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Intramolecular *ortho*-arylation of phenols utilized in the synthesis of the aporphine alkaloids (±)-lirinidine and (±)-nuciferine

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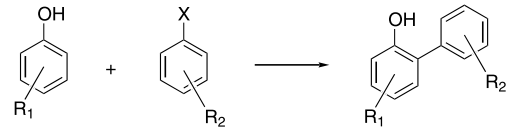
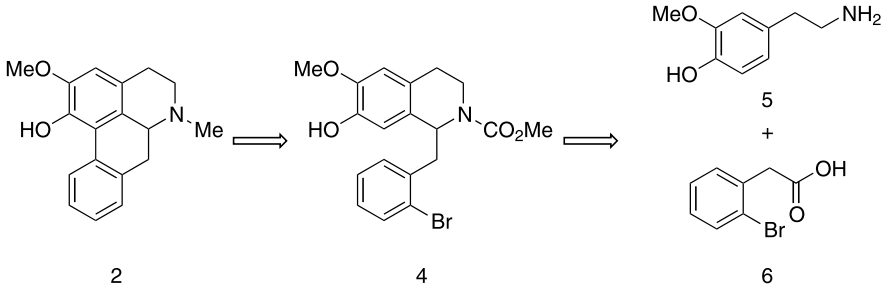
Abstract—A palladium-mediated intramolecular phenol *ortho*-arylation reaction applied to the construction of aporphine alkaloids is reported. Most significantly, the efficiency of this transformation was enhanced by the utilization of trialkylphosphine (i.e. tricyclohexylphosphine) or trialkylphosphonium salts (i.e. di-*tert*-butylmethyl-phosphonium tetrafluoroborate) as co-catalysts in the presence of cesium carbonate. This methodology was employed in the syntheses of the aporphine alkaloids (±)-lirinidine and (±)-nuciferine.

Ortho-aryl phenols are an important structural component found in a wide array of organic compounds. One of the most attractive strategies for constructing this molecular motif involves the direct *ortho*-arylation of phenols with aryl halides. Several approaches have been described to mediate this type of process, including enzymatic,[1] photochemical,[2] and oxidative.[3] Multi-step processes, including most notably the Pinhey–Barton aryl-lead coupling route, have also been described.[4]

Recently, the utilization of transition metals to affect this transformation has been explored.[5,6] For example, an anion-accelerated intramolecular coupling of phenols with aryl halides was accomplished with a palladium complex (Herrmann's catalyst) and cesium carbonate in dimethylacetamide (DMA) to yield a variety of *ortho*-aryl phenol containing heterocycles and carbocycles.[5d] Similarly, a palladium-mediated cyclization of an aryl iodide and a phenol, in the presence of the base t-$BuCO_2Na$, was utilized in the synthesis of pradimicinone.[5a] Recently, transition metal mediated *ortho*-arylation of phenols has been extended to intermolecular couplings employing a rhodium catalyst ($RhCl(PPh_3)_3$) in the presence of aryl dialkylphosphinite co-catalysts.[6]





Scheme 1.

Keywords: palladium; *ortho*-arylation; phenol; aporphine; lirinidine; nuciferine.
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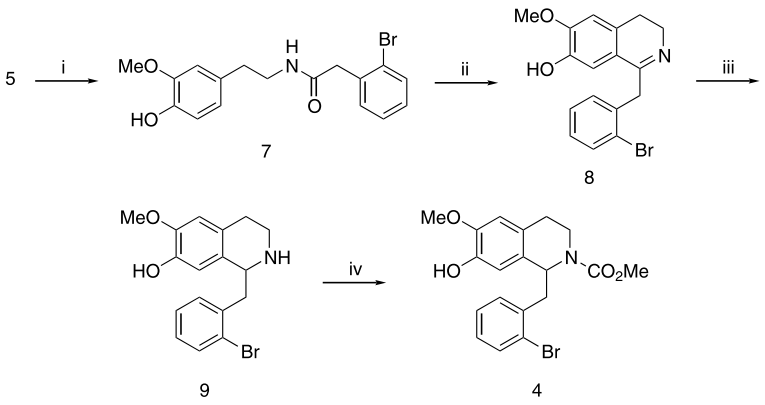
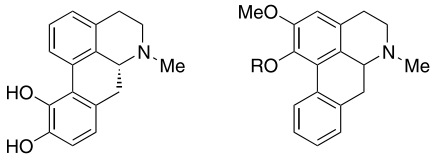


