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Pd-catalyzed *ortho*-arylation of 3,4-dihydroisoquinolones via C–H bond activation: synthesis of 8-aryl-1,2,3,4-tetrahydroisoquinolines

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ABSTRACT

An efficient route to synthesize biologically interesting 8-aryl-1,2,3,4-tetrahydroisoquinoline has been developed. It involves the Pd-catalyzed direct arylation of 3,4-dihydroisoquinolones via C–H bond activation with aryl iodides to afford a variety of 8-arylated cross-coupling products, which are subsequently reduced to 8-aryl-1,2,3,4-tetrahydroisoquinolines in good to excellent yields.

1. Introduction

The biaryl scaffold has been found in various biologically active compounds[1] and valuable building blocks for synthetic polymers.[2] Currently, the most widely used methods for the formation of aryl–aryl bonds involve Pd-catalyzed cross-coupling reactions between aryl halides and arylmetals.[3,4] However, these transformations suffer from the disadvantage that they require installation of functional groups on both coupling partners, which results in expensive and longer synthetic routes to prepare starting materials. In this sense, regioselective direct coupling of aromatic C–H with functionalized arenes has a tremendous potential from the viewpoint of atom economy and efficiency. Recently, transition metal-catalyzed C–H bond activation/arylation methods have been shown to be effective for C_{aryl}–H/C_{aryl}–X cross-coupling reactions.[5]

In our continuous effort to build a privileged scaffold library containing a biaryl moiety, we focused our attention on the family of aporphinoids. Aporphine is a large group of benzylisoquinoline-derived alkaloids with more than 500 members, characterized by the tetracyclic skeleton shown in Figure 1. The relevant structural features of these alkaloids are the presence of an isoquinoline core, together with a biaryl subunit and one stereogenic center at C-6a. A wide range of interesting biological activities have been studied, including anticancer,[6] antimalarial,[7] antiplatelet,[8] vasorelaxing,[9] and leischmanicidal activities.[10] These various pharmacological activities have prompted intensive structure–activity relationship studies over the past three decades.[11]

Despite many methods for the synthesis of isoquinolines[12] and tetrahydroisoquinolines,[13] only one attempt was made by Ellefson using aryloxazolines[14] as key intermediates to access the 8-aryl-1,2,3,4-tetrahydroisoquinolines, which possess the basic structural features of the aporphine skeleton without the C-7 methylene unit.[15] This limited synthetic route prompted us to investigate more efficient and convergent approaches to 8-aryl-1,2,3,4-tetrahydroisoquinolines. We now report our success.

2. Results and discussion

The key transformations in the synthesis of 8-aryl-1,2,3,4-tetrahydroisoquinolines involve the introduction of an aryl group at the

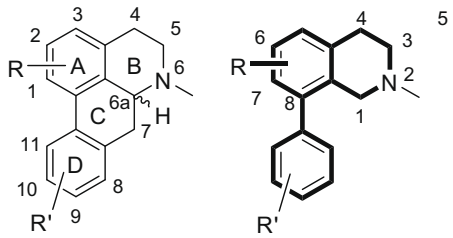

Figure 1. Aporphine alkaloids and 8-aryl-1,2,3,4-tetrahydroisoquinoline.

