic system under carbonylative conditions (Scheme 2, anionic iodide ligands are omitted for clarity). In fact, the initial intramolecular attack by the amino group to the coordinated triple bond can occur in a 5-*exo-dig* (path a) or a 6-*endo-dig* (path b) cyclization mode, leading to isomeric vinylpalladium intermediates **I** and **II**, respectively, with formal elimination of HI. In contrast to intermediate **I**, however, complex **II** can easily undergo loss of water with simultaneous aromatization to give the 3-quinolinylpalladium species **III**. Under CO pressure, both complexes **I** and **III** can insert carbon monoxide, to give the corresponding acylpalladium intermediates **IV** and **V**, respectively. Eventually, nucleophilic displacement by an external alcohol should afford the corresponding heterocyclic derivatives **VI** and **20**, respectively, with elimination of H−Pd−I [which is known to be in equilibrium with Pd(0)+HI].[3] Because intermediate **VI** still contains an allyl alcoholic function, it can react further with H−Pd−I, according to a known reactivity,[4,5] to give the allylpalladium complex **VII**. Protonolysis of the latter by HI would then lead to the indol-2-acetic ester **21** with regeneration of the catalytically active species PdI_2. On the other hand, the process leading to the quinoline-3-carboxylic ester **20** (path c) may become catalytic only in the presence of an external oxidant, such as oxygen, able to reoxidize Pd(0) to PdI_2.[6] However, in the absence of an oxidant, a catalytic cycle is possible also starting with a 6-*endo-dig* cyclization mode, because intermediate **III** may undergo protonolysis by HI to give the noncarbonylated quinoline **22** with simultaneous regeneration of PdI_2 (path d). This latter reactivity has been recently reported by us.[7]

On the basis of these mechanistic hypotheses, we have studied the reactivity of 1-(2-aminoaryl)-2-yn-1-ols bearing a primary amino group (R = H), such as **6**−**18**, with CO and MeOH in the presence of the PdI_2/KI catalytic system under oxidative (using oxygen as the oxidant) as well as nonoxidative conditions to verify the possibility to find novel approaches to important carbonylated heterocyclic derivatives **20** and **21**, starting from readily available substrates.

The first substrate we tested was 2-(2-aminophenyl)oct-3-yn-2-ol **6** (R = R^1 = R^2 = H, R^3 = Me, R^4 = Bu). Crude **6**, obtained by the reaction between commercially available 1-(2-aminophenyl)ethanone **1** and 1-hexynylmagnesium bromide, was already suitable as substrate for the subsequent reactions without further purification (see the Experimental Section for details). Substrate **6** was initially reacted under oxidative conditions, in MeOH as the solvent (0.22 mmol of substrate per mL of MeOH) at 100 °C and under 20 atm of a 4:1 mixture of CO—air, and in the presence of PdI_2 (2 mol %) and KI as the catalyst (KI: PdI_2 = 10). The substrate conversion was complete after 2 h, and the main reaction product turned out to be 2-butyl-4-methylquinoline **23** (79% isolated yield, based on starting **6**), whereas the carbonylated quinoline **24** was formed only in traces (Table 1, entry 1). This result shows that, under the above conditions, **6** selectively undergoes 6-*endo-dig* cyclization (Scheme 2, path b) followed by dehydration and protonolysis (path d) rather than carbonylation (path c). Because it is known that protonolysis by HI is slowed down working under less concentrated conditions,[8] we next tried the reaction at 0.02 rather then 0.22 mmol of **6** per mL of MeOH. As expected, the quinoline-3-carboxylic ester **24** was now obtained in appreciable yield (33% isolated), quinoline **23** still being the main reaction product (62% isolated yield, Table 1, entry 2). This result did not significantly change working under more diluted conditions. In order to improve the selectivity toward **24**, the reaction was then carried out under a higher CO pressure, which was expected to favor the carbon monoxide insertion with respect to protonolysis. Indeed, under the same conditions of

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(4) The possibility of obtaining aπ-allylpalladium complex directly from the reaction between an allyl alcohol and a palladium hydride species without any activator was disclosed by us some years ago: (a) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Mol. Catal.* **1996**, *111*, 43–48. (b) More recently, the formation of an allylpalladium intermediate from allyl alcohols and a hydridopalladium complex has been reported: Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H. *Organometallics* **2004**, *23*, 1698–1707.

