The Palladium-Catalyzed Transfer Hydrogenation/Heterocyclization of β-(2-Aminophenyl)-α,β-ynones. An Approach to 2-Aryl- and 2-Vinylquinolines

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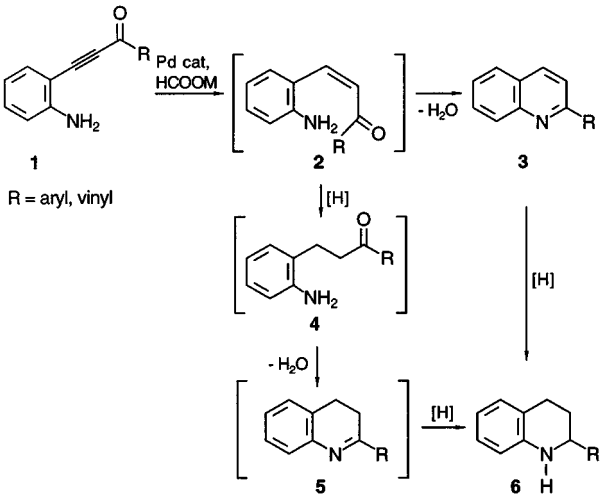
Abstract. The palladium-catalyzed transfer hydrogenation/cyclization of readily available β-(*o*-aminophenyl)-α,β-ynones **1** affords 2-aryl- and 2-vinylquinolines **3** in good yield.

Key words: quinolines, transfer hydrogenation, palladium catalysis, cyclization, alkynes

The quinoline nucleus is prevalent in a variety of biologically active compounds. In particular, the 2-substituted quinoline subunit is present in some naturally occurring substances[1] and in a new and structurally simple class of peptidoleukotriene LTD_4 antagonists, developed recently as very promising antiasthmatic therapeutics.[2] One of these compounds has also been shown to inhibit the platelet-activating factor (PAF) synthesis.[3]

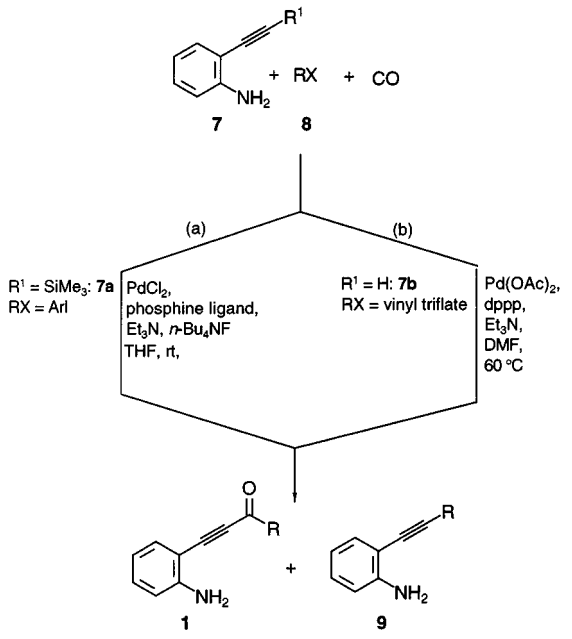
Numerous approaches to the construction of the quinoline skeleton have been reported[4] and palladium-mediated syntheses have drawn considerable interest in recent years. Palladium catalysis in this area has been applied to the hydroarylation(hydrovinylation)/cyclization of 3,3-diethoxy-1-(*o*-acetamidophenyl)-1-propyne with aryl and vinyl halides;[5] to the reaction of *o*-iodoanilides with substituted alkenes followed by a cyclization step;[6a-d] to the coupling/oxidation/cyclization of *o*-iodoanilides with acetylenic carbinols;[7] and the carbonylative coupling/conjugate addition/cyclization of *o*-ethynylanilines with aryl iodides.[8]

Herein we report that the palladium-catalyzed transfer hydrogenation[9,10]/ cyclization of readily available β-(*o*-aminophenyl)-α,β-ynones **1** may provide a promising, new approach to 2-aryl- and 2-vinylquinolines **3** (Scheme 1).



