An Aromatic Amination Approach towards Ancistrocladinium A/B

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Abstract: We report a high yielding approach to *N*-aryl tetrahydroisoquinolines and tetrahydroquinolines in one step from readily available starting materials. We have used this methodology to prepare the full carbon skeleton of the ring system of ancistrocladinium A in one step.

Key words: amination, natural products, palladium, Buchwald–Hartwig, tetrahydroquinoline, tetrahydroisoquinoline

Atropoisomerism is now a common structural motif in organic chemistry, particularly in catalysis and ligand design, for example, in the BINAP-derived systems. There are even a few natural products which contain axial chirality[1–4] and these have been the subject of increasing interest in recent years. For example, the naphthylisoquinoline alkaloids (Figure 1) are a rapidly expanding class of important secondary metabolites from tropical lianas of the *Ancistrocladaceae* and *Dioncophyllaceae* families.

These natural products are of interest for their significant pharmacological activities,[1,3] for example, against *Plasmodium falciparum*,[4] and their unprecedented biosynthetic origin through the acetate-malonate pathway.[5] Of particular significance to us were the recently isolated isoquinoline-based natural products ancisheynine and ancistrocladinium A/B[5,6] which are based on an isoquinolinium backbone, the chemistry of which we have considerable experience.[7]

These unique azabinaphthyl structures contain an atropoisomeric unit by virtue of restricted rotation about the C–N bond. We believed that this C–N bond could be constructed using the Buchwald–Hartwig amination reaction.[8,9] Buchwald–Hartwig amination of tetrahydroisoquinolines has previously been reported, however, only a few substrates were examined and product yields were unsatisfactory (<50%).[10]

We have previously reported a Buchwald–Hartwig approach to N-heterocyclic carbene ligands; and we decided to apply this methodology to the synthesis of the key C–N bond in ancistrocladinium A.[11] Initial amination studies were directed towards the synthesis of ancisheynine by direct amination of bromobenzene with isoquinoline using

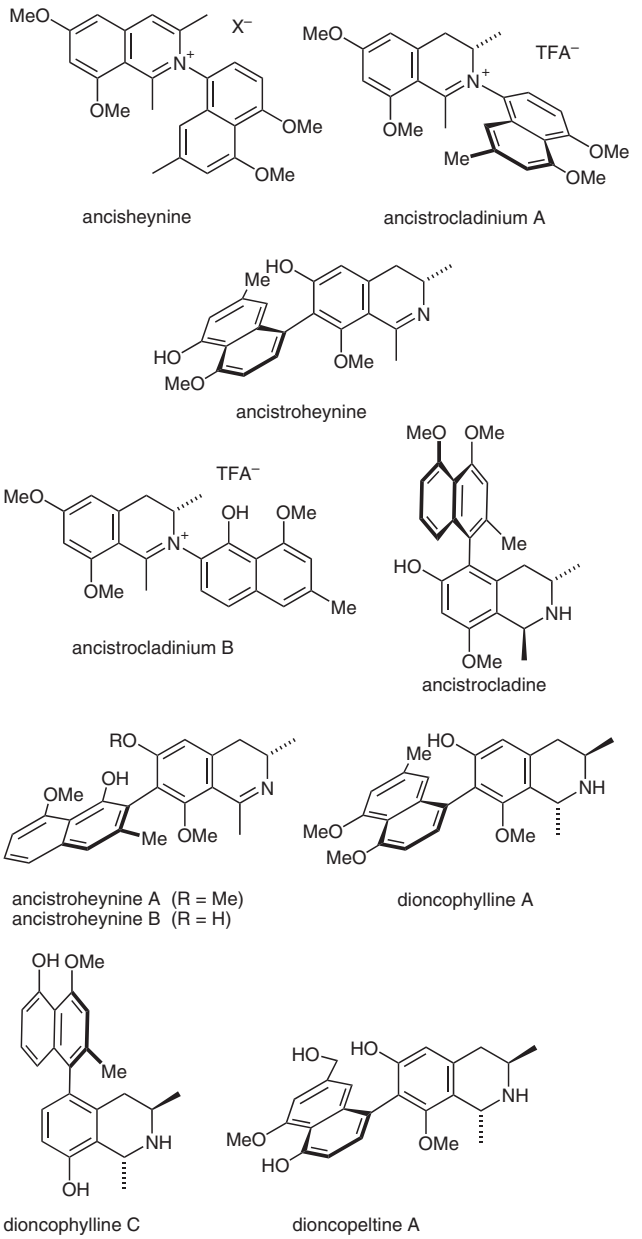

Figure 1 Secondary metabolites from tropical lianas of the *Ancistrocladaceae* and *Dioncophyllaceae* families

