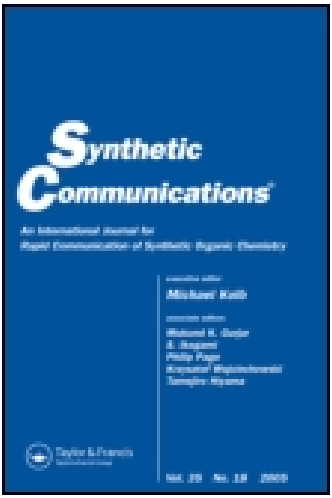

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A FACILE ROUTE FOR THE PREPARATION OF N-PHENYL TETRAHYDROQUINOLINES AND TETRAHYDROISOQUINOLINES

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ABSTRACT

A convenient N-arylation of tetrahydroquinoline and tetrahydroisoquinoline is described using electron-poor, electron-neutral, or electron-rich arylhalide derivatives and palladium(II)-BINAP as a catalyst.

During the course of our investigations, we wanted to form a bond between the 1,2,3,4-tetrahydroquinoline nitrogen and various aromatic nuclei, especially polymethoxylated benzenes. To the best of our knowledge, N-arylation of tetrahydroquinoline with electron-poor, electron-neutral, or electron-rich halogeno derivatives has been scarcely studied. On the one hand, four N-*o* and/or N-*p*-nitrophenyl derivatives have been prepared in less than 20% yield by condensation of tetrahydroquinoline and nitrohalogenobenzenes in refluxing collidine.[1–3] Barton, on the other

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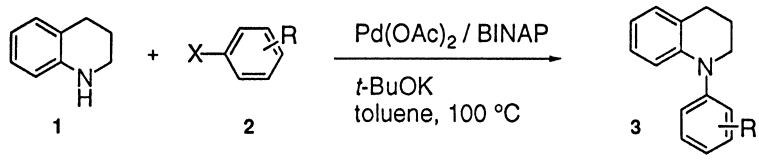
hand, has synthesized 1-(4-methylphenyl) and 1-(2,4-dimethoxyphenyl)-1,2,3,4-tetrahydroquinoline in three steps from aryllead triacetate with copper (II) acetate as a catalyst in 59% and 25% yields, respectively.[4]

We decided to investigate the efficiency of the palladium-catalyst arylation of tetrahydroquinoline **1** with arylhalides (Scheme 1) using palladium (II) acetate, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP). The mild conditions of the palladium-catalyzed aryl amination[5–7] offer considerable advantages over classic methods, which require either activated halogenobenzenes or drastic reaction conditions.



Scheme 1.

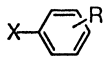
To examine the scope of this palladium-catalyzed system, the coupling of various substituted halides **2** with **1** was studied, and the results are summarized in the Table. The reaction time varied from 15 min to 180 min, depending on the nature of the aryl halide. Various N-aryltetrahydroquinolines **3** can be prepared not only from bromobenzene (entry 1), but also from halogenobenzenes bearing electron-donor (entries 3–6) or electron-attracting groups (entries 8, 9) in good to excellent yields.

There is no difference in reactivity between unsubstituted, trimethoxy, or monomethoxy halogenobenzenes and this, for the latters, whatever the position of the methoxy group on the aromatic ring (entries 3–5). A similar reaction using Ullmann conditions (copper catalyzed) did not allow us to obtain the expected product. The reaction proceeds also efficiently with electron-poor derivatives (entries 8–9) although longer reaction times were necessary. Interestingly, the catalyst system showed efficient even if a much lower concentration of palladium was used (2.5 mol%, entry 7; 0.5 mol%, entry 2).

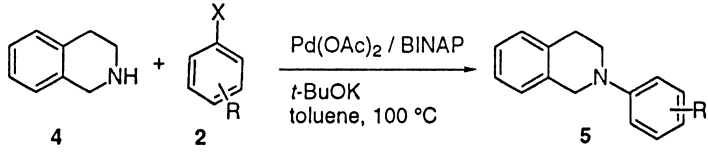
It is worth noting that, compared to the syntheses described in the literature,[1–4] this one-step palladium-catalyzed N-arylation of tetrahydroquinoline is an improvement in terms of yields, ease of execution and work-up.

