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Direct intramolecular arylation of unactivated arenes: application to the synthesis of aporphine alkaloids†

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The direct intramolecular C–H arylation of unactivated arenes is a viable strategy for the synthesis of aporphine alkaloids. These reactions occur with 3 to 5 mol% catalyst and generate the aporphine skeleton in up to 99% yield.

The direct arylation of aromatic C–H bonds is currently an area of intense study because of its potential to reduce reliance on stoichiometric organometallic activating groups in the formation of biaryl molecules.[1] These reactions rely on the latent nucleophilicity of delocalized arene π-electron systems. To enhance this π-nucleophilicity, substrates such as heterocyclic arenes, benzamides and arenes possessing a pendant directing group are most commonly employed.[2] In contrast, reactions with unactivated arenes commonly suffer from lower yields, very high catalyst loadings and harsh reaction conditions.[3,4] These limitations likely explain why this approach has seldom been used in synthesis, despite its tremendous potential and high efficiency. The establishment of reaction conditions capable of efficiently achieving C–H arylation of unactivated substrates in the context of total synthesis would have a significant impact on the preparation of biaryl molecules.

The aporphine alkaloids have received increased attention in recent years due to their demonstrated serotonergic,[5] dopaminergic, antiplatelet[6] and vasorelaxing activity.[7] Numerous methods for their preparation have been reported, yet the biaryl linkage remains a consistent synthetic challenge.[8] Cuny has shown that the direct arylation of *activated ortho*-phenolate substrates could be a potential solution to this challenging bond formation.[9] Unfortunately, even with activated molecules and high catalyst loadings (20–50 mol%), only moderate yields (50–60%) could be obtained. We recently reported a catalyst system that enables direct intramolecular arylation reactions to be performed with unactivated model substrates, in very high yield and with low catalyst loadings. Herein, we report conditions for the preparation of aporphine alkaloids *via* the direct arylation of *unactivated substrates* (Fig. 1) with substantially reduced catalyst loadings and with excellent yields.

There were three structural aspects of the aporphine core whose impact on the arylation chemistry needed to be addressed. First, the aliphatic tether of **1** was found to be the most challenging case in our methodological studies. Additionally, the nitrogen functionality on the tether (and associated protecting group) and the rigidifying effect of the isoquinoline ring differentiate these substrates from those we had previously examined. To assess the compatibility of these features, isoquinolines **9a–c** and **10a,b** were selected as test substrates and prepared with various *N*-protecting groups as outlined in Scheme 1. Reaction of carboxylic acid **6** with oxallyl chloride followed by treatment with the corresponding benzylamine gave amides **7a,b** in >95% yield. Bischler–Napieralski cyclization of **7a** occurred upon treatment with phosphorous oxychloride in refluxing dichloromethane to give dihydroisoquinoline **8a** in 99% yield. Imine reduction with sodium borohydride followed by protection as the *tert*-butylcarbamate (Boc), acetate (Ac) and *para*-toluenesulfonate (Ts) gives isoquinolines **9a–c** in good yields. Unsubstituted isoquinolines **10a,b** were prepared *via* an analogous route, but with a more forcing Bichler–Napieralski protocol. In this case, cyclization of **7b** could be achieved in high yield by reaction in polyphosphoric acid at 150 °C for 4 h. Dihydroisoquinoline **8b** proved to be unstable to flash chromatography and so was immediately reduced and protected to give isoquinolines **10a,b** in high yield.

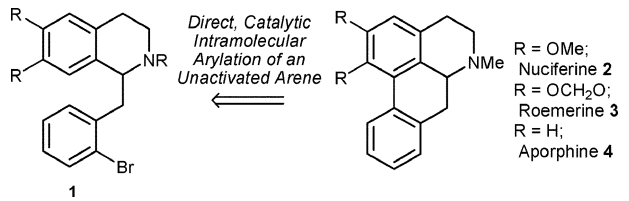
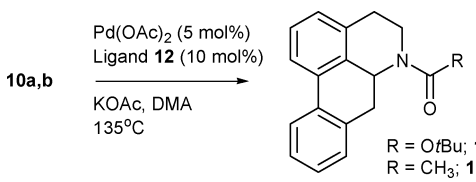


Fig. 1 Direct arylation of unactivated arenes in aporphine synthesis.

Since the most likely mechanism for C–H functionalization involves oxidative addition of the palladium catalyst into the carbon–bromide bond followed by an electrophilic attack of the resulting arylpalladium(II) moiety on the adjacent aromatic ring, we anticipated that a more facile transformation would arise with reaction of electron-rich isoquinolines **9a–c**. With isoquinoline **9a** the influence of solvent and base were investigated (Table 1). The optimal solvent is dimethylacetamide (DMA). Less polar solvents including mesitylene, acetonitrile and dioxane all gave poor outcomes. A variety of bases were also screened. Optimal results are obtained with K_2CO_3, KOAc and Cs_2CO_3. Organic bases such as diisopropylethylamine and DBU are incompatible. Under optimal conditions, reaction of **9a** with only 3 mol% $Pd(OAc)_2$, 6 mol% 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)-biphenyl **12**, 2 equivalents of KOAc in DMA at 130 °C gives aporphine **11a** in greater than 90% isolated yield (Scheme 2). Importantly, no dehalogenated by-product is observed which is a common side reaction associated with these processes. Aporphine **11a** can be easily deprotected and transformed to nuciferine **2** according to known literature procedures.[10]

The *N*-protecting group of **9** can be varied without any appreciable difference in reaction outcome. For example, *N*-acetyl **9b** reacts to give the natural product *N*-acetylnuciferine in quantitative yield. The *N*-toluenesulfonyl substrate **9c** also reacts well, giving **11c** in 99% isolated yield.

