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Pd-catalyzed regioselective hydroarylation of α-(2-aminoaryl)-α,β-ynones with organoboron derivatives as a tool for the synthesis of quinolines: experimental evidence and quantum-chemical calculations

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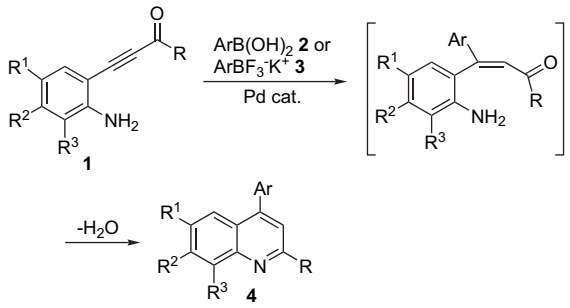
ABSTRACT

The Pd-catalyzed hydroarylation of β-(2-aminoaryl)-α,β-ynones with organoboron derivatives, leading to 2,4-diarylquinolines in good to excellent yields through sequential cycloamination, has been investigated. The reaction is catalyzed by both Pd(II) and Pd(0) precatalysts, and can be carried out even under neutral conditions. The regiochemical outcome is inverted with respect to the Pd-catalyzed hydroarylation of β-(2-aminoaryl)-α,β-ynones with aryl iodides. This aspect has been rationalized using quantum-chemical calculations, which show significant differences between the energy barriers of the regioisomeric transition states for the migratory insertion (hydropalladation) step, and are consistent with the charge density of the π complex that undergoes such insertion.

1. Introduction

The quinoline scaffold is prevalent in a variety of pharmacologically active compounds as well as in naturally occurring products.[1] Quinoline-containing drugs are widely used in the treatment of malaria[2] and current reports concerning the study of novel quinoline derivatives include selective melanin concentrating hormone antagonists for treating obesity,[3] HIV-1 replication inhibitors,[4] antimicrobial and anti-tuberculosis drugs,[5] antihelmintic properties,[6] inhibitors of VEGF receptors[7] and liver X receptor modulators.[8] In particular, 4-arylquinolines show anti West Nile Virus activity,[9] and are promising positron emission tomography (PET) tracers for the in vivo monitoring of neurodegenerative processes.[10] Besides pharmacological activity, compounds containing the 4-arylquinoline substructure have found applications, for example, as chemosensors for fluoride ion,[11] and as fluorescent sensors for metal ions in aqueous solution.[12] As a consequence of the great importance of the quinoline ring system, new cyclization processes leading to these heterocycles are being investigated.[13]

In this context, we have recently reported that the sequential Rh-catalyzed hydroarylation of β-(2-aminoaryl)-α,β-ynones **1** with organoboron derivatives/cycloamination represents a useful entry to 4-substituted quinoline derivatives **4**.[14] On the other hand, the Pd-catalyzed hydroarylation of alkynes with arylboronic acids has been reported,[15] and a sequential Pd-catalyzed hydroarylation/cyclization process has been applied to the synthesis of butenolides.[16] Our previous investigations of Pd-catalyzed hydroarylation of alkynes with organic halides and triflates as a versatile tool for the synthesis of heterocycles[17] prompted us to study the sequential Pd-catalyzed hydroarylation/cycloamination of ynones **1** with organoboron derivatives (Scheme 1) as an alternative route to quinolines **4**. Moreover, since this process was very regioselective (in contrast with the palladium-catalyzed hydroarylation of



Scheme 1.

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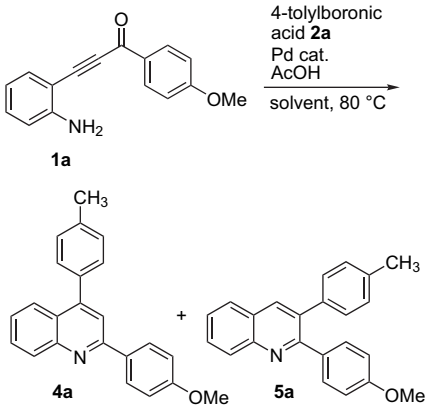
1 with aryl iodides[18]), we attempted to rationalize the observed regioselectivity through quantum-chemical calculations by Density Functional Theory and continuum solvation model. Herein, we report our results.

2. Results and discussion

The hydroarylation of **1a** with 4-tolylboronic acid **2a** (Scheme 2) was chosen as a model for the present study, and the results are reported in Table 1.



Scheme 2.

As stated before, the previously reported sequential Pd-catalyzed hydroarylation/cycloamination of **1a** with 4-iodotoluene in the presence of formate salts gave a mixture of the two regioisomers **4a** and **5a** in low yield.[18] In this example, a moderate regioselectivity towards the formation of **5a** was observed only using $Pd_2(dba)_3$ as catalyst in ethyl acetate as solvent. By contrast, the present process led to the regioselective formation of the quinoline **4a** under all reaction conditions tested. The structural assignments of **4a** and **5a** were confirmed by comparison with authentic samples prepared as described.[14,18]