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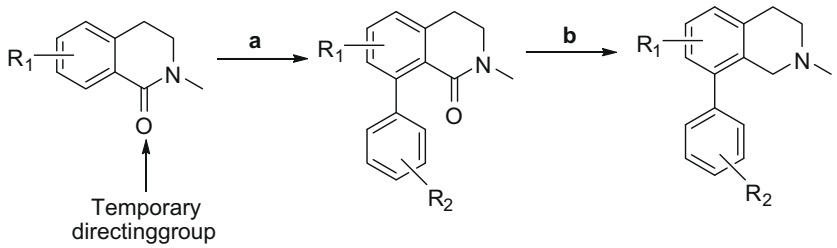
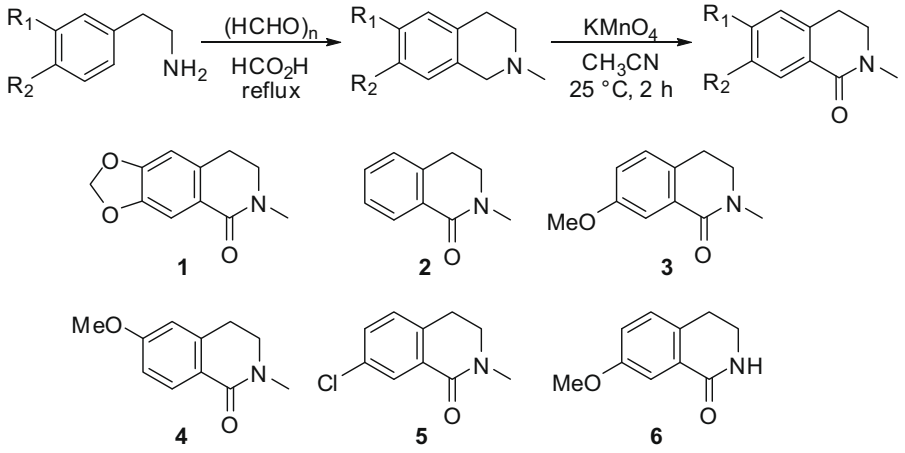


Scheme 1. Key transformations.



Scheme 2. Synthesis of 3,4-dihydroisoquinolones.

C-8 position regioselectively directed by a carbonyl group via C–H bond activation and subsequent reduction (Scheme 1). Recently, many research groups have shown a significant progress in the regioselective C–H bond activation of arenes containing a directing group under Pd, Ru, or Rh catalysis.[16] However, the direct arylation of 3,4-dihydroquinolones is unprecedented to the best of our knowledge.

The 3,4-dihydroisoquinolones (**1–6**) required for this methodology are readily prepared by a modified protocol shown in Scheme 2.

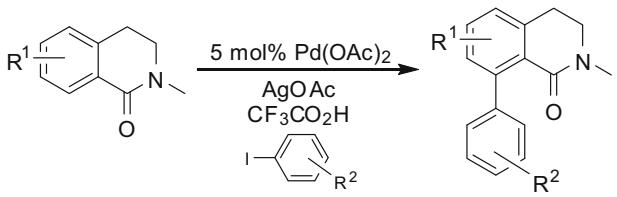
With various 3,4-dihydroisoquinolones in hand, the direct arylation of 3,4-dihydroisoquinolones with aryl iodides was investigated. The initial optimization was carried out with respect to **1** with 4-iodoacetophenone using Pd catalysis in different solvents. To our delight, the regioselective arylation went quite smoothly using $Pd(OAc)_2$ as a catalyst and AgOAc as an additive at the elevated temperature to give 8-arylated adduct **8** in 83% isolated yield. The regioselectivity was confirmed with other known compounds in the literature.[17] The optimized conditions for the regioselective direct arylation are the combination of 1.0 equiv of substrate, 3.0 equiv of aryl iodide, 1.3 equiv of AgOAc as an additive, 5 mol % of $Pd(OAc)_2$, and trifluoroacetic acid as a solvent. The results are summarized in Table 1.[18] The reactions proceeded well at the elevated temperatures (110–130 °C) in 5–24 h, depending on the substitution patterns in the 3,4-dihydroisoquinolones and the functional groups on the aryl iodides. Regarding the 3,4-dihydroisoquinolones, electron-rich substrates **1** and **4** reacted faster than unsubstituted or more hindered substrates **2** and **3** (Table 1, compare entries 8, 13, and 18). Electron-poor substrate **5** failed to give any desired products. This implies that the electron-nature of the aromatic ring is also a critical factor for the successful C–H bond activation. In the case of *N*–H substrate **6,** most of the starting material was recovered intact, and only trace amounts of cross-coupling product were isolated (<10%). Presumably, the nitrogen atom in the amide coordinates with the palladium catalyst, resulting in much lower yields. Good results have been obtained with both electron-rich and electron-poor aryl iodides (entries 2–5). It is noteworthy that 4-bromo-iodobenzene also proceeds smoothly to afford bromo-substituted product **12**, which could be further modified by Heck[19] and Suzuki[3] reactions (entry 6).