We were also pleased to find that even in the absence of electron-donating activating groups, isoquinolines **10a,b** reacted to give aporphines **13a,b** in 99% and 76% isolated yield respectively (eqn. (1)). *N*-Acetyl **13b** can be easily converted to aporphine **4** by known protocols.[9] These results indicate that this approach should be useful in the preparation of a wide range of aporphines, possessing a diverse range of arene substituents.



(1)

† Electronic supplementary information (ESI) available: general methods and procedures. See http://www.rsc.org/suppdata/cc/b4/b410394g/

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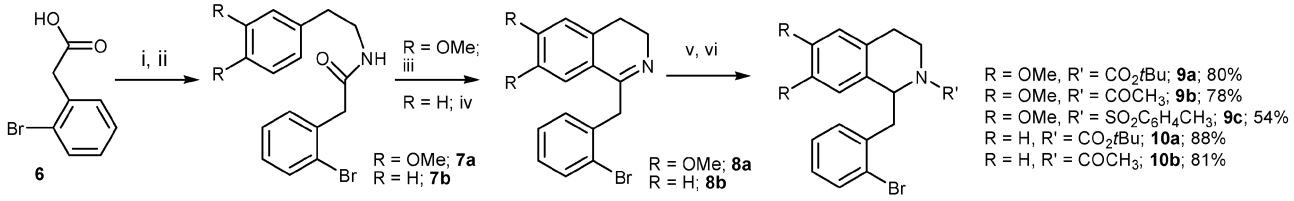
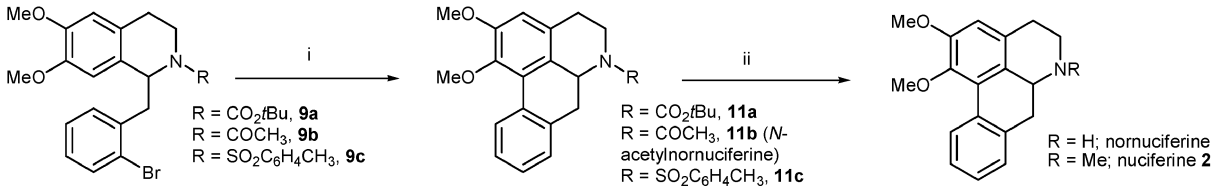


Reagents and Conditions. (i) $(COCl)_2$, CH_2Cl_2; (ii) $ArCH_2NH_2$, Et_3N, CH_2Cl_2,, two steps >95%; (iii) $POCl_3$, CH_2Cl_2, reflux, 99%; (iv) polyphosphoric acid, 150°C, 90%; (v) $NaBH_4$, MeOH, 99%; (vi) $(ROC)_2O$, DMAP (cat.), *i*Pr_2EtN, yield indicated.

Scheme 1 Preparation of starting materials.



Reagents and Conditions. (i) See Table 1; **9a-c**, $Pd(OAc)_2$ (2-5mol%), ligand **12** (4-10 mol%), base (2 equiv.) dissolved in DMA and heated to 135°C; (ii) R = $COCH_3$: (reference 9)

Scheme 2 Synthesis of aporphine alkaloids.

Table 1 Solvent, base and temperature effects on the intramolecular C–H arylation of **9a–c** to give **11a–c**[a]

Entry	Protecting group	Solvent	Base	% Conv.[b] (yield)[c]
1	Boc	DMA	K_2CO_3	>95 (87)
2	Boc	DMA	KOAc	>95 (90)
3	Boc	DMA	Na_2CO_3	17
4	Boc	DMA	Cs_2CO_3	>95
5	Boc	DMA	*i*-Pr_2EtN	<5
6	Boc	DMA	DBU	<5
7	Boc	DMF	KOAc	54
8	Boc	DMSO	KOAc	51
9	Boc	Mesitylene	KOAc	5
10	Boc	CH_3CN[d]	KOAc	<5
11	Boc	Dioxane[d]	KOAc	<5
12	Ts	DMA	KOAc	(99)
13	Ac	DMA	KOAc	(97)

[a] *Reaction Conditions:* isoquinoline **9a–c**, $Pd(OAc)_2$ (5 mol%), 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)-biphenyl **12** (2 equiv. per Pd), base (2 equiv.) dissolved in the indicated solvent and heated to 135 °C for 3 h. [b] As determined by crude ^1H NMR. [c] Isolated yield. [d] Heated to reflux.