We were unable to obtain the quinoline **4a** in satisfactory yield (entry 1) under the reaction conditions (1.2 equiv of **2a**, $Pd(OAc)_2$, dppe, acetic acid, dioxane, 80 °C) reported by Oh and co-workers for the regioselective sequential hydroarylation/cyclization of 4-hydroxyalkynoates.[16] According to our previous findings concerning the Rh-catalyzed process,[14] we isolated **4a** in higher yield and good selectivity in the presence of a larger excess of **2a** (entries 2–4) and best results were obtained in the presence of 3 equiv of **2a** (entry 4). A further increase in the amount of boronic acid did not produce better results (entry 5). When $Pd(OAc)_2$ alone (entries 6 and 7) or a combination of $Pd(OAc)_2$/*t*-Bu_3P (entry 8) were tested in place of $Pd(OAc)_2$/dppe, we observed a dramatic loss of efficiency together with a less pronounced decrease in the selectivity. Conversely, the $Pd(OAc)_2$/tricyclohexylphosphine catalytic system gave good results (entry 9), showing that the use of a bidentate ligand is not compulsory. The hydroarylation can be catalyzed also by Pd(0) precatalysts (entries 10–12). The catalytic system $Pd_2(dba)_3$/dppe gave nearly the same yield of $Pd(OAc)_2$/dppe (compare entries 3 and 11), while $Pd(PPh_3)_4$ was much less effective (entry 10). Finally, we tested the use of $Pd_2(dba)_3$ without phosphine ligands in EtOAc as solvent (entry 12). As reported before, this catalyst/solvent combination favoured the formation of **5a** in the hydroarylation with 4-iodotoluene.[18] In the present process, its use resulted in the regioselective formation of **4a**, although in low yield (entry 11). This observation suggests a sharp difference in the nature of the pathways involved in the Pd-catalyzed reactions of the alkyne **1a** with aryl boron derivatives and aryl iodides, respectively.

Table 1
Pd-catalyzed hydroarylation of **1a** with 4-tolylboronic acid **2a**[a]

Entry	Solvent	Catalyst[b]	Equiv of **2a**	Time (h)	Yield of **4a**+**5a**	**4a**:**5a**[c]
1	Dioxane	$Pd(OAc)_2$/dppe	1.2	7	18	92:8
2	Dioxane	$Pd(OAc)_2$/dppe	2	9	66	94:6
3	Dioxane	$Pd(OAc)_2$/dppe	3	7	90	94:6
4	Ethanol	$Pd(OAc)_2$/dppe	3	7.5	92	97:3
5	Dioxane	$Pd(OAc)_2$/dppe	5	7	92	91:9
6	Dioxane	$Pd(OAc)_2$	5	24	24	83:17
7	Ethanol	$Pd(OAc)_2$	3	20	27	85:15
8	Dioxane	$Pd(OAc)_2$/*t*-Bu_3P	5	16	36	75:25
9	Dioxane	$Pd(OAc)_2$/Cy_3P	5	5	78	95:5
10	Dioxane	$Pd(PPh_3)_4$	3	22	21	97:3
11	Dioxane	$Pd_2(dba)_3$/dppe	3	6	84	98:2
12	EtOAc	$Pd_2(dba)_3$	2	22	32	97:3

[a] Reactions were carried out on a 0.25 mmol scale in 1 mL of solvent at 80 °C under N_2 atmosphere, using the following molar ratios: **1a**/AcOH/Pd=1:0.15:0.05.
[b] P/Pd ratio: 2:1, if phosphines were added.
[c] Determined by HPLC analysis (RP-18, MeOH/H_2O 85:15 v/v).

Interestingly, the environmentally benign ethanol can be a suitable reaction medium (compare entries 3 and 4) and this solvent was used when the process was extended to the reaction of various ynones and boron derivatives. The results obtained are reported in Table 2. The sequential Pd-cataltzed hydroarylation/cycloamination afforded quinolines **4a**–**o** in good to excellent yields, with high regioisomeric purity (>95%, as judged by GC/MS analysis). Various substituents are allowed both on the boron derivative and on the alkynone. Although 0.05 equiv of dppe (Pd/P=1:2) has been generally used, slightly better yields have been observed in some cases by increasing the amount of dppe to 0.1 equiv (Table 2, compare entries 13 and 14); however, no systematic investigation was carried out on this aspect. Aryltrifluoroborate salts[19] gave results comparable with arylboronic acids (Table 2, entries 1, 3 and 18). To the best of our knowledge, these salts have not been previously used in the Pd-catalyzed hydroarylation of alkynes. Moreover, the reaction of **1a** with the aryltrifluoroborate **3a** and **3b** proceeds also without adding acetic acid (Table 2, entries 2 and 4). Although these reaction conditions resulted less effective than the standard protocol (that requires 0.15 equiv of AcOH) and further optimization is necessary, the possibility of carrying out the Pd-catalyzed hydroarylation under neutral conditions is undoubtedly worth of interest.

According to the previous studies of Oh and co-workers,[15a] a plausible catalytic cycle for the hydroarylation is depicted in Scheme 3. The active Pd(0) catalyst can be generated in situ from Pd(II) species in several ways, including oxidation of dppe[20] and homocoupling of arylboronic acid.[21, 22] The oxidative addition of Pd(0) to AcOH affords the hydride complex **6** (it is likely that under neutral conditions this step can take place through the insertion of Pd(0) into the O–H bond of ethanol).[23] Then, **6** coordinates the ynone **1** to give the π-complex **7**. Subsequent hydropalladation followed by trans-metallation with arylboronic acid **2** (or potassiom trifluoroborate **3**) generates the species **9**, from which the hydroarylation product **10** is obtained through reductive elimination of Pd(0). Sequential cycloamination (that could take place also from intermediates **8**–**9**) results in the formation of quinoline ring. A similar catalytic cycle has been probed by ESI-FTMS in the related hydroarylation of allenes with $ArB(OH)_2$ in the presence of AcOH.[24]

An alternative pathway for the hydroarylation could also be considered (Scheme 4). Initial trans-metallation[25] of $Pd(OAc)_2$ with boron derivatives **2** or **3** generates an Ar–PdOAc complex; carbopalladation of **1** by this species gives the intermediate **12**, and protonolysis of **12** affords the alkene **10** and regenerates the

Table 2
Pd-catalyzed synthesis of 4-arylquinolines **4** from α,β-ynones **1** and boron derivatives **2**–**3**[a]