$Pd_2(dba)_3$, BINAP, and sodium *tert*-butoxide in toluene. Unfortunately, we only recovered unreacted starting materials. Hence we decided to attempt reactions using the

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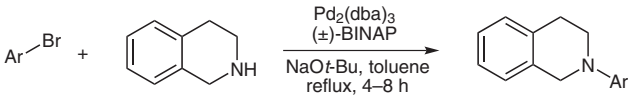
saturated tetrahydroisoquinoline system. Experiments were conducted with bromobenzene, tetrahydroisoquinoline, $Pd_2(dba)_3$, BINAP, and sodium *tert*-butoxide in toluene. This time an excellent yield of the corresponding aminated product was observed (93%, Table 1, entry 1).[12] Application of this methodology to a range of aryl bromides afforded the desired N-arylated products in good to excellent yields (Scheme 1, Table 1). The only exceptions to this were the bulky triisopropyl derivative (Table 1, entry 4) and the bromo-aniline (presumably due to some degree of polymerization, Table 1, entry 8).



Scheme 1 General scheme for the N-arylation of tetrahydroisoquinolines

Table 1 Synthesis of Aryl Tetrahydrisoquinolines **1–9**[a]

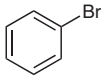
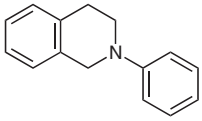
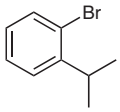
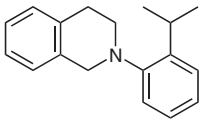
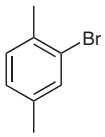
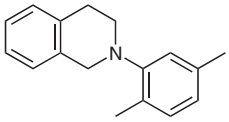
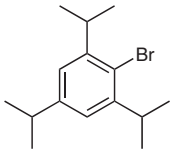
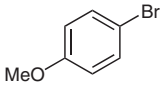
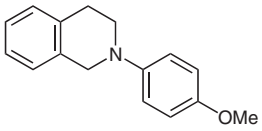
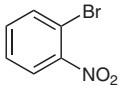
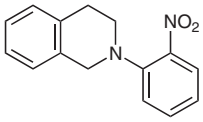
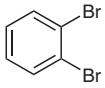
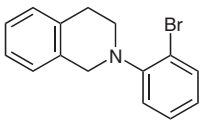
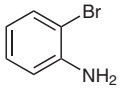
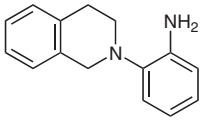
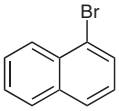
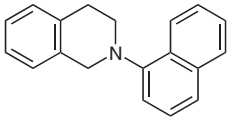
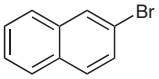
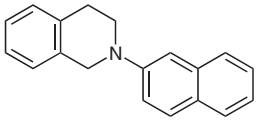
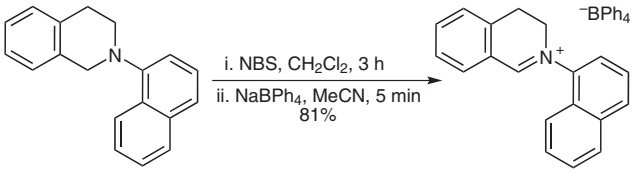
Entry	Bromide	Product	Yield (%)[b]
1		 **1**	93
2		 **2**	86
3		 **3**	89
4		starting material	–
5		 **4**	68
6		 **5**	69
7		 **6**	78
8		 **7**	51

Table 1 Synthesis of Aryl Tetrahydrisoquinolines **1–9**[a] (continued)

Entry	Bromide	Product	Yield (%)[b]
9		 **8**	96
10		 **9**	99

[a] Conditions: $Pd_2(dba)_3$, (±) BINAP, NaO*t*-Bu, toluene, reflux, 4–18 h.
[b] Isolated yield.