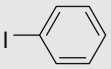
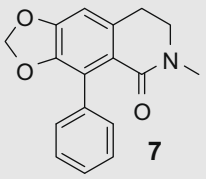
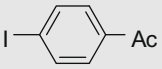
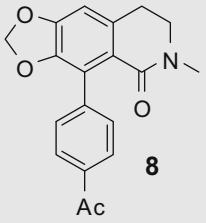
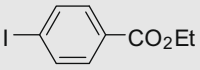
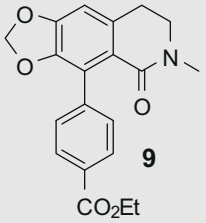
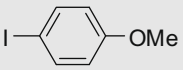
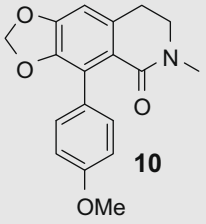
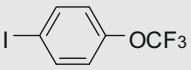
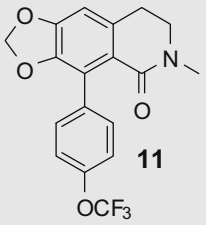
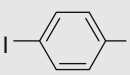
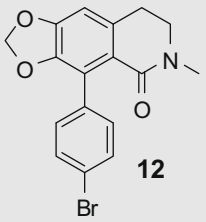
After we have proven the efficiency of this process to access a variety of 8-aryl-3,4-dihydroisoquinolones, we next reduced these cross-coupling products into the corresponding 1,2,3,4-tetrahydroisoquinolines with $LiAlH_4$ in THF for 2 h. The selected results are shown in Table 2.[20]

3. Conclusions

In conclusion, we have developed a new, concise, and convergent procedure for biologically interesting 8-aryl-1,2,3,4-tetrahydroisoquinolines from readily available starting materials. Extensions of this method to the synthesis of other biologically interesting biaryls are underway.

Table 1
Synthesis of 8-aryl-3,4-dihydroisoquinolones by Pd-catalyzed *ortho*-arylation[a]



Entry	Substrate	Aryl iodide	Temp time	Product	Yield[b] (%)
1	**1**		110 °C 17 h	 **7**	68
2	**1**		130 °C 17 h	 **8**	83
3	**1**		110 °C 5 h	 **9**	75
4	**1**		110 °C 5 h	 **10**	57
5	**1**		110 °C 15 h	 **11**	81
6	**1**		110 °C 15 h	 **12**	86

(*continued on next page*)

Table 1 (*continued*)