Scheme 2. *Reagents and conditions*: (i) **6**, HBTU, *i*-Pr_2EtN, CH_2Cl_2, rt, 18 h, 100%; (ii) $POCl_3$, CH_3CN, Δ, 1.5 h, 86%; (iii) $NaBH_4$, MeOH, rt, 1 h; (iv) ClC(O)OMe, THF, rt, 1 h, 76% for two steps.

The *ortho*-aryl phenol motif is found among many members of the aporphine alkaloid class of natural products.[7] Apomorphine, **1**, is an example of a molecule from this class that has a variety of pharmacological effects rendering it potentially useful for the treatment of maladies such as erectile dysfunction and Parkinson's Disease.[8] Other aporphine alkaloids that contain an *ortho*-aryl phenol (or alkylated phenol) include lirinidine[9] and nuciferine.[10] The thesis of this communication is that transition metal mediated intramolecular *ortho*-arylation of phenols provides an efficient means to construct aporphine alkaloids, such as (±)-lirinidine, **2**, and (±)-nuciferine, **3**.[5e]

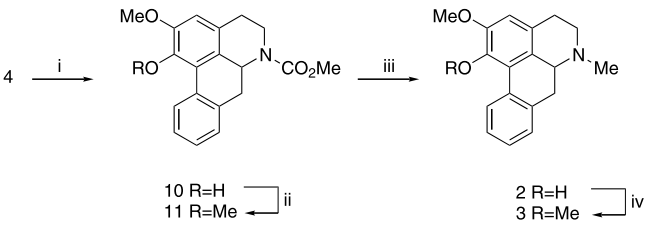


1 2 R=H 3 R=Me

A retrosynthetic analysis of **2** is shown is Scheme 1. Disconnection of the *ortho*-aryl phenol gives a benzyl tetrahydroisoquinoline derivative **4**. Further disconnections lead to readily available phenethyl amine **5** and phenyl acetic acid **6**.

Utilizing *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (HBTU), **5** and **6** were coupled in the presence of diisopropylethylamine to give a quantitative yield of amide **7** (Scheme 2).[11] The amide was subjected to a Bischler–Napieralski cyclization upon treatment with phosphorous oxychloride in refluxing acetonitrile to yield the dihydroisoquinoline **8**.[12] Sodium borohydride reduction of **8** in methanol gave the amine **9**, which was subsequently treated with methyl chloroformate in tetrahydrofuran to give the tetrahydroisoquinoline **4** in 76% yield over the two steps.[13]

Various conditions were evaluated to facilitate the intramolecular *ortho*-arylation of **4** to yield the aporphine compound **10** (Scheme 3 and Table 1). Initially, Herrmann's catalyst was tried without success (Entry 1). However, in the presence of $Pd(OAc)_2$, triphenylphosphine and anhydrous sodium acetate in DMA **10** was obtained in low yield (Entry 2). The remaining material was unreacted starting material. A further increase in yield was obtained when the triphenylphosphine ligand was replaced with tricyclohexylphosphine (Entry 3). Recently, the utilization of trialkylphosphine ligands in metal mediated processes has proven very successful.[14] Furthermore, air and moisture stable di-*tert*-butylmethylphosphonium tetrafluoroborate could also serve as co-catalyst with equal efficiency (Entry 4).[15] Addition of 4 Å powdered molecular sieves to the $Pd(OAc)_2/Cy_3P$ conditions did not have any noticeable effect on the reaction (Entry 5). Increasing the amount of palladium to sub-stoichiometric quantities further improved the yield of **10** (Entry 6). Utilization of $Pd_2(dba)_3$ (Entry 7) or an imidazolium ligand (Entry 8; IMesHCl: 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride) were found to be disadvantageous. Replacing sodium acetate with potassium *tert*-butoxide was also found to be detrimental (Entry 9) to the yield of **10**. However, substituting sodium acetate with cesium carbonate improved the yield (Entry 10).[16] Addition of lithium iodide to the reaction completely inhibited coupling (Entry 11). A similar observation has been reported for some Heck reactions.[17] In light of the detrimental effects from lithium iodide, the reaction was conducted in the presence of silver nitrate in order to sequester the bromide produced. This strategy has proven useful in some Pd-mediated coupling reactions.[18] However, in the