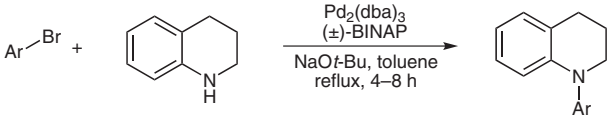
Pleasingly, amination of 1-bromonaphthalene with tetrahydroisoquinoline worked in excellent yield to afford the full carbon skeleton of the ring system of ancistrocladinium A in one step (compound **8**). Installation of the iminium bond can easily be achieved by treatment of the N-arylated tetrahydroisoquinoline with NBS in dichloromethane. For example, **8** was treated with NBS in refluxing dichloromethane to afford the corresponding dihydroisoquinolinium salt **10** in 81% yield which was isolated as its tetraphenylborate derivative for ease of manipulation (Scheme 2).[13]



8 **10**

Scheme 2 Formation of iminium salts using NBS

Following our success with the isoquionoline derivatives we also examined the reactions using tetrahydroquinoline (Scheme 3, Table 2). Again good to excellent yields of the desired aminated products were observed and a similar trend in product yield was obtained; for example, the aniline derivative **17** was formed in low yield (entry 7, Table 2). The structure of compound **18** was also confirmed by X-ray crystallography (Figure 2).[14]



Scheme 3 General scheme for the N-arylation of tetrahydroquinolines

Table 2 Synthesis of Aryl Tetrahydquinolines **11–19**[a]

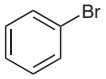
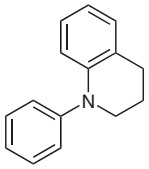
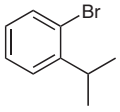
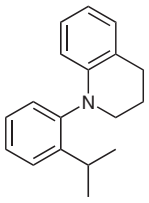
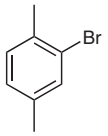
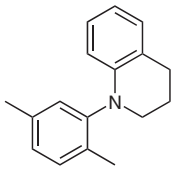
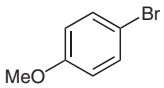
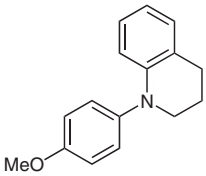
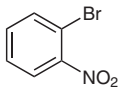
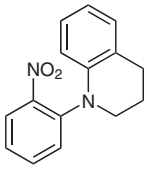
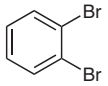
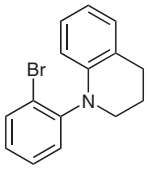
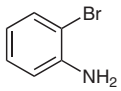
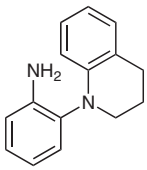
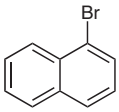
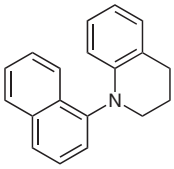
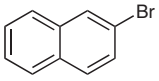
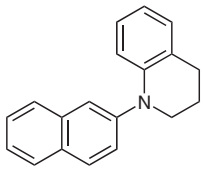
Entry	Bromide	Product	Yield (%)[b]
1		 **11**	94
2		 **12**	89

Table 2 Synthesis of Aryl Tetrahydquinolines **11–19**[a]

Entry	Bromide	Product	Yield (%)[b]
3		 **13**	87
4		 **14**	64
5		 **15**	69
6		 **16**	78
7		 **17**	56
8		 **18**	94
9		 **19**	87

[a] Conditions: $Pd_2(dba)_3$, (±) BINAP, NaO*t*-Bu, toluene, reflux, 4–18 h.
[b] Isolated yield.

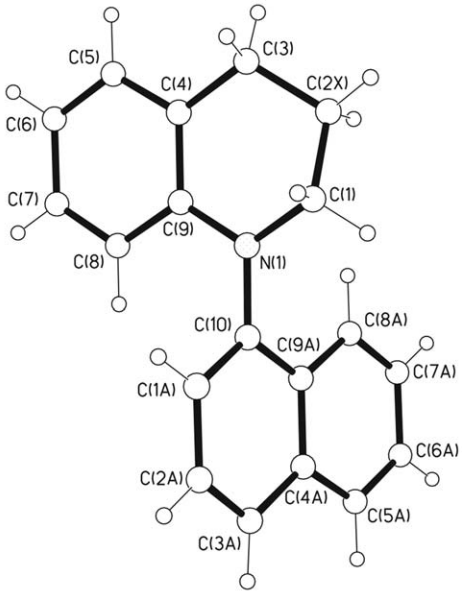


Figure 2 X-ray crystal structure of compound **18**

In conclusion we have developed a high yielding approach to *N*-aryl tetrahydroisoquinolines and tetrahydroquinolines in one step from readily available starting materials. We have used this methodology to prepare the full carbon skeleton of the ring system of ancistrocladinium A in one step, and we are currently pursuing this methodology for the total synthesis of several secondary metabolites from the tropical lianas of the *Ancistrocladaceae* and *Dioncophyllaceae* families.