Scheme 1

Aryl α,β-ynones, **1a-h**, have been synthesized through the carbonylative coupling of *o*-trimethylsilylethynylaniline **7a**[11] and aryl iodides (Scheme 2a). The preparations have been carried out in the presence of $PdCl_2$, a bidentate phosphine ligand and *n*-Bu_4NF, under a balloon of carbon monoxide, according to our standard conditions (Scheme 2a).[12] Our results are summarized in Table 1.



Scheme 2

This procedure gave good results with aryl iodides bearing electron-donating substituents (Table 1, entries 1 and 2). However, in the presence of electron-withdrawing substituents, the corresponding α,β-ynones were obtained in low yield. The competitive non-carbonylative coupling leading to **9** was found to be a significant side reaction or the main reaction pathway (Table 1, entries 4 and 9). Changing phosphine ligands to evaluate their possible influence on the reaction outcome proved unsatisfactory.

Table 1. Preparation of β-(*o*-Aminophenyl)-α,β-ynones **1** from *o*-Trimethylsilylethynylaniline **7a** and Aryl Iodides **8**.[a]

entry	aryl iodide 8	ligand	concentration of **7a** (M)	1 yield (%)[b]	9 yield (%)[b]
1	*p*-MeO-C_6H_4-I	dppf	0.14	**1a** 70	
2	*m*-Me-C_6H_4-I	dppf	0.14	**1b** 73	
3		dppf	0.1	**1c** 79	4
4	*m*-F-C_6H_4-I	dppf	0.14	**1d** 25	35
5	"	dppp	0.14	**1d** 30	22
6	"	ttmpp	0.14	**1d** traces	
7	"	dppf	0.06	**1d** 64	traces
8	"	dppp	0.06	**1d** 62	27
9	*m*-CF_3-C_6H_4-I	dppf	0.17	**1e** 21	59
10	"	ttmpp	0.17	**1e** 60	
11	"	dppf	0.06	**1e** 65	
12	"	dppp	0.06	**1e** 58	21
13	*p*-MeCO-C_6H_4-I	dppf	0.06	**1f** 60	
14	"	dppp	0.06	**1f** 69	18
15	*p*-MeOOC-C_6H_4-I	dppp	0.06	**1g** 67	13
16	*p*-Cl-C_6H_4-I	dppf	0.06	**1h** 67	4

[a] Reactions were carried out at room temperature in anhydrous THF, overnight, under a balloon of carbon monoxide, using the following molar ratios: **7a**:**8**:*n*-Bu_4NF:Et_3N:$PdCl_2$:bidentate phosphine ligand = 1:1.5:1.2:10:0.05:0.05. [b] Yields refer to single runs and are given on isolated products. All compounds had satisfactory elemental analysis and spectral data were consistent with postulated structures.

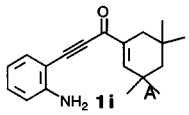
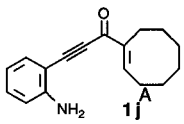
For example, the sterically encumbered electron-donating ligand tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) did not consistently give the highest yields (Table 1, entries 6 and 10) and the use of 1,3-bis(diphenylphosphino)propane (dppp) was found to afford reaction mixtures similar to those obtained with 1,1'-bis(diphenyl phosphino)ferrocene (dppf) (Table 1, compare entry 4 with entry 5). A simple solution to the problem was found by decreasing the concentration of the alkyne component and aryl iodide from 0.14-0.17 M and 0.21-0.25 M, respectively, to 0.06 M and 0.09 M. Under these conditions - that increased the concentration of carbon monoxide in the reaction - a remarkable increase of the yield of **1** as well as of the **1**:**9** ratio was observed (Table 1, compare entry 4 with entry 7, entry 5 with entry 8 and entry 9 with entry 11). It has been reported elsewhere[13] that the concentration of the reagents plays an important role in determining the regioselectivity of the carbonylative coupling of iodophenol with norbornene.