Scheme 3. *Reagents and conditions*: (i) see Table 1; (ii) MeI, K_2CO_3, DMF, rt, 4 h, 68%; (iii) $LiAlH_4$, THF, Δ, 22 h, 86%; (iv) CH_2N_2, $MeOH/Et_2O$ (1:1), rt, 6 h, 80%.

Table 1.

Entry	Pd source (mol%)	Ligand (mol%)	Base (equiv.)	Additive	Isolated yield of **10** (%)
1	Hermann's (5)	–	Cs_2CO_3 (3)	–	0
2	$Pd(OAc)_2$ (20)	PPh_3 (40)	NaOAc (3.2)	–	15
3	$Pd(OAc)_2$ (20)	PCy_3 (40)	NaOAc (3.2)	–	45
4	$Pd(OAc)_2$ (20)	$(t\text{-Bu})_2MePHBF_4$ (40)	NaOAc (3.2)	–	43
5	$Pd(OAc)_2$ (20)	PCy_3 (40)	NaOAc (3.2)	4 Å mol. sieves	46
6	$Pd(OAc)_2$ (50)	PCy_3 (100)	NaOAc (3.2)	–	64
7	$Pd_2(dba)_3$ (10)	PCy_3 (40)	NaOAc (3.2)	–	19
8	$Pd(OAc)_2$ (20)	IMesHCl (40)	NaOAc (3.2)	–	<10
9	$Pd(OAc)_2$ (20)	PCy_3 (40)	KO-*t*-Bu (1.5)	–	24
10	$Pd(OAc)_2$ (20)	PCy_3 (40)	Cs_2CO_3 (3.2)	–	58
11	$Pd(OAc)_2$ (20)	PCy_3 (40)	Cs_2CO_3 (3.2)	LiI (3.2 equiv.)	0
12	$Pd(OAc)_2$ (20)	PCy_3 (40)	Cs_2CO_3 (3.2)	$AgNO_3$ (1.0 equiv.)	17
13	$PdBr_2$ (20)	PCy_3 (40)	Cs_2CO_3 (3.2)	–	49

Temp.: 110°C; solvent: DMA; time: 24 h; atmosphere: Ar.

present case **10** was only obtained in 17% yield (Entry 12). Finally, using $PdBr_2$ in place of the $Pd(OAc)_2$ was found to have a slight negative effect on the reaction (Entry 13). It is noteworthy that in all the conditions evaluated, neither de-brominated nor salutaridine-like products were isolated.[5e]

Having accomplished the conversion of **4** to **10** in moderate yield, the syntheses of the natural products **2** and **3** were completed (Scheme 3). The carbamate **10** was reduced with lithium aluminum hydride (LAH) in refluxing THF to give **2**[19] in 86% yield.[2d,20] In addition, **10** was converted to its corresponding methyl ether **11** in 68% yield by treatment with methyl iodide in the presence of potassium carbonate in DMF.[21] Reduction of **11** with LAH gave **3**,[22] but also resulted in concomitant de-methylation producing **2** (**3**:**2** = 7:1). De-methylation of 1,2-dimethoxyaporphines has been previously reported under acidic conditions (i.e. concentrated H_2SO_4 or $AlCl_3$),[23] but not for reducing conditions like those described herein. Alternatively, **2** was converted to **3** in the presence of excess diazomethane in a mixture of methanol and diethyl ether in good yield (80%).[24]