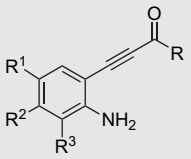
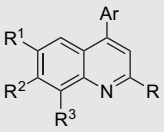
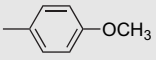
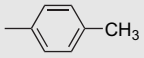
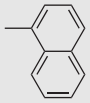
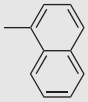
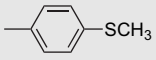
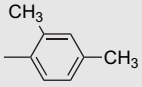
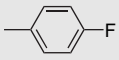
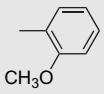
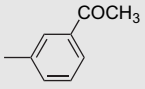
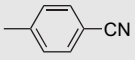
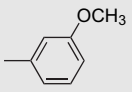
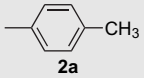
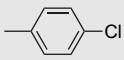
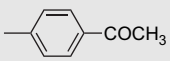
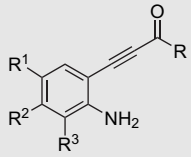
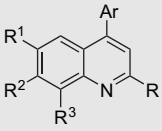
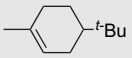
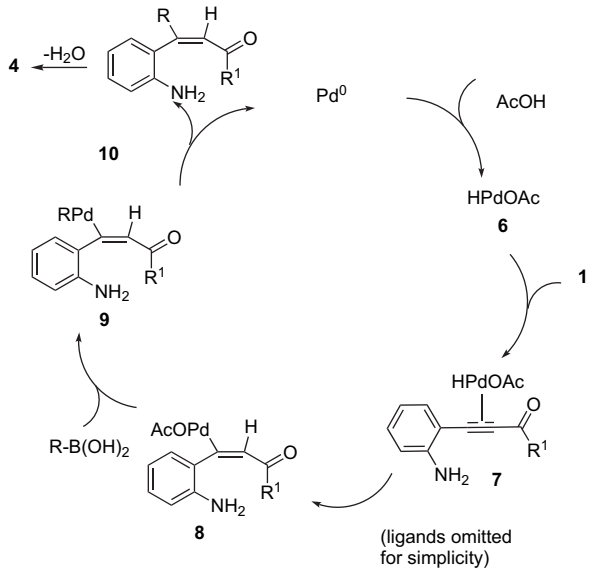
Entry	α,β-ynone **1** 	–R	$-R^1$	$-R^2$	$-R^3$	$ArB(OH)_2$ **2** or $ArBF_3^-K^+$ **3**, –Ar	Time (h)	Quinoline **4** 	Yield[b] (%)
1	**1a**		–H	–H	–H	 **3a**	8	**4a**	90
2	**1a**					**3a**	24	**4a**	68[c]
3	**1a**					–Ph **3b**	8	**4b**	76
4	**1a**					**3b**	24	**4b**	61[c]
5	**1a**					 **2c**	8	**4c**	93
6	**1b**		–H	–H	–H	–Ph **2b**	7.5	**4d**	78
7	**1b**					 **2d**	7	**4e**	70
8	**1c**		–H	–H	–H	 **2e**	16	**4f**	90
9	**1d**		–F	–H	–F	**2b**	20	**4g**	66[d]
10	**1d**					 **2f**	20	**4h**	60[d]
11	**1e**		–H	$-CF_3$	–H	 **2g**	3	**4i**	70[d]
12	**1e**					 **2a**	3	**4j**	92[d]
13	**1f**		–H	–H	–H	**2f**	24	**4k**	68
14	**1f**					**2f**	24	**4k**	76[d]
15	**1f**					**2e**	24	**4l**	77[d]
16	**1g**		–H	–H	–H	**2c**	24	**4m**	70[d]

Table 2 (*continued*)

Entry	α,β-ynone **1**	–R	$–R^1$	$–R^2$	$–R^3$	$ArB(OH)_2$ **2** or $ArBF_3K^+$ **3**, –Ar	Time (h)	Quinoline **4**	Yield[b] (%)
									
17	**1h**		–H	–H	–H	**2d**	24	**4n**	74
18	**1h**		–H	–H	–H	**3b**	30	**4o**	60

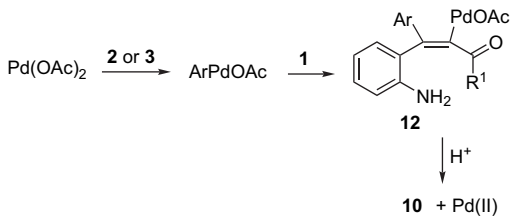
[a] Reactions were carried out in EtOH at 80 °C under N_2 atmosphere using the following molar ratios: **1**/**2**(**3**): AcOH/Pd(OAc):dppe=1:3:0.15:0.05:0.05.
[b] Yields refer to single runs and are for pure isolated products.
[c] Without AcOH.
[d] dppe (0.1 equiv).



Scheme 3.

catalyst. This cycle can however be ruled out when the reaction is carried out using a Pd(0) precatalyst (Table 1, entries 10–12). The regiochemical outcome of the present reaction also suggests that the formation of the product via Ar–PdOAc is unlikely. Indeed, on the basis of experimental[26] and theoretical[27] results concerning the insertion of α,β-alkynones and alkynals into the Ar–Pd bond, the isolation of 3-aryl quinolines **5** as the main product should be expected in this case.

A third possibility, involving the initial oxidative addition of Ar–$B(OH)_2$ to Pd(0) to give an Ar–Pd–$B(OH)_2$ species that carbopalladates the triple bond,[15b] seems to be in contrast with recent results[28] showing that such an oxidative addition does not take place.



Scheme 4.

Assuming therefore that the catalytic cycle depicted in Scheme 3 is operating in the present reaction, in order to shed some light on the observed regioselectivity, we carried out quantum-chemical calculations in the framework of Density Functional Theory.[29] In this respect, we decided to focus our computational efforts on the reaction between HPdOAc (the postulated active species under our conditions) and the α,β-ynone **1a**. In particular, we compared the height of the free-energy barriers for the two possible migratory insertions of triple bond into Pd–H bond, that result in the H addition on α or β sp-carbon with respect to the carbonyl group.