The vinyl α,β-ynones **1i** and **1j** have been prepared from 2-ethynylaniline **7b** and the corresponding vinyl triflates in 48 and 58% yield, respectively, in the presence of $Pd(OAc)_2$, dppp and triethylamine, under a balloon of carbon monoxide (Scheme 2b), as described in the literature.[14]

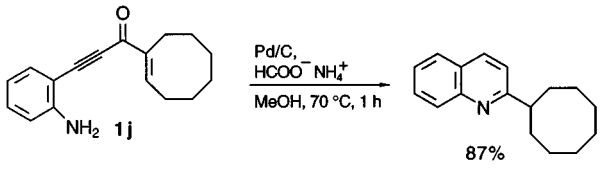
Three basic procedures have been developed for the palladium-catalyzed transfer hydrogenation/cyclization step: procedure A, 3.8 equiv of HCOOH, 5 equiv of *n*-Bu_3N, 4 mol % $Pd(OAc)_2(PPh_3)_2$[15] in DMF (8 mL/mmol) at 70 °C; procedure B, 3 equiv of $HCOONH_4$, 10 mol % Pd/C[16] in MeOH (58 mL/mmol) at 70 °C; procedure C, 5.5 mol % of dppf, 3.8 equiv of HCOOH, 3 equiv of Et_3N, 5 mol % $Pd(OAc)_2$[17] at 70 °C.

Using these procedures, a variety of α,β-ynones **1** have been successfully converted into 2-substituted quinolines as summarized in Table 2. Heterogeneous conditions (procedure B) have been found to give **3** in good yield. However, significant amounts of overreduction derivatives, the tetrahydroquinolines **6**, have been sometimes isolated. No attempts have been made to establish whether **6** is generated via transfer hydrogenation of **3**[10j] and/or cyclization of saturated intermediates **4** followed by reduction of the resultant 3,4-dihydro quinolines **5**. Higher product selectivity has been observed under homogeneous conditions, though quinoline products have been often isolated in lower yield. With vinyl α,β-ynones the employment of procedure B may lead to the formation of quinoline derivatives containing a saturated 2-substituent. For example, subjection of **1j** to the ammonium formate-Pd/C system produced 2-cyclooctylquinoline[18] in high yield (Scheme 3).

Table 2. Palladium-Catalyzed Transfer Hydrogenation/Cyclization of β-(*o*-Aminophenyl)-α,β-ynones **1**.[a]

entry	α,β-ynone 1	procedure	HCOOH or HCOOK (equiv)	time (h)	3 yield (%)[b]	6 yield (%)[b]
1	**1a**	A	3.8	8	**3a** 54	
2	**1a**	B	3.0	1	**3a** 67	**6a** 20
3	**1b**	A	3.8	2.5	**3b** 70	
4	**1c**	A	7.6	24	**3c** 38	
5	**1c**	B	3.5	5	**3c** 85[c]	**6c** traces
6	**1c**	C	7.6	24	**3c** 46	**6c** 8
7	**1d**	A	3.8	3.5	**3d** 60	
8	**1d**	B	3.0	1	**3d** 72	**6d** 24
9	**1e**	A	3.8	2	**3e** 61	
10	**1e**	B	3.5	1.5	**3e** 71	**6e** 12
11	**1f**	B	5.0	3	**3f** 55	
12	**1f**	C	3.8	3	**3f** 77	
13	**1g**	A	3.8	20	**3g** 35	
14	**1g**	B	10	3.5	**3g** 73[c,d]	
15	**1h**	B	3.0	2	**3h** 66[c]	**6h** 12
16		A	3.8	2.5	**3i** 78	
17		A	3.8	2	**3j** 55	

[a] Procedure A: **1**:*n*-Bu_3N:HCOOH:$Pd(OAc)_2(PPh_3)_2$ = 1:5:3.8:0.04; DMF, 70 °C. Procedure B: **1**:$HCOONH_4$:Pd/C = 1:3:0.1; MeOH, 70 °C. Procedure C: **1**:HCOOH:Et_3N:$Pd(OAc)_2$:dppf = 1:3.8:4:0.05:0.055; DMF, 70 °C. [b] Yields refer to single runs and are given on isolated products. All compounds had satisfactory elemental analysis and spectral data were consistent with postulated structures. [c] **1**:Pd/C = 1:1.14. [d] MeOH (80 mL/mmol).