(5) The possibility of reducing an allyl alcohol moiety through the reaction with an H—Pd—I species with formation of aπ-allyl complex followed by protonolysis has been recently demonstrated by us: see references 2a, d, f and: (a) Gabriele, B.; Mancuso, R.; Salerno, G.; Plastina, P. *J. Org. Chem.* **2008**, *73*, 756–759. (b) Chiusoli, G. P.; Costa, M.; Cucchia, L.; Gabriele, B.; Salerno, G.; Veltri, L. *J. Mol. Catal. A: Chem.* **2003**, *204*, 133–142.

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SCHEME 2

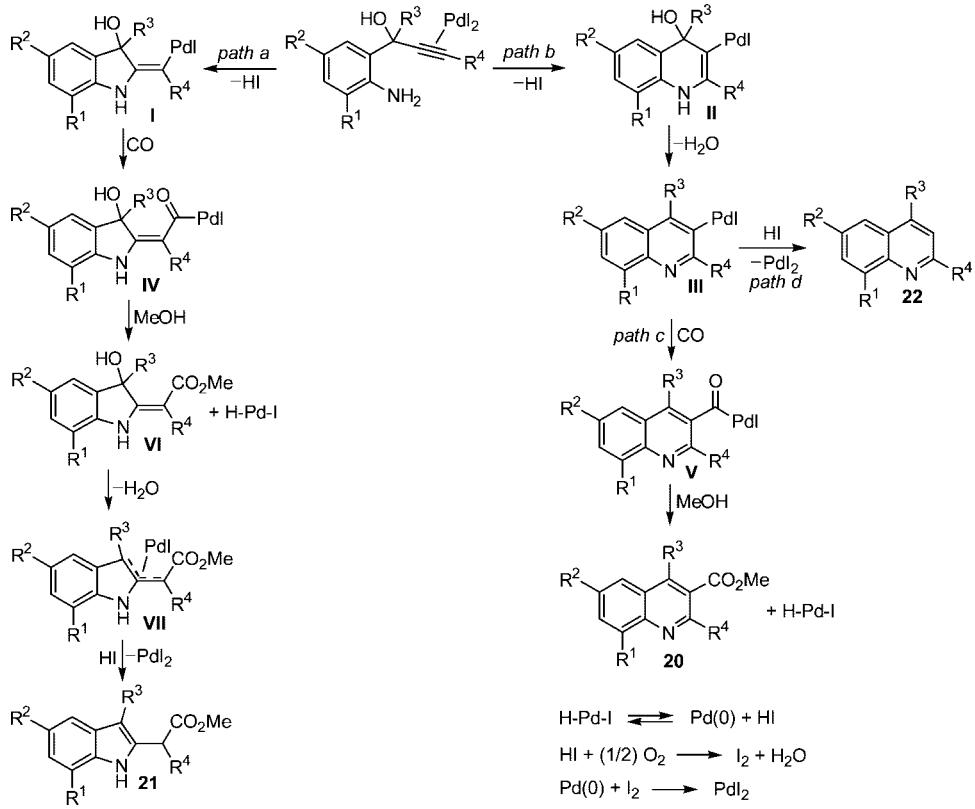
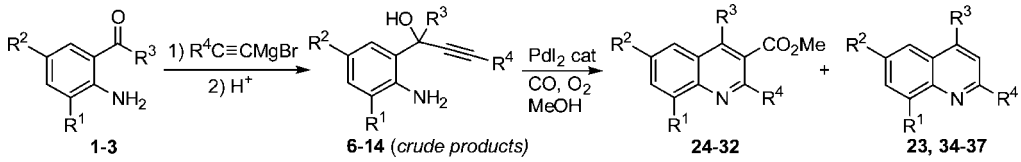