Our computational strategy was designed trying to simplify as much as possible the system without the loss of its chemical peculiarities. Following this concept, dppe was not included in the model: although the efficiency of the process appears to be influenced by the presence and the nature of added ligand, regioselective hydroarylation can be achieved also with monophosphines (Table 1, entries 9 and 10) or without phosphine ligands (Table 1, entries 6 and 7). However, in order to realistically mimic the valence shell of the Pd, a coordinated solvent molecule was considered. Although the reaction was carried out in ethanol, an explicit methanol molecule was added. This choice can be justified by the fact that methanol should provide an effect on the Pd valence shell essentially indistinguishable from ethanol, but at the same time it is conformationally more confined. For the same reasons, the acetate ligand was replaced by a formyl group. We hereafter term this adduct as HPdX(MeOH) (**13**), where X=–OCOH. The choice of the environmental effects is another crucial aspect. Reactions in solutions do represent a tremendously complicated task,[30] which, for a system like the present one, require a drastic simplification. The continuum solvation model, which basically mimic the presence of the solvent inserting the molecule into a dielectric cavity, is one of the most popular methods.[31] Obviously the related results may be affected by large systematic errors, which, however, can be minimized in cases like the present one where *relative* values are concerned.

Therefore the two processes under investigation were:

$$\mathbf{13} + \mathbf{1a}_{\text{ethanol}} \rightarrow \text{HPdX(MeOH)}/\mathbf{1a}_{\text{ethanol}} \rightarrow \text{TS}_a$$

$$\mathbf{13} + \mathbf{1a}_{\text{ethanol}} \rightarrow \text{HPdX(MeOH)}/\mathbf{1a}_{\text{ethanol}} \rightarrow \text{TS}_b$$

According to this picture, HPdX–MeOH **13** and **1a** form an intermediate π-complex, termed $\text{HPdX(MeOH)}/\mathbf{1a}_{\text{ethanol}}$ (**14**) (showed in Fig. 1), which eventually evolves through the two alternative TSs to the related products.

The HF/BS1 optimized structure of the intermediate **14** shows the migrating hydrogen perpendicular to the plane defined by Pd and the two sp-carbon atoms, in a somewhat symmetrical position

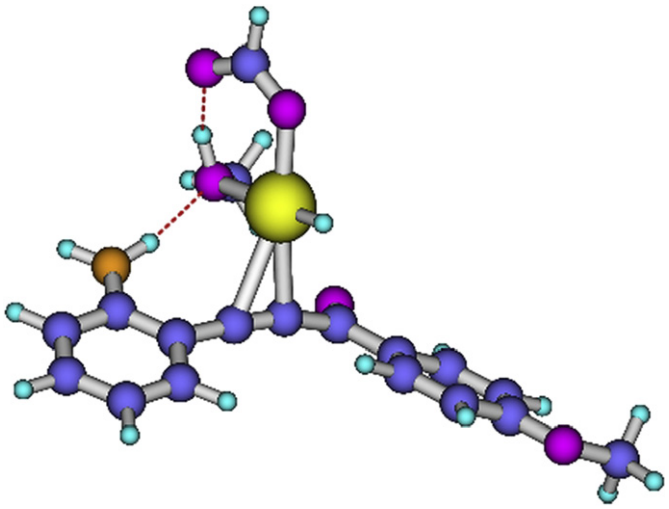


Figure 1. Schematic view of HF/BS1 optimized **14**.

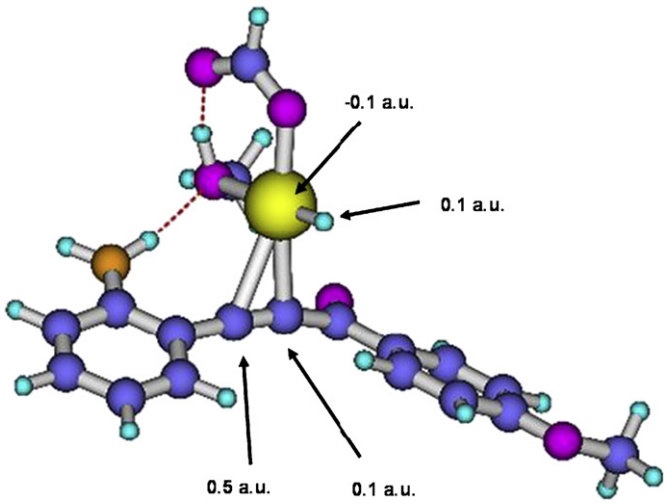


Figure 3. Atomic point charges of **14** calculated at HF/BS1//Becke3LYP/BS2+PCM level of theory.

with respect to the two target atoms. Interestingly, NH_2 group forms a hydrogen bond with OH group of the coordinated methanol molecule. However, this structure does not show any geometrical implication suggesting the observed regioselectivity. Considering the same thermodynamic stability of the reactants and intermediates (being the same in the two processes under investigation), the problem to tackle is the different stability of the transition structures, i.e., the estimation of the free-energy barriers. The reaction energies, determined as described in the Supplementary data, are shown in Figure 2.

The above results clearly indicate that migration of the hydride to C_α is energetically favourable in ethanol solution, in nice agreement with experimental observations. Moreover, the difference in the activation free energies, accounting for about 2 kcal/mol, does definitely explain the observed large selectivity at 298 K.[32] Nevertheless, any simple rationalization of such a result is frustrated by the fact that both TS geometries do not show any relevant geometrical feature (e.g., strained conformations) or sterical effects justifying their free-energy difference.