In conclusion, a palladium-mediated intramolecular phenol *ortho*-arylation reaction was demonstrated as an efficient means to construct aporphine alkaloids. Most significantly, the efficiency of this transformation was enhanced by the utilization of trialkylphosphine or trialkylphosphonium salts as co-catalysts in the presence of the base anhydrous cesium carbonate. This methodology was employed in the syntheses of two aporphine alkaloids, (±)-lirinidine, **2**, and (±)-nuciferine, **3**. Further optimization of this methodology and applications of the strategy described herein to the synthesis of other aporphine alkaloids as well as other classes of natural and non-natural compounds is underway.

Acknowledgements

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16. A mixture of **4** (23.3 mg, 0.0576 mmol), tricyclohexylphosphine (6.9 mg, 0.0246 mmol), anhydrous cesium carbonate (60 mg, 0.184 mmol, finely ground powder) and palladium acetate (2.8 mg, 0.0123 mmol) in DMA (1 mL) under an argon atmosphere was heated at 110°C for 24 h. The reaction mixture was allowed to cool and then carefully diluted with 1N HCl. The reaction mixture was extracted several times with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel using hexane/ethyl acetate (65:35) as eluant to give 10.9 mg of **10** (58%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.62 (m, 1H); 2.83–2.88 (m, 2H); 2.96–3.01 (m, 2H); 3.78 (s, 3H); 3.98 (s, 3H); 4.45–4.49 (bm, 1H); 4.74–4.80 (bm, 1H); 6.17 (s, 1H); 6.62 (s, 1H); 7.23 (dt, 1H, $J_1=7$ Hz, $J_2=1$Hz); 7.27 (d, 1H, $J=7$ Hz); 7.34 (dt, 1H, $J_1=8.5$ Hz, $J_2=1$ Hz); 8.43 (d, 1H, $J=8.5$ Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 30.29, 35.42, 39.31, 51.87, 52.86, 56.47, 109.80, 120.25, 125.08, 126.48, 126.92, 127.46, 128.52, 128.87, 132.12, 136.62, 142.13, 145.95, 156.23; HRESMS $[M+H]^+$: 326.1393 (calculated for $[C_{19}H_{19}NO_4+H]^+$: 326.1392). For a reference to **10** see: Tschesche, R.; Welzel, P.; Moll, R.; Legler, G. *Tetrahedron* **1964**, *20*, 1435–1447.
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19. **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51–2.54 (m, 1H); 2.56 (s, 3H); 2.61–2.70 (m, 2H); 3.04–3.20 (m, 4H); 3.91 (s, 3H); 6.17 (bs, 1H); 6.59 (s, 1H); 7.20–7.28 (m, 2H); 7.32 (t, 1H, $J=7.2$ Hz); 8.37 (d, 1H, $J=7.6$ Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 29.08, 35.18, 44.10, 53.67, 56.37, 62.54, 109.64, 119.57, 123.97, 126.90, 127.14, 128.04, 128.56, 129.87, 132.48, 136.19, 141.59, 146.02; HRESMS $[M+H]^+$: 282.1494 (calculated for $[C_{18}H_{19}NO_2+H]^+$: 282.1494).
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22. **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56–2.60 (m, 1H); 2.57 (s, 3H); 2.65–2.74 (m, 2H); 3.04–3.14 (m, 3H); 3.16–3.25 (m, 1H); 3.65 (s, 3H); 3.89 (s, 3H); 6.64 (s, 1H); 7.20–7.34 (m, 3H); 8.36 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 29.15, 35.12, 43.92, 53.42, 56.07, 60.44, 62.51, 111.45, 127.12, 127.27, 127.59, 127.68, 128.08, 128.55, 128.66, 132.29, 136.42, 145.45, 152.32; HRESMS $[M]^+$: 295.1580 (calculated for $[C_{19}H_{21}NO_2]^+$: 295.1572).
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