TABLE 1. Reactions of 1-(2-Aminoaryl)-2-yn-1-ols 6−14 with CO, O_2, and MeOH in the Presence of the PdI_2−KI Catalytic System[a]



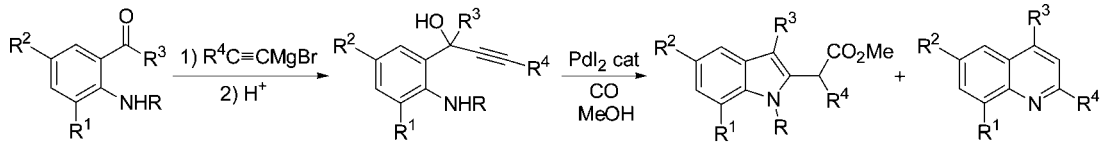
entry			R^1	R^2	R^3	R^4		yield[b] (%)		yield[b] (%)
1[c,d]	**1**	**6**	H	H	Me	Bu	**24**	traces	**23**	79
2[d]	**1**	**6**	H	H	Me	Bu	**24**	33	**23**	62
3	**1**	**6**	H	H	Me	Bu	**24**	69	**23**	24
4	**2**	**7**	OMe	H	Me	Bu	**25**	65	**33**	28
5	**3**	**8**	H	Cl	Me	Bu	**26**	60		
6	**1**	**9**	H	H	Me	Ph	**27**	45	**34**	30
7	**2**	**10**	OMe	H	Me	Ph	**28**	63	**35**	25
8	**3**	**11**	H	Cl	Me	Ph	**29**	65		
9[e]	**1**	**12**	H	H	Me	*t*-Bu	**30**	69	**36**	13
10	**2**	**13**	OMe	H	Me	*t*-Bu	**31**	70	**37**	10
11	**3**	**14**	H	Cl	Me	*t*-Bu	**32**	58		

[a] Crude substrates **6**−**14** [obtained from the reaction between 1-(2-aminoaryl) ketones **1**−**3** and alkynylmagnesium bromides] were directly used as substrates without need for further purification (see the Experimental Section for details). Unless otherwise noted, all reactions were carried out in MeOH as the solvent (0.02 mmol of starting **1**−**3** per mL of MeOH, 1 mmol scale based on **1**−**3**) for 2 h in the presence of PdI_2 and KI (**1**−**3**/KI/PdI_2 molar ratio = 50:10:1) at 100 °C and under 80 atm of a 4:1 mixture of CO−air. Substrate conversion was quantitative in all cases. [b] Isolated yield based on starting **1**−**3**. [c] Substrate concentration was 0.22 mmol/mL of MeOH. [d] The reaction was carried out under 20 atm of a 4:1 mixture CO−air. [e] The reaction also led to the formation of small amounts of 3,3-dimethyl-2-(3-methyl-1*H*-indol-2-yl)butyric acid methyl ester **38** (7%, based on starting **1**).

entry 2, but under 80 atm of a 4:1 mixture of CO−air, **24** was the main reaction product (69% isolated yield), quinoline **23** being formed in only 24% yield (Table 1, entry 3). Under the same conditions of entry 3, other 1-(2-aminoaryl)-2-yn-1-ols **7**−**14**, bearing different substituents on the triple bond and on the aromatic ring, were converted into the corresponding quinoline-3-carboxylic esters **25**−**32** in fair to good yields, thus allowing a general synthesis of this class of heterocyclic compounds (Table 1, entries 4−11). Minor amounts of non-carbonylated quinolines **33**−**37** were obtained in some cases (entries 4, 6, 7, 9, 10).