For this reason, we have further analyzed the charge distribution in the chemically relevant portions of the intermediate π-complex **14**, i.e., Pd, migrating hydrogen and the two sp carbons. The result, reported in Figure 3, shows a negative charge density on the Pd, whereas hydrogen possess some 'protic' character. This calculated charge distribution suggests that electronic factors could provide the main explanation for the observed regioselectivity, since the more electrophilic β-carbon atom conceivably shows larger affinity for the palladium.

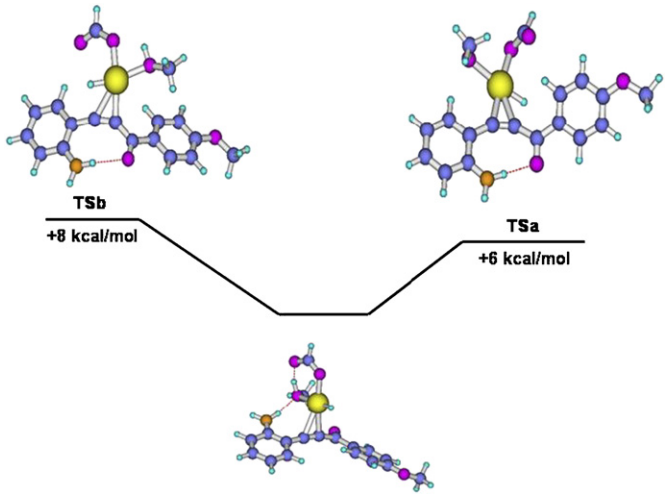


Figure 2. Free-energy diagram calculated at the HF/BS1//Becke3LYP/BS2+PCM level of theory at 298 K.

3. Conclusions

In summary, we have demonstrated that the Pd-catalyzed hydroarylation of readily available ynones **1** with organoboron derivatives is highly regioselective, takes place using arylboronic acids as well as potassium aryltrifluoroborates, and could be carried out under neutral conditions. The sequential Pd-catalyzed hydroarylation/cycloamination can provide an alternative route for the regioselective synthesis of 4-arylquinolines, with respect to the previously reported procedure,[14] because it can be efficiently carried out in a more environmentally benign solvent such as ethanol, and the molar excess of boron derivatives has been reduced. The observed regioselectivity is in accord with the difference in calculated energy barriers for the two alternative migratory insertion paths of the alkyne moiety into the Pd–H bond of the π-complex **14**. An attempt to rationalize such calculated difference showed that the charge distribution in **14** is in accord with the observed products distribution.

4. Experimental

4.1. General methods

Temperatures are reported as bath temperature. Compounds were visualized on analytical thin-layer chromatograms (TLC) by UV light (254 nm). The products, after usual work-up, were purified by flash chromatography on silica gel (230–400 mesh) eluting with *n*-hexane/ethyl acetate mixtures. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz with a Bruker AC 200 E spectrometers. IR were recorded with Perkin–Elmer 683 spectrometer. Only the most significant IR absorptions are given. Mass spectra were recorded with a Saturn 2000 T GC/MS apparatus. CHN analyses were recorded with an Eager 200 analyser. All starting materials, catalysts, and solvents, if not otherwise stated, are commercially available and were used as purchased, without further purification. The synthesis of β-(2-aminoaryl)-α,β-ynones **1** from 2-trimethylsilanyl-ethynylaniline was previously described.[33] The synthesis of **1**

has been also carried out from 2-ethynylanilines,[34] as described below. Compounds **1a**, **1b**, **1f** and **1g**[33] and quinolines **4a**, **4b**, **4d**, **4f** and **4g**[14] were previously characterized.

4.2. General procedure for the synthesis of β-(2-aminoaryl)-α,β-ynones 1 from 2-ethynylanilines

To a solution of 2-ethynylaniline (0.70 mmol) in anhydrous THF (15 mL) were added the aryl halide or the vinyl triflate (1.05 mmol), triethylamine (3.50 mmol), $PdCl_2$ (0.014 mmol) and dppf (0.014 mmol). The resulting mixture was stirred at room temperature overnight under CO atmosphere (P_{CO}=10 bar[35]), then extracted with 0.05 M HCl (75 mL) and ethyl acetate (3×75 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (hexane/EtOAc mixtures) to give **1**.

4.2.1. 3-(2-Aminophenyl)-1-(2,4-dimethylphenyl)prop-2-yn-1-one ***1c***

Bright yellow solid (146 mg) was obtained (84% yield). Mp 98–100 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, *J*=7.9 Hz, 1H), 7.40 (dd, J_1=7.6 Hz, J_2=1.3 Hz, 1H), 7.23–7.09 (m, 2H), 7.04 (s, 1H), 6.72–6.63 (m, 2H), 4.59 (br s, 2H), 2.62 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 179.3, 140.4, 143.7, 140.4, 133.5, 133.4, 133.0, 132.3, 126.6, 117.7, 114.7, 104.0, 94.8, 89.5, 21.9, 21.5. IR (KBr): 3480, 3390, 2150, 1620 cm^{-1}. MS (EI) *m*/*z*: 249 (M^+, 60), 232 (100). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.70; H, 6.05; N, 5.62.

4.2.2. 3-(2-Amino-3,5-difluorophenyl)-1-(2-methoxyphenyl) prop-2-yn-1-one ***1d***

Bright yellow solid (153 mg) was obtained (76% yield). Mp 95–97 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00 (dd, J_1=7.8 Hz, J_2=1.7 Hz, 1H), 7.61–7.52 (m, 1H), 7.10–6.89 (m, 4H), 4.50 (br s, 2H), 3.98 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 175.7, 159.7, 153.3 (dd, J_1=238 Hz, J_2=11.9 Hz, C–F), 150.3 (dd, J_1=243 Hz, J_2=12.2 Hz, C–F), 135.3, 131.9, 126.7, 120.8, 114.3 (dd, J_1=23.0 Hz, J_2=3.9 Hz), 112.5, 107.4 (d, *J*=22.4 Hz), 106.9 (d, *J*=22.6 Hz), 96.5, 86.4, 56.1. IR (KBr): 3490, 3390, 2160, 1610 cm^{-1}. MS (EI) *m*/*z*: 287 (M^+, 100), 269 (44). Anal. Calcd for $C_{16}H_{11}F_2NO_2$: C, 66.90; H, 3.86; N, 4.88. Found: C, 67.05; H, 3.84; N, 4.87.