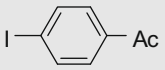
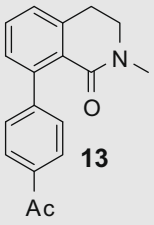
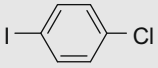
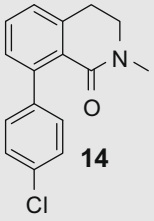
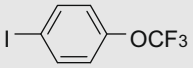
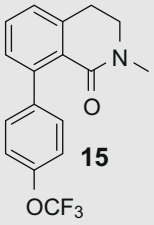
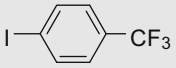
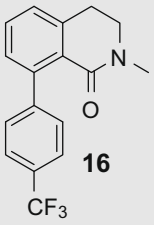
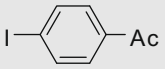
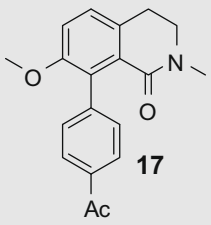
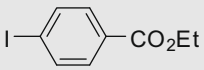
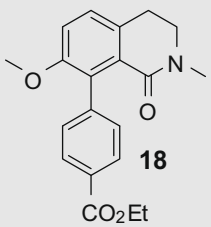
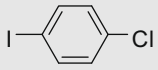
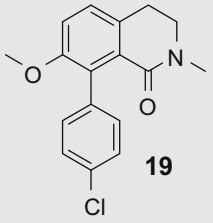
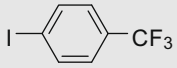
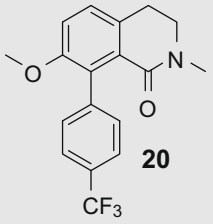
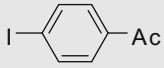
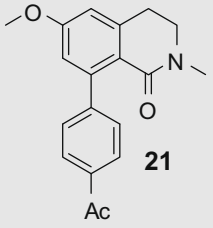
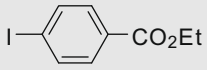
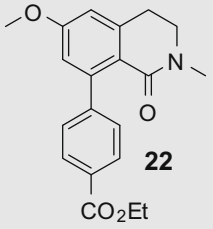
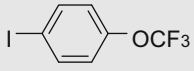
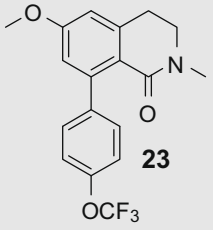
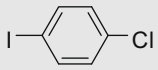
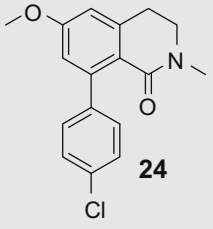
Entry	Substrate	Aryl iodide	Temp time	Product	Yield[b] (%)
7	**2**		110 °C 24 h	 **13**	55
8	**2**		110 °C 17 h	 **14**	73
9	**2**		110 °C 17 h	 **15**	63
10	**2**		110 °C 14 h	 **16**	70
11	**3**		120 °C 15 h	 **17**	50
12	**3**		120 °C 15 h	 **18**	59

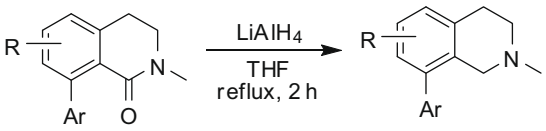
Table 1 (*continued*)

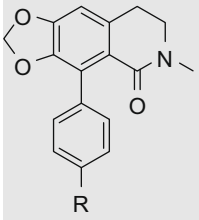
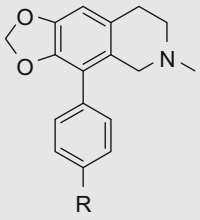
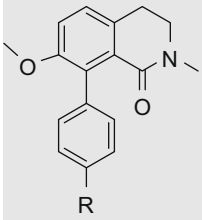
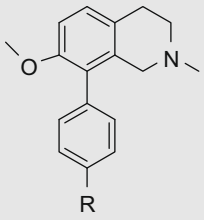
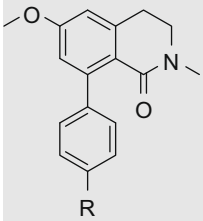
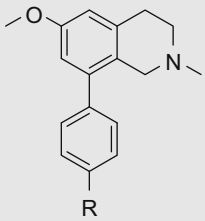
Entry	Substrate	Aryl iodide	Temp time	Product	Yield[b] (%)
13	**3**		110 °C 20 h	 **19**	63
14	**3**		110 °C 16 h	 **20**	62
15	**4**		110 °C 7 h	 **21**	50
16	**4**		110 °C 5 h	 **22**	68
17	**4**		110 °C 7 h	 **23**	80
18	**4**		110 °C 7 h	 **24**	76

[a] All reactions were run under the following conditions unless otherwise specified: substituted 3,4-dihydroisoquinolone (1.0 equiv), aryl iodide (3.0 equiv), 5 mol % $Pd(OAc)_2$, AgOAc (1.3 equiv), trifluoroacetic acid (1.25 mL/substrate mmol).