The reaction worked well also with substrates bearing a *tert*-butyl group on the triple bond, such as **30**−**32**, which led to the corresponding quinolines in 58−70% isolated yields based on starting amino ketones **1**−**3** (Table 1, entries 9−11). In the case of **12**, the formation of small amounts (7%) of 3,3-

TABLE 2. Reactions of 1-(2-Aminoaryl)-2-yn-1-ols 8−19, 49 with CO and MeOH in the Presence of the PdI_2−KI Catalytic System[a]



1-5 **8-19, 49** (*crude product*) **38, 41-43, 45-47, 50** **34-37, 39, 40, 44, 48**

entry			R	R^1	R^2	R^3	R^4		yield[b] (%)		yield[b] (%)
12[c]	**1**	**9**	H	H	H	Me	Ph			**34**	59
13[c]	**2**	**10**	H	OMe	H	Me	Ph			**35**	54
14[c]	**3**	**11**	H	H	Cl	Me	Ph			**39**	39
15[c]	**3**	**8**	H	H	Cl	Me	Bu			**40**	49
16[c]	**1**	**12**	H	H	H	Me	*t*-Bu	**38**	66	**36**	36
17	**1**	**12**	H	H	H	Me	*t*-Bu	**38**	75	**36**	6
18	**2**	**13**	H	OMe	H	Me	*t*-Bu	**41**	45	**37**	30
19	**3**	**14**	H	H	Cl	Me	*t*-Bu	**42**	68		
20	**4**	**15**	H	H	H	Ph	*t*-Bu	**43**	60	**44**	22
21	**1**	**16**	H	H	H	Me	TMS	**45**[d]	88		
22	**2**	**17**	H	OMe	H	Me	TMS	**46**[d]	42		
23	**4**	**18**	H	H	H	Ph	TMS	**47**[d]	63	**48**[d]	14
24[e]	**5**	**49**	Me	H	H	Me	Bu				
25	**5**	**19**	Me	H	H	Me	*t*-Bu	**50**	44		

[a] Crude **8−19, 49** [obtained from the reaction between 1-(2-aminoaryl) ketones **1−5** and alkynylmagnesium bromides] were directly used as substrates without need for further purification (see the Experimental Section for details). Unless otherwise noted, all reactions were carried out in MeOH as the solvent (0.02 mmol of **1−5**/mL of MeOH, 1 mmol scale based on **1−5**) for 2 h in the presence of PdI_2 and KI (**1−5**/KI/PdI_2 molar ratio = 50:10:1) at 100 °C and under 90 atm of CO. Substrate conversion was quantitative in all cases. [b] Isolated yield based on starting **1−5**. [c] Reaction was carried out under 60 atm of CO. [d] R^4 = H in the final product (see text for details). [e] Decomposition of the substrate, with formation of unidentified chromatographically immobile materials, was observed.

dimethyl-2-(3-methyl-1*H*-indol-2-yl)butyric acid methyl ester **38**, deriving from path a (Scheme 2), was observed (Table 1, entry 9). Thus, under oxidative conditions, the reaction pathway beginning with a 6-*endo-dig* cyclization (Scheme 2, path b) is preferentially followed with respect to that beginning with a 5-*exo-dig* cyclization (Scheme 2, path a), even in the presence of a bulky substituent on the terminal *sp* carbon. This apparently unusual result can be explained as follows. The pathway beginning with a 6-*endo-dig* cyclization is particularly favored by the stabilization ensuing from the subsequent aromatization with formation of the quinoline ring. On the other hand, the pathway beginning with a 5-*exo-dig* cyclization can lead to aromatization only after the reaction between intermediate **VI** and the H−Pd−I species; however, this latter reaction is hindered by the fact that, under oxidative conditions, H−Pd−I is readily reconverted to PdI_2,[1a,b,k–m,6] which may begin a new catalytic cycle leading to **20**.

It was interesting at this point to test the reactivity of 1-(2-aminoaryl)-2-yn-1-ols under nonoxidative conditions. We found that substrates not bearing a bulky group on the triple bond preferentially underwent 6-*endo-dig* rather than 5-*exo-dig* cyclization. For example, the reaction of 2-(2-aminophenyl)-4-phenylbut-3-yn-2-ol **9** (bearing a phenyl group on the triple bond), carried out under the same conditions of entry 3 (Table 1) but under 60 atm of CO and in the absence of oxygen, selectively led to 4-methyl-2-phenylquinoline **34** (59% isolated yield, Table 2, entry 12), ensuing from 6-*endo-dig* cyclization (Scheme 2, path b) followed by aromatization and protonolysis (Scheme 2, path d). This result shows that, for a substrate bearing a phenyl on the triple bond, the route leading to indoles **21** (Scheme 2, path a) it is not competitive with the pathway leading to quinolines **22**. As expected, other substrates bearing a phenyl or a butyl group on the triple bond, such as **10**, **11**, and **8**, behaved similarly, leading to the corresponding noncarbonylated quinolines **35**, **39**, and **40** in 39−49% yields, as shown by the results reported in Table 2, entries 13−15.