4.2.3. 4-{3-[2-Amino-4-(trifluoromethyl)phenyl]prop-2-ynoyl} benzonitrile ***1e***

Yellow-orange solid (132 mg) was obtained (60% yield). Mp 162–163 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.33 (d, *J*=7.8 Hz, 2H), 8.10 (d, *J*=7.8 Hz, 2H), 7.69 (d, *J*=8.1 Hz, 1H), 7.13 (s, 1H), 6.87 (d, *J*=8.3 Hz, 1H), 6.42 (br s, 2H), 3.37 (s, 3H). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 175.6, 152.2, 139.0, 135.1(q, *J*=7 Hz), 132.9, 132.5 (q, *J*=31.5 Hz), 129.8, 123.8 (q, *J*=273 Hz, CF_3), 118.0, 116.2, 111.6, 111.0, 104.4, 92.8, 91.6. IR (KBr): 3440, 3350, 2200, 2150, 1640 cm^{-1}. MS (EI) *m*/*z*: 314 (M^+, 100). Anal. Calcd for $C_{17}H_9F_3N_2O$: C, 64.97; H, 2.89; N, 8.91. Found: C, 65.09; H, 2.89; N, 8.93.

4.2.4. 3-(2-Aminophenyl)-1-(4-tert-butylcyclohex-1-en-1-yl)prop-2-yn-1-one ***1h***

Bright yellow solid (137 mg) was obtained (70% yield). Mp 140–142 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.43 (m, 2H), 7.19 (t, *J*=7.5 Hz, 1H), 6.72–6.63 (m, 2H), 4.52 (br s, 2H), 2.68–2.58 (m, 1H), 2.45–2.36 (m, 1H), 2.15–1.90 (m, 3H), 1.31–1.06 (m, 2H), 0.90 (s, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 179.2, 150.1, 147.5, 140.4, 133.4, 132.0, 117.7, 114.6, 104.2, 92.3, 88.7, 43.5, 32.1, 28.3, 27.1, 23.9, 23.2. IR (KBr): 3450, 3350, 2180, 2150, 1640 cm^{-1}. MS (EI) *m*/*z*: 281 (M^+, 100). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.87; H, 8.22; N, 4.99.

4.3. Representative procedure for the sequential hydroarylation/cycloamination of 1 with arylboronic acids. Synthesis of 2-(4-methoxyphenyl)-4-(1-naphthyl) quinoline 4c

To a solution of 3-(2-aminophenyl)-1-(4-methoxyphenyl) prop-2-yn-1-one **1a** (0.128 g, 0.51 mmol) in ethanol (4 mL) were added 1-naphtaleneboronic acid **2c** (0.263 g, 1.53 mmol), acetic acid (4.5 μL, 0.075 mmol), $Pd(OAc)_2$ (0.006 g, 0.027 mmol) and 1,2-bis (diphenylphosphino)ethane (0.011 g, 0.027 mmol). The mixture was stirred at 80 °C for 8 h under nitrogen atmosphere. After cooling, the mixture was purified by column chromatography (silica gel; hexane–ethyl acetate 97:3 v/v) to give **4c** as pale brown solid (0.171 g, 93% yield). Mp 123–124 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.24 (d, *J*=8.5 Hz, 1H), 8.16 (d, *J*=8.8 Hz, 2H), 7.91 (t, *J*=7.2 Hz, 2H), 7.85 (s, 1H), 7.71–7.01 (m, 8H), 7.00 (d, *J*=8.8 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 160.9, 156.4, 148.6, 147.8, 136.1, 133.5, 132.14, 132.05, 129.9, 129.5, 128.9, 128.7, 128.3, 127.8, 127.4, 126.8, 126.4, 126.1, 125.9, 125.7, 125.3, 119.9, 114.2, 55.3. IR (KBr): 3020, 1600, 1580, 1530 cm^{-1}. IR (KBr): 3010, 1600, 1580, 1530 cm^{-1}. MS (EI) *m*/*z*: 361 (M^+, 100). Anal. Calcd for $C_{26}H_{19}NO$: C, 86.40; H, 5.30; N, 3.88. Found: C, 86.71; H, 5.28; N, 3.86.

4.3.1. 4-[4-(Methylthio)phenyl]-2-(1-naphthyl)quinoline ***4e***

Pale yellow solid (137 mg) was obtained from 140 mg of **1b** and 260 mg of **2d** (70% yield). Mp 140–142 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.29 (d, *J*=8.3 Hz, 1H), 8.23–8.19 (m, 1H), 8.02 (d, *J*=8.3 Hz, 1H), 7.94–7.88 (m, 2H), 7.73 (d, *J*=6.7 Hz, 2H), 7.63 (s, 1H), 7.59–7.44 (m, 6H), 7.36 (d, *J*=8.4 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 159.1, 148.8, 148.1, 139.5, 138.7, 134.6, 134.1, 131.3, 130.2, 130.0, 129.6, 129.1, 128.4, 127.8, 126.6, 126.4, 125.9, 125.7, 125.6, 125.3, 123.2, 15.6. IR (KBr): 3020, 1580 cm^{-1}. MS (EI) *m*/*z*: 377 (M^+, 98), 362 (100). Anal. Calcd for $C_{26}H_{19}NS$: C, 82.72; H, 5.07; N, 3.71. Found: C, 82.98; H, 5.08; N, 3.70.