Acknowledgment

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(12) **General Procedure**
A 50 mL round-bottomed flask was charged with $Pd_2(dba)_3$ (0.088 mmol), (±)-BINAP (0.18 mmol), and toluene (6 mL). The resulting solution was degassed for 10 min before being heated to 110 °C for 15 min. The reaction mixture was allowed to cool to r.t. before NaO*t*-Bu (4.1 mmol), the aryl bromide (2.2 mmol), and tetrahydroquinoline or tetrahydroisoquinoline (4.4 mmol) were added. The resulting mixture was heated under reflux for 4–16 h, before being cooled to r.t. and filtered through a pad of Celite®. Solvents were removed under reduced pressure and the crude material purified by column chromatography (silica gel, 99:1 light PE–EtOAc).
Data for Compound 9
Colorless solid, 99% yield (0.56 g). IR (thin film): ν_{max} = 1627, 1265, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.04 (2 H, t, *J* = 11.6 Hz, CH_2CH_2), 3.67 (2 H, t, *J* = 11.6 Hz, CH_2CH_2), 4.51 (2 H, s, CH_2), 7.17–7.21 (5 H, m, ArH), 7.26–7.28 (1 H, m, ArH), 7.33–7.36 (1 H, m, ArH), 7.39–7.41 (1 H, m, ArH), 7.76–7.68 (3 H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.19 (CH_2), 47.18 (CH_2), 51.13 (CH_2), 109.37 (ArCH), 118.73 (ArCH), 123.01 (ArCH), 126.10 (ArCH), 126.29 (ArCH), 126.42 (ArCH), 126.58 (ArCH), 126.60 (2 ArCH), 127.46 (ArCH), 128.07 (ArC), 128.64 (ArCH), 128.84 (ArCH), 134.36 (ArC), 134.76 (ArC), 148.39 (ArCN). MS (FAB$^+$): *m/z* (%) = 259 (100) [M$^+$], 258 (64). HRMS (ES): *m/z* calcd for [$C_{19}H_{17}N$]: 259.1361; found [M$^+$]: 259.1365.
(13) We have found that isolation of isoquinolinium salts as crystalline solids can be easily achieved when counterion exchange with sodium tetraphenylborate is carried out. See, for example, ref. 7a.
(14) **Crystal Data for 18**
$C_{19}H_{17}N$, *M* = 259.34, *a* = *b* = 7.0515 (8), *c* = 28.297 (3) Å, *a* = *b* = *g* = 90°, *V* = 1407.0(3) Å^3. pale yellow crystal, 1.04 × 0.47 × 0.25 mm^3, D_{calc} = 1.224 g cm^{-3}, *m* = 0.071 mm^{-1}; 13580 data, 1247 unique (R_{int} = 0.0757). Data were measured on a Bruker APEX II diffractometer with MoKα radiation at 150 K.[15] Data were corrected for absorption. The structure was solved by direct methods and refined on F^2 values.[16,17] Half the molecule is unique and the structure is 50/50 disordered at C(2A)/C(2X) and at N(1)/C(10). *R* = 0.0489 [for 1134 observed data with $F^2 > 2\sigma(F^2)$] and *wR* = 0.1278 (for all data). Crystal data have been deposited with the Cambridge Crystallographic Data Centre. CCDC: 758059. Data can be retrieved in CIF format by quoting the relevant deposition number in an e-mail request to deposit@ccdc.cam.ac.uk.
(15) SAINT and APEX 2 (2008) software for CCD diffractometers. Bruker AXS Inc., Madison, USA.
(16) Sheldrick, G. M. *SHELXTL User Manual, Version 6.10*; Bruker AXS Inc.: Madison USA, **2000**.
(17) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112.