On the basis of these results and observations, the next logical step was to test the reactivity of substrates bearing a bulky *tert*-butyl or TMS group on the triple bond, under nonoxidative conditions. In this case, in fact, the 5-*exo-dig* pathway leading to indoles **21** was expected to become competitive with the 6-*endo-dig* route leading to quinolines **22** (Scheme 2) for steric reasons. Indeed, the reaction of 2-(2-aminophenyl)-5,5-dimethylhex-3-yn-2-ol **12** (R^4 = *tert*-butyl) carried out under the same conditions as those of entries 12−15 (Table 2) led to 3,3-dimethyl-2-(3-methyl-1*H*-indol-2-yl)butyric acid methyl ester **38** in 66% isolated yield [based on starting 1-(2-aminophenyl)ethanone **1**], 2-*tert*-butyl-4-methylquinoline **36** being formed as byproduct (36% isolated yield based on **1a**, Table 2, entry 16). The selectivity toward **38** could be improved working under a higher CO pressure: at 90 atm, the yields of **38** and **36** were 75 and 6%, respectively, based on **1** (entry 17, Table 2). Under these latter conditions, other substrates bearing a *tert*-butyl group on the triple bond, such as **13**−**15**, led to the corresponding indoles **41**−**43** with good yields and selectivities (entries 18−20, Table 2). Minor amounts of noncarbonylated quinolines **37** and **44** were obtained from substrates **13** and **15**, respectively (entries 18 and 20).

As we have already observed in other PdI_2-catalyzed cyclization and oxidative carbonylation reactions,[1a,b,k–m,2b,h,j,l,7] in the case of substrates bearing a trimethylsilyl substituent on the triple bond, such as **16**−**18**, the TMS group was lost in the course of the process, thus allowing the synthesis of α-unsubstituted indol-2-acetic esters **45**−**47** (entries 21−23, Table 2). 4-Phenylquinoline **48** was obtained as byproduct in the case of the reaction of **18** (entry 23).

We also tested the reactivity of 1-(2-alkylaminoaryl)-2-yn-1-ols bearing a secondary rather than a primary amino group. Clearly, for these substrates, bearing only one hydrogen bonded to nitrogen, paths c and d (Scheme 2) could not be followed, thus the possibility to obtain quinoline derivatives **20** or **22** was prevented. The reaction of 2-(2-methylaminophenyl)-oct-3-yn-

2-ol **49** (substituted with a butyl group on the triple bond), carried out under nonoxidative conditions, similar to those reported in entry 17 (Table 2), led to decomposition of the starting material, with formation of unidentified chromatographically immobile materials (Table 2, entry 24). This is conceivable, because, as we have seen, if the substituent on the triple bond is not sterically demanding, the 5-*exo-dig* cyclization (path a, Scheme 2) is not favored and, as a consequence, the substrate preferentially undergoes decomposition. On the other hand, the reaction of 5,5-dimethyl-2-(2-methylaminophenyl)-hex-3-yn-2-ol **19**, bearing a *tert*-butyl group on the triple bond, did afford the corresponding indol-2-acetic derivative **50**, even though in moderate yield [44% isolated, based on starting 1-(2-methylaminophenyl)ethanone **5**, Table 2, entry 25].