4.3.2. 1-{3-[6,8-Difluoro-2-(2-methoxyphenyl)quinolin-4-yl] phenyl}ethanone ***4h***

Light yellow solid (75 mg) was obtained from 92 mg of **1d** and 158 mg of **2f** (60% yield). Mp 145–146 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08–8.06 (m, 2H), 7.99–7.93 (m, 2H), 7.77–7.61 (m, 1H), 7.71 (s, 1H), 7.42 (dd, J_1=7.4 Hz, J_2=1.8 Hz, 1H), 7.27 (s, 1H), 7.22 (d, *J*=1 Hz, 1H), 7.19–7.08 (m, 1H), 7.01(d, *J*=8.5 Hz, 1H), 3.85 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 197.5, 159.5 (dd, J_1=247 Hz, J_2=11.8 Hz), 158.9 (dd, J_1=260 Hz, J_2=13.2 Hz), 157.3, 156.1, 145.7, 138.3, 137.7, 133.8, 131.7, 130.9, 129.16, 129.13, 128.5, 125.5, 121.4, 111.6, 105.2 (d, *J*=22.8 Hz), 104.5 (d, *J*=22.8 Hz), 55.7, 26.7. IR (KBr): 3010, 1680, 1630, 1600, 1550 cm^{-1}. MS (EI) *m*/*z*: 389 (M^+, 100). Anal. Calcd for $C_{24}H_{17}F_2NO_2$: C, 74.03; H, 4.40; N, 3.60. Found: C, 73.85; H, 4.42; N, 3.60.

4.3.3. 4-[4-(3-Methoxyphenyl)-7-(trifluoromethyl)quinolin-2-yl]benzonitrile ***4i***

Yellow solid (126 mg) was obtained from 140 mg of **1e** and 203 mg of **2g** (70% yield). Mp 178–180 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.34 (d, *J*=8.3 Hz, 2H), 8.09 (d, *J*=8.8 Hz, 1H), 7.94 (s, 1H), 7.82 (d, *J*=8.3 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 1H), 7.51 (t, *J*=7.6 Hz, 1H), 7.13–7.07 (m, 3H), 3.90 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 159.9, 155.7, 149.8, 147.8, 142.9, 138.5, 132.7, 130.1, 128.1, 127.9, 127.2, 123.9 (q, *J*=272 Hz), 122.65, 122.60, 122.1, 120.4, 118.7, 115.3, 114.3, 113.3, 55.5. IR (KBr): 3020, 2200, 1600, 1580, 1560 cm^{-1}. MS (EI) *m*/*z*: 404 (M^+, 100), 374 (39). Anal. Calcd for $C_{24}H_{15}F_3N_2O$: C, 71.28; H, 3.74; N, 6.93. Found: C, 71.47; H, 3.75; N, 6.95.

4.3.4. 4-[4-(4-Methylphenyl)-7-(trifluoromethyl)quinolin-2-yl]benzonitrile ***4j***

Yellow solid (161 mg) was obtained from 142 mg of **1e** and 185 mg of **2a** (92% yield). Mp 163–164 °C. ^{1}H NMR (200 MHz,

$CDCl_3$): δ 8.53 (s, 1H), 8.33 (d, *J*=8.4 Hz, 2H), 8.08 (d, *J*=8.7 Hz, 1H), 7.91 (s, 1H), 7.81 (d, *J*=8.4 Hz, 2H), 7.66 (dd, J_1=8.8 Hz, J_2=1.6 Hz, 1H), 7.45 (d, *J*=8.4 Hz, 2H), 7.40 (d, *J*=8.4 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 155.8, 150.1, 148.0, 143.0, 139.2, 134.3, 132.7, 129.7, 129.4, 128.1, 127.3, 123.9 (q, *J*=272 Hz), 122.5 (q, *J*=2.7 Hz), 120.4, 118.6, 116.2, 113.4, 30.2. IR (KBr): 3010, 2200, 1580 cm^{-1}. MS (EI) *m*/*z*: 388 (M^+, 100), 374 (31). Anal. Calcd for $C_{24}H_{15}F_3N_2$: C, 74.22; H, 3.89; N, 7.21. Found: C, 73.99; H, 3.90; N, 7.22.

4.3.5. 1-{3-[2-(4-Chlorophenyl)quinolin-4-yl]phenyl}ethanone ***4k***

Off-white solid (127 mg) was obtained from 120 mg of **1f** and 230 mg of **2f** (76% yield). Mp 117–119 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.23 (d, *J*=8.4 Hz, 1H), 8.12 (d, *J*=8.5 Hz, 2H), 8.16–8.08 (m, 2H), 7.82–7.61 (m, 4H), 7.77 (s, 1H), 7.47 (d, *J*=8.5 Hz, 2H), 7.51–7.45 (m, 1H), 2.66 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 197.7, 155.5, 148.7, 148.2, 138.7, 137.7, 137.5, 135.7, 134.0, 130.2, 129.9, 129.2, 129.0, 128.8, 128.4, 126.9, 125.5, 125.2, 118.9, 26.8. IR (KBr): 3020, 1680, 1590 cm^{-1}. MS (EI) *m*/*z*: 359 (M^++2, 35), 357 (M^+, 100), 317 (24), 315 (65). Anal. Calcd for $C_{23}H_{16}$ ClNO: C, 77.20; H, 4.51; N, 3.91. Found: C, 76.94; H, 4.50; N, 3.92.