An extension of this reaction was performed on 1,2,3,4-tetrahydroisoquinoline **4** (Scheme 2). Unsubstituted, 4-methoxy and 3,4,5-trimethoxyphenyl derivatives **5a–c** were prepared in lower yields as compared to the tetrahydroquinoline series (entries 10–12).

Table. Palladium-Catalyzed Coupling of Tetrahydroquinoline **1** and Tetrahydroisoquinoline **4** with Arylhalides[a]

Entry	Amine	X	 R	Pd mol%	Product	Time (h)	Yield (%)	m.p. (°C)
1	**1**	Br	H	5	**3a**	0.25	80	oil[b]
2	**1**	Br	H	0.5	**3a**	3	82	
3	**1**	Br	2-OMe	5	**3b**	0.25	80	oil
4	**1**	Br	3-OMe	5	**3c**	0.25	79	oil
5	**1**	Br	4-OMe	5	**3d**	0.25	79	69
6	**1**	I	3,4,5-triOMe	5	**3e**	0.25	87	91
7	**1**	I	3,4,5-triOMe	2.5	**3e**	0.5	80	
8	**1**	I	4-NO_2	5	**3f**	2.5	62	123[c]
9	**1**	Br	4-CHO	5	**3g**	3	64	85
10	**4**	Br	H	5	**5a**	0.75	50	45[d]
11	**4**	Br	4-OMe	5	**5b**	0.75	39	95[e]
12	**4**	I	3,4,5-triOMe	5	**5c**	0.75	40	oil

[a]Reactions were performed with **1** equiv. of arylhalide, 1.2 equiv. of amine, 1.4 equiv. of *t*-BuOK, cat. $Pd(OAc)_2$, and BINAP 1.1 equiv./Pd; [b]m.p. of HI salt 147°C, ref. (8); [c]no m.p. in ref. (1); [d]m.p. 44.5°–45.5°C., ref. (9); [e]m.p. 93°–95°C, ref. (4).



4 2 5

Scheme 2.

In conclusion, we have described the first intermolecular palladium-catalyzed N-arylation of tetrahydroquinoline with substituted halogenobenzenes. This one-step reaction can be carried out using both electron-rich and electron-poor arylhalides. Consequently, this simple method is very interesting compared to the previously described reactions; furthermore, it gives us an easy access to many new N-arylated compounds in the quinoline and isoquinoline series.

EXPERIMENTAL

All melting points were determined on a Maquenne apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 1600 infrared

spectrophotometer. NMR spectra were recorded on Bruker AC-300 spectrometer; chemical shift values are given in ppm (δ). Flash column chromatographies were performed using Merck silica gel 60, 70–230 mesh ASTM.

General Procedure

To a solution of palladium (II) acetate (14 mg, 0.063 mmol), BINAP (43 mg, 0.069 mmol) in dry toluene (2 mL), arylhalide (1.25 mmol), and tetrahydroquinoline or tetrahydroisoquinoline (200 mg, 1.5 mmol) were added and then *t*-BuOK (197 mg, 1.75 mmol). The solution was vigorously stirred at 100°C. The reaction was then quenched with water. After extraction with dichloromethane and evaporation of the solvents under reduced pressure, the crude mixture was purified by flash chromatography (eluent: CH_2Cl_2/cyclohexane from 20/80 to 50/50) to give pure **3** or **5**.

1-(2-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline **3b**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.03 (quint., 2H, 6 Hz); 2.88 (t, 2H, 6 Hz); 3.52 (t, 2H, 6 Hz); 3.78 (s, 3H); 6.24 (d, 1H, 7.5 Hz); 6.60 (t, 1H, 7.5 Hz); 6.84 (t, 1H, 7.5 Hz); 6.90–7.00 (m, 3H); 7.20 (t, 2H, 7.5 Hz). **^{13}C NMR (75.43 MHz, $CDCl_3$)** δ: 22.2; 28.0; 50.3; 55.6; 112.7; 113.6; 116.6; 121.3; 122.1; 126.5; 126.9; 129.1; 129.5; 136.0; 145.1; 156.2. **IR (film)**: 1499; 1453; 1303; 1248.