Conclusions

In conclusion, we have shown that 1-(2-aminoaryl)-2-yn-1-ols **6**−**19** [used as crude products deriving from the Grignard reaction between 1-(2-aminoaryl)ketones **1**−**5** and alkynylmagnesium bromides] may follow different reaction pathways when let to react in the presence of the PdI_2−KI catalytic system under oxidative or nonoxidative carbonylation conditions, depending on the nature of the substrate and on reaction conditions. In particular, 1-(2-aminoaryl)-2-yn-1-ols, bearing a primary amino group, such as **6**−**14**, selectively undergo 6-*endo-dig* cyclization when allowed to react under oxidative conditions, with selective formation of quinoline-3-carboxylic esters **24**−**32** in fair to good yields [45−70% isolated, based on starting 1-(2-aminoaryl)ketones **1**−**3**]. On the other hand, indol-2-acetic esters **38**, **41**−**43**, **45**−**47**, and **50**, deriving from 5-*exo-dig* cyclization, are obtained in moderate to good yields [42−88%, based on starting 1-(2-aminoaryl)ketones **1**−**5**] under nonoxidative conditions, when the starting material is substituted with a bulky group on the triple bond, as in the case of **12**−**19**. In this latter case, a primary as well as a secondary amino group can be present in the substrate, and α-unsubstituted indol-2-acetic esters are formed from substrates bearing a TMS group on the triple bond, ensuing from loss of the TMS group in the course of the process. Quinoline and indole derivatives are particular important classes of heterocyclic derivatives, with many important applications.[9–11] The present methodology represents a simple and direct approach to the synthesis of functionalized quinolines and indoles starting from readily available starting materials.[12–15]

Experimental Section

Typical Procedure for the Synthesis of Quinoline-3-carboxylic Esters. We report here as a typical procedure the preparation of 2-butyl-4-methylquinoline-3-carboxylic acid methyl ester **24** (Table 1, entry 3). Details for the preparation of all the other quinoline-3-carboxylic esters **25**−**32** can be found in the Supporting Information. To a suspension of Mg turnings (700.0 mg, 28.8 mmol) in anhydrous THF (2.0 mL), maintained under nitrogen and under reflux, was added pure EtBr (0.5 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise (ca. 20 min) in THF solution (1.5 mL of EtBr in 15.0 mL of THF; total amount of EtBr added: 2.92 g, 26.8 mmol). The mixture was then allowed to reflux for an additional 20 min. After cooling, the

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Pure 2-butyl-4-methylquinoline **23** was a yellow oil (60.3 mg, 24% based on starting **1**), whose spectroscopic data agreed with those we already reported.[7] 2-Butyl-4-methylquinoline-3-carboxylic acid methyl ester **24** was a yellow oil [221.3 mg, 69% based on starting 1-(2-aminophenyl)ethanone **1**]. IR (film): ν = 1731 (s), 1588 (m), 1456 (m), 1435 (m), 1290 (m), 1235 (s), 1161 (w), 1056 (w), 759 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.08−8.05 (m, 1 H), 8.01−7.96 (m, 1 H), 7.70 (ddd, J = 8.3, 6.9, 1.4, 1 H), 7.53 (ddd, J = 8.3, 6.9, 1.4, 1 H), 3.99 (s, 3 H), 2.96−2.88 (m, 2 H), 2.63 (s, 3 H), 1.85−1.72 (m, 2 H), 1.44 (sext, J = 7.4, 2 H), 0.95 (t, J = 7.4, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 158.3, 147.3, 141.6, 130.0, 129.5, 127.7, 126.3, 125.7, 124.0, 52.4, 37.1, 31.8, 22.9, 15.9, 13.9 ; GC-MS: m/z = 257 (6) [M^+], 242 (17), 228 (23), 226 (11), 216 (16), 215 (100), 200 (53), 198 (10), 171 (10), 167 (12), 158 (13), 157 (88), 143 (10), 115 (13); anal. calcd for $C_{16}H_{19}NO_2$ (257.33): C, 74.68; H, 7.44; N, 5.44. Found C, 74.76; H, 7.46; N, 5.43.