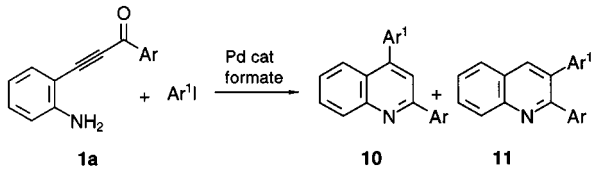
Scheme 3

The utilization of α,β-ynones **1** as precursors of diarylquinolines through our hydroarylation/cyclization methodology[19] has been briefly explored (Scheme 4). However, the reaction of **1a** with *m*-iodotoluene, used as model system, resulted in the formation of a mixture of regioisomeric quinolines (Table 3, entries 1 and 2). The employment of conditions reported[20] to favor the role of coordinating effects in directing the carbopalladation step gave rise to increased regioselectivity, with the main product arising from the adduct bearing the palladium fragment close to the *o*-aminophenyl substituent. However, hydroarylation derivatives were isolated in poor yield from a complex reaction mixture we have not further analyzed (Table 3, entry 3).

Table 3. Palladium-Catalyzed Hydroarylation of 3-(*o*-Aminophenyl)-1-(*p*-methoxyphenyl)propynone **1a** with *p*-Iodotoluene.

entry	catalyst	solvent	time (h)	temperature (°C)	overall yield (%)	**10:11**
1	$Pd(OAc)_2$[a]	DMF	48	40	32	47:53
2	$Pd(OAc)_2$/2 P(*o*-tol)$_2$[b]	DMF	24	60	41	45:55
3	$Pd(dba)_2$[c]	EtOAc	24	reflux	16	13:87

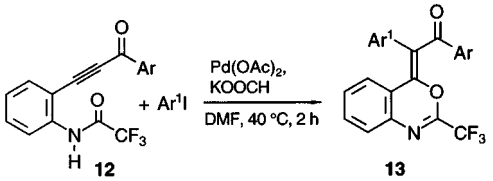
[a] **1a**:*p*-iodotoluene:HCOOK = 1:2.4:2.4. [b] **1a**:*p*-iodotoluene:HCOOH:*n*-Bu_3N = 1:2.4:2.6:3.4. [c] **1a**:*p*-iodotoluene:HCOOH:Et_3N = 1:1.2:2.6:3.3.



Ar = *p*-MeO-C_6H_4-
Ar¹= *p*-Me-C_6H_4-

Scheme 4

Interestingly, when the *N*-trifluoroacetyl derivative **12** was subjected to *m*-iodotoluene in the presence of $Pd(OAc)_2$ and HCOOK to assess the possible influence of the amino group of **1** on the regiochemistry of the carbopalladation step, no quinoline derivative was formed. The main reaction product (42% yield) was in this case the 4-alkylidenebenzoxazine **13** (Scheme 5), most probably generated through the oxypalladation/reductive elimination tandem mechanism.[21] The *Z* stereochemistry of **13** was assumed on the grounds of previously described heteropalladation/reductive elimination tandem reactions of alkynes with organopalladium complexes.[22]



Ar = *p*-MeO-C_6H_4-
Ar¹ = *p*-MeO-C_6H_4-

Scheme 5

In conclusion, the palladium-catalyzed transfer hydrogenation/ cyclization approach of 2-aryl and 2-vinylquinolines described here may provide a useful entry into this class of compounds. It appears to be quite simple, can tolerate a wide range of functional groups and allows the preparation of numerous quinoline derivatives from readily available building blocks under mild conditions.

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(11) Compound **7a** was prepared in 88% isolated yield upon reaction of *o*-iodoaniline (5.4 g, 24.6 mmol) with trimethylsilylacetylene (4.15 mL, 29.6 mmol) in the presence of diethylamine (4 mL), $Pd(PPh_3)_4$ (0.071 g, 0.06 mmol) and CuI (0.023 g, 0.12 mmol) in DMF (2 mL) at room temperature under a nitrogen atmosphere overnight.