[b] Isolated yields after column chromatography.

Table 2
Reduction to 8-aryl-1,2,3,4-tetrahydroisoquinolines



Substrate	Product		Yield[a] (%)
		R = H	**25**	87
		Cl	**26**	90
		OMe	**27**	70
		CF_3	**28**	93
		R = Cl	**29**	72
		OCF_3	**30**	77
		CF_3	**31**	73
		R = Cl	**32**	89
		OCF_3	**33**	88

[a] Isolated yields after column chromatography.

Acknowledgment

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References and notes

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18. *General procedure for Pd-catalyzed direct arylation*: A mixture of substituted 3,4-dihydroisoquinolone **1** (100 mg, 0.487 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol, 5 mol %), AgOAc (106 mg, 0.633 mmol, 1.3 equiv), and iodobenzene (164 μL, 1.46 mmol, 3.0 equiv) in trifluoroacetic acid (610 μL, 1.25 mL/substrate mmol) was heated at 110 °C in a sealed tube for 15 h. After being cooled to 25 °C, the reaction mixture was diluted with CH_2Cl_2, and was filtered through a pad of Celite®. The filtrate was washed with H_2O (2 × 10 mL), and the resulting organic layer was dried over Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified via flash column chromatography (hexanes/EtOAc, 2:1→1:1 and then CH_2Cl_2/MeOH, 30:1) to give direct arylation product **7** (92 mg, 68%) as a white solid; mp = 133–134 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.38 (m, 2H), 7.31–7.29 (m, 3H), 6.63 (s, 1H), 5.94 (s, 2H), 3.53 (t, J = 6.4 Hz, 2H), 3.02 (s, 3H), 2.92 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 149.0, 145.5, 136.3, 135.3, 128.8, 127.8, 127.3, 125.5, 121.9, 106.3, 101.5, 48.0, 35.2, 29.7; IR (film) 2896, 1648, 1458, 1259, 1054 cm^{-1}; TLC R_f (hexanes:EtOAc 1:1) = 0.44; HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_3$ (M+H)$^+$ 282.1130, found 282.1134.

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20. *General Procedure for reduction of 8-aryl-3,4-dihydroisoquinolones to 8-aryl-1,2,3,4-tetrahydroisoquinolines*: A solution of 8-aryl-3,4-dihydroisoquinolone **7** (40 mg, 0.142 mmol) and $LiAlH_4$ (12 mg, 0.284 mmol) in THF (1.6 mL) was refluxed for 2 h. The reaction mixture was quenched by the successive addition of H_2O (200 μL), 1 N NaOH (200 μL), and H_2O (600 μL) at 0 °C. The mixture was then extracted with $CHCl_3$ (3 × 10 mL)/H_2O (5 mL). The combined organic layers were washed with brine, and were dried over Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified via flash column chromatography to compound **25** (33 mg, 87%) as a yellow solid; mp = 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.40 (m, 2H), 7.37–7.33 (m, 1H), 7.31–7.29 (m, 2H), 6.59 (s, 1H), 5.84 (s, 2H), 3.26 (s, 2H), 2.90 (t, J = 6.4 Hz, 2H), 2.63 (t, J = 6.4 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 143.4, 134.3, 129.5, 128.4, 127.7, 127.2, 125.4, 121.5, 107.7, 100.6, 56.5, 52.7, 46.1, 29.7; IR (film) 2931, 2777, 1462, 1375, 1043 cm^{-1}; TLC R_f (CH_2Cl_2:MeOH 30:1) = 0.11; HRMS (ESI) m/z calcd for $C_{17}H_{18}NO_2$ (M+H)$^+$ 268.1338, found 268.1342.