In conclusion, we have successfully applied the direct C–H arylation of unactivated substrates to the synthesis of aporphine alkaloids. In addition to obviating the need to use activating groups on the arene moiety, greatly reduced catalyst loadings can be employed and substantially higher yields are obtained compared to previous reports. This methodology provides a very efficient route to these molecules, and also lends support for the viability of this approach in natural product synthesis.

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Notes and references

1 For recent reviews, see: (*a*) F. Kakiuchi and S. Murai, *Acc. Chem. Res.*, 2002, **35**, 826; (*b*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (*c*) M. Miura and M. Nomura, *Top. Curr. Chem.*, 2002, **219**, 211; (*d*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077.

2 For example, see: (*a*) B. Sezen and D. Sames, *J. Am. Chem. Soc.*, 2003, **125**, 5274; (*b*) C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek and V. Gevorgyan, *Org. Lett.*, 2004, **6**, 1159; (*c*) B. Glover, K. A. Harvey, B. Liu, M. J. Sharp and M. Tymoschenko, *Org. Lett.*, 2003, **5**, 301; (*d*) T. Okazawa, T. Satoh, M. Miura and M. Nomura, *J. Am. Chem. Soc.*, 2002, **124**, 5286; (*e*) R. B. Bedford, S. J. Coles, M. B. Hursthouse and M. E. Limmert, *Angew. Chem., Int. Ed.*, 2003, **42**, 112; (*f*) T. Satoh, Y. Kawamura, M. Miura and M. Nomura, *Angew. Chem., Int. Ed.*, 1997, **36**, 1740; (*g*) F. Kakiuchi, S. Kan, K. Igi, N. Chatani and S. Murai, *J. Am. Chem. Soc.*, 2003, **125**, 1698; (*h*) Y. Kametani, T. Satoh, M. Miura and M. Nomura, *Tetrahedron Lett.*, 2000, **41**, 2655; (*i*) S. Oi, S. Fukita and Y. Inoue, *Chem. Commun.*, 1998, 2439; (*j*) S. Oi, S.-i. Watanabe, S. Fukita and Y. Inoue, *Tetrahedron Lett.*, 2003, **44**, 8665 and references therein; (*k*) D. D. Hennings, S. Iwasa and V. H. Rawal, *J. Org. Chem.*, 1997, **62**, 2.

3 With 30 mol% catalyst: (*a*) M. Kitamura, K. Ohmori, T. Kawase and K. Suzuki, *Angew. Chem., Int. Ed.*, 1999, **38**, 1229; (*b*) J. E. Rice, Z.-W. Cai, Z.-M. He and E. J. LaVaoie, *J. Org. Chem.*, 1995, **60**, 8101; with 26 mol% catalyst: (c) T. Hosoya, E. Takashiro, T. Matsumoto and K. Suzuki, *J. Am. Chem. Soc.*, 1994, **116**, 1004; with 25 mol% catalyst: (d) T. Matsumoto, T. Hosoya and K. Suzuki, *J. Am. Chem. Soc.*, 1992, **114**, 3568; with 20–25 mol% catalyst: (e) G. D. Cuny, *Tetrahedron Lett.*, 2003, **44**, 8149; (f) G. Qabaja and G. B. Jones, *J. Org. Chem.*, 2000, **65**, 7187; with 10mol% catalyst: (g) G. Bringmann, M. Heubes, M. Breuning, L. Gobel, M. Ochse, B. Schoner and O. Schupp, *J. Org. Chem.*, 2000, **65**, 722; (h) G. Bringmann, M. Ochse and R. Gotz, *J. Org. Chem.*, 2000, **65**, 2069; (i) T. Harayama and H. Yasuda, *Heterocycles*, 1997, **46**, 61; with 4–5 mol% catalyst: (j) M. A. Campo, Q. Huang, T. Yao, Q. Tian and R. C. Larock, *J. Am. Chem. Soc.*, 2003, **125**, 11506; (k) Q. Huang, A. Fazio, G. Dai, M. A. Campo and R. C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 7460; (l) R. B. Bedford and C. S. J. Cazin, *Chem. Commun.*, 2002, 2310

4 L.-C. Campeau, M. Parisien, M. Leblanc and K. Fagnou, *J. Am. Chem. Soc.*, 2004, **126**, 9186.

5 T. Linnanen, M. Brisander, N. Mohell and A. M. Johansson, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 367.

6 Y.-C. Chia, K.-S. chen, Y.-L. Chang, C.-M. Teng and Y.-C. Wu, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3295.

7 Y.-C. Wu, F.-R. Chang, Y.-C. Chao and C.-M. Teng, *Phytotherapy Res.*, 1998, **12**, S39.

8 For example, see: (*a*) F. Roblot, R. Hocquemiller and A. Cavé, *Bull. Soc. Chim. Fr.*, 1990, **127**, 258; (*b*) Y. Landais and J. P. Robin, *Tetrahedron*, 1992, **48**, 7185.

9 G. D. Cuny, *Tetrahedron Lett.*, 2004, **45**, 5167 and ref. 3*e*.

10 S. M. Kupchan, J. L. Moniot, R. M. Kanojia and J. B. O'Brien, *J. Org. Chem.*, 1971, **36**, 2413.