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(15) A typical preparation according to procedure A is as follows: to a stirred solution of **1b** (0.208g, 0.88 mmol) in DMF (3 mL) were added, in this order, *n*-Bu_3N (1.05 mL, 4.42 mmol), $Pd(OAc)_2(PPh_3)_2$ (0.026g, 0.035 mmol) and formic acid (0.127 mL, 3.36 mmol). The reaction mixture was stirred at 70 °C for 4.5 h, then cooled and extracted (0.1 M HCl, EtOAc). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography eluting with a *n*-hexane/EtOAc (95/5 v/v) mixture to give 0.136 g of **3b** (70 % yield): mp 38-40 °C; IR (KBr) 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (d, J = 8 Hz, 2H), 8.01(bs, 1H), 7.94-7.68 (m, 4H), 7.55-7.45 (m, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.30-7.25 (m, 1H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.5, 147.9, 138.6, 137.0, 130.3, 129.8, 129.4, 128.7, 128.3, 127.4, 126.3, 124.8, 119.0, 21.6; MS *m/e* (relative intensity) 239 (M^+, 100), 208 (22), 132 (41).

(16) A typical preparation according to procedure B is as follows: to a stirred solution of **1a** (0.200g, 0.80 mmol) in MeOH (45 mL) were added, in this order, 10% Pd/C (0.085 g, 0.080 mmol) and ammonium formate (0.150 g, 2.39 mmol). The reaction mixture was stirred under N_2 at 70 °C for 2 h. Then, it was cooled and filtered. The filtrate was extracted (0.5 M $NaHCO_3$, EtOAc). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography eluting with a *n*-hexane/EtOAc (99/1 v/v) mixture to give 0.038 g of **6a** (20% yield) and 0.126 g of **3a** (67% yield).

6a: mp 61-63 °C; IR (KBr) 3380, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (d, J = 8.8 Hz, 2H), 7.02-6.96 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.67-6.59 (m, 1H), 6.50 (d, J = 8.5 Hz, 1H), 4.36 (dd, J = 9.2, 3.5 Hz, 1H), 3.79 (s, 3H), 2.90-2.65 (m, 2H), 2.09-1.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.9, 144.8, 136.8, 129.3, 127.6, 126.8, 120.8, 117.1, 113.93,113.86, 55.7, 55.3, 31.1, 26.5; MS *m/e* (relative intensity) 239 (M^+, 100), 208 (22), 132 (41).

3a: mp 123-124 °C; IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15-8.06 (m, 4H), 7.81-7.64 (m, 3H), 7.51-7.42 (m, 1H), 7.02 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.7, 156.8, 148.2, 136.6, 132.1, 129.5, 129.4, 128.8, 127.4, 126.8, 125.8,118.5, 114.1, 55.3; MS *m/e* (relative intensity) 235 (M^+, 100), 220 (37), 192 (34).

(17) A typical preparation according to procedure C is as follows: to a stirred solution of **1f** (0.140g, 0.53 mmol) in DMF (3 mL) were added, in this order, triethylamine (0.3 mL, 2.13 mmol), $Pd(OAc)_2$ (0.006g, 0.027 mmol), dppf (0.016g, 0.029 mmol) and formic acid (0.076 mL, 2.02 mmol). The reaction mixture was stirred at 70 °C for 3 h, then cooled and extracted (0.1 M HCl, EtOAc). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (silica gel 40-60 μm, *n*-hexane/EtOAc 90/10) to give 0.101 g of **3f** (77% yield): mp 138-139 °C; IR (KBr) 1730, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30-8.18 (m, 4H), 8.11 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8 Hz, 1H), 7.87-7.71 (m, 2H), 7.60-7.52 (m, 1H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.9, 155.8, 148.0, 143.5, 137.4, 137.2, 130.0, 129.7, 128.8, 127.7, 127.5, 127.4, 126.9, 119.0, 26.8; MS *m/e* (relative intensity) 247 (M^+, 59), 232 (100), 204 (60).

(18) 2-Cyclooctylquinoline: mp oil; ^1H NMR ($CDCl_3$) δ 8.06 (d, J = 8.5 Hz, 2H), 7.75 (dd, J = 7.9, 1.3 Hz, 1H), 7.66 (td, J = 7.0, 1.3 Hz, 1H), 7.46 (td, J = 7.4, 1.1 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 3.17 (m, 1 H), 2.15-1.6 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 147.7, 136.4, 129.3, 129.1, 127.5, 126.9, 125.6, 120.1, 118.2, 47.7, 33.5, 26.7, 26.5, 26.2; MS *m/e* (relative intensity) 239 (M^+, 30), 182 (50), 156 (100).

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