4.3.6. 2-(4-Chlorophenyl)-4-(4-fluorophenyl)quinoline ***4l***

White solid (121 mg) was obtained from 120 mg of **1f** and 197 mg of **2e** (77% yield). Mp 92–94 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.21 (d, *J*=8.4 Hz, 1H), 8.11 (d, *J*=8.5 Hz, 2H), 7.83 (d, *J*=8.4 Hz, 1H), 7.70 (s, 1H), 7.76–7.69 (m, 1H), 7.46 (d, *J*=8.5 Hz, 2H), 7.53–7.45 (m, 3H), 7.22 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 162.9 (d, *J*=248 Hz), 155.4, 148.5 (d, *J*=23 Hz), 137.8, 135.6, 134.1, 131.3, 130.1, 129.8, 129.0, 128.8, 128.5, 126.7, 125.7, 125.4, 118.9, 115.7 (d, *J*=22 Hz). IR (KBr): 3020, 1600, 1540 cm^{-1}. MS (EI) *m*/*z*: 335 (M^++2, 36), 333 (M^+, 100). Anal. Calcd for $C_{21}H_{13}$ClFN: C, 75.56; H, 3.93; N, 4.20. Found: C, 75.40; H, 3.95; N, 4.21.

4.3.7. 1-{4-[4-(1-Naphthyl)quinolin-2-yl]phenyl}ethanone ***4m***

Pale brown solid (129 mg) was obtained from 130 mg of **1g** and 255 mg of **2c** (70% yield). Mp 158–160 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.30 (d, *J*=8.3 Hz, 2H), 8.32–8.25 (m, 1H), 8.07 (d, *J*=8.3 Hz, 2H), 8.02–7.92 (m, 2H), 7.93 (s, 1H), 7.75–7.25 (m, 8H), 2.63 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 197.8, 155.4, 148.5, 148.3, 143.6, 137.4, 135.7, 133.5, 131.9, 130.1, 129.9, 128.9, 128.8, 128.4, 127.7, 127.4, 127.3, 126.9, 126.6, 126.2, 125.9, 125.3, 120.4, 26.8. IR (KBr): 3020, 1680, 1600 cm^{-1}. MS (EI) *m*/*z*: 373 (M^+, 100), 359 (35). Anal. Calcd for $C_{27}H_{19}NO$: C, 86.84; H, 5.13; N, 3.75. Found: C, 87.05; H, 5.11; N, 3.75.

4.3.8. 2-(4-tert-Butyl-cyclohex-1-enyl)-4-(4-methylsulfanyl-phenyl)-quinoline ***4n***

Orange solid (86 mg) was obtained from 84 mg of **1h** and 150 mg of **2d** (74% yield). Mp 60–62 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11 (d, *J*=8.4 Hz, 1H), 7.83 (d, *J*=8.3 Hz, 1H), 7.65 (t, *J*=7.1 Hz, 1H), 7.47 (s, 1H), 7.45–7.35 (m, 5H), 6.79 (t, *J*=2.5 Hz, 1H), 3.05–2.90 (m, 1H), 2.55 (s, 3H), 2.55–2.00 (m, 4H), 1.45–1.25 (m, 2H), 0.93 (s, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 158.5, 148.4, 147.5, 139.0, 137.6, 135.3, 130.6, 129.9, 129.1, 126.3, 125.7, 125.5, 125.3, 118.2, 43.9, 32.2, 27.8, 27.5, 27.2, 24.2, 15.7. IR (KBr): 3020, 2970, 1600, 1590 cm^{-1}. MS (EI) *m*/*z*: 388 (M^+, 51), 373 (15), 331 (100). Anal. Calcd for $C_{26}H_{29}NS$: C, 80.57; H, 7.54; N, 3.61. Found: C, 80.83; H, 7.56; N, 3.61.

4.3.9. 2-(4-tert-Butyl-cyclohex-1-enyl)-4-phenyl-quinoline ***4o***

Yellow solid (60 mg) was obtained from 83 mg of **1h** and 163 mg of **3b** (60% yield). Mp 41–42 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.12 (d, *J*=8.4 Hz, 1H), 7.82 (d, *J*=7.9 Hz, 1H), 7.65 (dt, J_1=7.5 Hz, J_2=1.2 Hz, 1H), 7.50–7.35 (m, 7H), 6.79 (t, *J*=2.7 Hz, 1H), 3.05–2.90 (m, 1H), 2.60–2.30 (m, 2H), 2.15–2.00 (m, 2H), 1.45–1.20 (m, 2H), 0.93 (s, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 158.4, 148.3, 148.1, 138.7, 137.6, 130.7, 129.8, 129.5, 129.1, 128.5, 128.2, 125.7, 125.6, 125.4, 118.3, 43.8, 32.2, 27.8, 27.5, 27.2, 24.2. IR (KBr): 3020, 2890, 1600, 1540 cm^{-1}. MS (EI) *m*/*z*: 341 (M^+, 40), 327 (16), 285 (100). Anal. Calcd for $C_{25}H_{27}N$: C, 87.93; H, 7.97; N, 4.10. Found: C, 87.67; H, 7.99; N, 4.12.

4.4. Representative procedure for the sequential hydroarylation/cycloamination of 1 with aryltrifluoroborate salts. Synthesis of 2-(4-methoxyphenyl)-4-(4-methylphenyl)quinoline 4a

To a solution of 3-(2-aminophenyl)-1-(4-methoxyphenyl) prop-2-yn-1-one **1a** (0.128 g, 0.51 mmol) in ethanol (4 mL) were added potassium 4-methylphenyltrifluoroborate **3a** (0.303 g, 1.53 mmol), acetic acid (4.5 μL, 0.075 mmol), $Pd(OAc)_2$ (0.006 g, 0.027 mmol) and 1,2-bis(diphenylphosphino)ethane (0.011 g, 0.027 mmol). The mixture was stirred at 80 °C for 8 h under nitrogen atmosphere. After cooling, the mixture was purified by column chromatography (silica gel; hexane–ethyl acetate 97:3 v/v) to give **4a** (0.149 g, 90% yield).

Acknowledgements

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Supplementary data

Details of the computational study. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.015.

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