1-(3-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline **3c**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.07 (quint., 2H, 6 Hz); 2.87 (t, 2H, 6 Hz); 3.63 (t, 2H, 6 Hz); 3.80 (s, 3H); 6.68 (d, 1H, 7 Hz); 6.75 (t, 1H, 7 Hz); 6.80–6.90 (m, 3H); 6.98 (t, 1H, 7 Hz); 7.07 (d, 1H, 7 Hz); 7.25 (t, 1H, 7 Hz). **^{13}C NMR (75.43 MHz, $CDCl_3$)** δ: 22.8; 27.7; 50.6; 55.2; 108.8; 110.0; 116.6; 118.5; 124.9; 126.3; 129.3; 129.9; 144.1; 149.6; 160.5. **IR (film)**: 1595; 1575; 1491; 1456; 1197; 1161.

1-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline **3d**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.05 (quint., 2H, 6 Hz); 2.88 (t, 2H, 6 Hz); 3.56 (t, 2H, 6 Hz); 3.81 (s, 3H); 6.50 (d, 1H, 8.5 Hz); 6.65 (t, 1H, 8.5 Hz); 6.90 (m, 3H), 7.02 (d, 1H, 8.5 Hz); 7.19 (d, 2H, 9 Hz). **^{13}C NMR**

(75.43 MHz, $CDCl_3$) δ: 22.6; 27.0; 51.7; 55.5; 114.3; 114.9; 117.3; 123.0; 126.6; 127.7; 129.6; 141.4; 145.6; 156.8; **IR (film)**: 1508; 1492; 1241.

1-(3,4,5-Trimethoxyphenyl)-1,2,3,4-tetrahydroquinoline **3e**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.02 (quint., 2H, 6 Hz); 2.85 (t, 2H, 6 Hz); 3.55 (t, 2H, 6 Hz); 3.78 (s, 6H); 3.84 (s, 3H); 6.44 (s, 2H); 6.62 (m, 2H); 6.89 (t, 1H, 7 Hz); 6.98 (d, 1H, 7 Hz). **^{13}C NMR (75.43 MHz, $CDCl_3$)** δ: 22.5; 27.5; 51.1; 55.9; 60.7; 102.7; 115.0; 117.6; 123.5; 144.1; 144.6; 153.6. **IR (film)**: 1588; 1504; 1454; 1232; 1127.

1-(4-Nitrophenyl)-1,2,3,4-tetrahydroquinoline **3f**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.05 (quint., 2H, 6 Hz); 2.77 (t, 2H, 6 Hz); 3.72 (t, 2H, 6 Hz); 7.00 (t, 1H, 7 Hz); 7.10–7.30 (m, 5H); 8.11 (d, 2H, 7 Hz). **^{13}C NMR (75.43 MHz, $CDCl_3$)** δ: 24.2; 27.3; 48.9; 117.5; 120.7; 123.0; 125.6; 126.6; 129.4; 131.1; 140.8; 153.5. **IR (film)**: 1589; 1495; 1311; 1111.

4-(3,4-Dihydro-2H-quinolin-1-yl)benzaldehyde **3g**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.03 (quint., 2H, 6 Hz); 2.75 (t, 2H, 6 Hz); 3.71 (t, 2H, 6 Hz); 6.90–7.30 (m, 6H); 7.75 (d, 2H, 7.5 Hz); 9.82 (s, 1H). **^{13}C NMR (75.43 MHz, $CDCl_3$)** δ: 23.8; 27.2; 48.7; 118.5; 119.9; 122.0; 126.3; 129.0; 129.1; 129.9; 131.2; 131.9; 153.2; 190.3. **IR (film)**: 1686; 1592; 1490; 1328; 1165.

1-(3,4,5-Trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **5c**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.47 (t, 2H, 6 Hz); 3.96 (t, 2H, 6 Hz); 4.30 (s, 3H); 4.38 (s, 6H); 4.82 (s, 2H); 6.70 (s, 2H); 7.60–7.70 (m, 4H). **^{13}C NMR (75.43 MHz, $CDCl_3$)** δ: 29.0; 47.2; 51.4; 55.8; 60.7; 93.5; 104.3; 125.8; 126.1; 128.3; 134.0; 134.4; 147.4; 153.4. **IR (film)**: 1605; 1583; 1510; 1451; 1238; 1126.

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