Typical Procedure for the Synthesis of Indol-2-acetic Esters. We report here as a typical procedure the preparation of **38** (Table 2, entry 17). Details for the preparation of all the other indol-2-acetic esters **41**-**43**, **45**−**47**, and **50** can be found in the Supporting Information. To a suspension of Mg turnings (700.0 mg, 28.8 mmol) in anhydrous THF (2.0 mL), maintained under nitrogen and under reflux, was added pure EtBr (0.5 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise (ca. 20 min) in THF solution (1.5 mL of EtBr in 15.0 mL of THF; total amount of EtBr added: 2.92 g, 26.8 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the solution of EtMgBr thus obtained was transferred under nitrogen to a dropping funnel and was added dropwise to a solution of 2,2-dimethyl-1-butyne (2.2 g, 26.8 mmol) in anhydrous THF (7.0 mL) at 0 °C with stirring. After additional stirring at 0 °C for 15 min, the mixture was allowed to warm up to room temperature, then it was maintained at 50 °C for 2 h and used as such at the same temperature for the next step. 1-(2-Aminophenyl)ethanone **1** (1.2 g, 8.9 mmol) was dissolved under nitrogen in anhydrous THF (7.0 mL) and then added dropwise to the solution of the alkynylmagnesium bromide in THF (prepared as described above) under nitrogen. After stirring at 50 °C for 2 h, the mixture was cooled to room temperature. Saturated NH_4Cl was added with stirring to achieve weakly acidic pH. After additional stirring at room temperature for 15 min, AcOEt (ca. 20 mL) was added and phases were separated. The aqueous phase was extracted with AcOEt (3 × 30 mL), and the collected organic layers were washed with brine to ca. neutral pH and eventually dried over Na_2SO_4. After filtration, the solvent was evaporated and crude 2-(2-aminophenyl)-5,5-dimethylhex-3-yn-2-ol **12** was diluted with MeOH and transferred into volumetric flask (50 mL). To 7.0 mL of the solution (formally deriving from 1.25 mml of **1**) were added 55.5 mL of MeOH (to adjust the substrate concentration to 0.02 mmol/mL of MeOH), and the resulting solution was transferred to a 250 mL autoclave, previously loaded with PdI_2 (9.0 mg, 2.5 × 10^{-2} mmol) and KI (41.5 mg, 0.25 mmol). The autoclave was sealed, purged at room temperature several times with CO with stirring (10 atm) and eventually pressurized at 90 atm of CO. After being stirred at 100 °C for 2 h, the autoclave was cooled, degassed, and opened. The solvent was evaporated, and products **36** and **38** were separated by column chromatography on silica gel using hexane-acetone from 99:1 to 95:5 (order of elution: **36**, **38**).

Pure 2-*tert*-butyl-4-methylquinoline **36** was a yellow oil (yield: 15.2 mg, 6% based on starting **1**), whose spectroscopic properties agreed with those we already reported.[7] 3,3-Dimethyl-2-(3-methyl-1*H*-indol-2-yl)acetic acid methyl ester **38** was a yellow solid, mp 115−117 °C (yield: 244.7 mg, 75% based on starting **1**). IR (KBr): ν = 3401 (s), 1727 (s), 1460 (w), 1340 (w), 1151 (m), 741 (m) cm^1; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.81 (s, br, 1 H), 7.56−7.48 (m, 1 H), 7.36−7.28 (m, 1 H), 7.21−7.03 (m, 2 H), 3.80 (s, 1 H), 3.69 (s, 3 H), 2.25 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 135.2, 129.0, 128.4, 121.6, 118.9, 118.4, 110.7, 109.7, 52.3, 51.7, 36.9, 28.0, 9.2 ; GC-MS: m/z = 259 (53) [M^+], 203 (45), 202 (45), 172 (14), 171 (100), 170 (92), 144 (27), 143 (28), 142 (16), 116 (10), 115 (30); anal. calcd for $C_{16}H_{21}NO_2$ (259.34): C, 74.10; H, 8.16; N, 5.40. Found C, 74.21; H, 8.14; N, 5.38.

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Supporting Information Available: General experimental methods, preparation of starting 1-(2-aminoaryl)ketones **1**-**5,** general procedure for the synthesis of quinoline-3-carboxylic esters **24**−**32**, general procedure for the synthesis of indol-2-acetic esters **38**, **41**−**43**, **45**−**47**, and **50**, characterization data and copy of ^1H and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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