Article:
Douglas, GE, Raw, SA and Marsden, SP orcid.org/0000-0002-2723-8954 (2019) Iron-Catalysed Direct Aromatic Amination with N-Chloroamines. European Journal of Organic Chemistry, 2019 (31-32). pp. 5508-5514. ISSN 1434-193X

https://doi.org/10.1002/ejoc.201900614

Iron-Catalysed Direct Aromatic Amination with N-Chloroamines

Gayle E. Douglas,[a] Steven A. Raw,[b] and Stephen P. Marsden*[a]

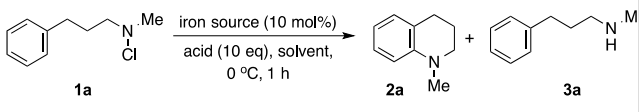
Abstract: An optimized procedure for the direct intra- and intermolecular amination of aromatic C-H bonds with aminium radicals generated from N-chloroamines under iron catalysis is reported. A range of substituted tetrahydroquinolines could be readily prepared, while extension to the synthesis of benzomorpholines was more limited in scope. A direct one-pot variant was developed, allowing direct formal oxidative N-H/C-H coupling.

Introduction

Aryl amines are common motifs in functional organic molecules including pharmaceuticals, agrochemicals, dyes and polymers.[1] Amongst the myriad methods for their synthesis, direct amination of aromatic C-H bonds is an area of growing interest since it offers synthetic efficiency compared with multi-step approaches from e.g. nitro- or haloarenes. The use of electrophilic nitrogen-centred radicals has been prominent amongst these approaches,[2] and methods are available for the introduction of primary,[3] secondary[4] or tertiary[5] amines, amides,[6] imides,[7] phosphonamides[8] and sulfonamides and their derivatives.[7b,9] These methods generally require the (sometimes multistep) synthesis of precursors to the nitrogen-centred radical, and approaches which allow the one-pot formal oxidative coupling of N-H and aryl C-H bonds are synthetically more attractive. This is most commonly achieved by in situ activation of amine derivatives bearing electron-withdrawing substituents,[7e,8,9a,c,e,h,i] and examples facilitating direct transfer of simple aliphatic amines are scarce: Nicewicz elegantly demonstrated direct photoredox-catalysed union of primary amines with arenes to generate secondary aryl amines.[4] The first reports of direct aromatic amination by aminium radicals were described by Minisci[5e,h] and Kompa,[5f,g] using N-chloroamines as the radical precursors under both photochemical and metal-catalysed conditions. The reactions were carried out in strongly acidic aqueous media which have limited scope for organic reactions and, more significantly, preclude the in situ generation of the N-chloroamine radical precursors. We recently revisited this chemistry and developed practical homogeneous media for the amination reactions under photolytic conditions,[5a,b] which allowed us to (i) explore the structural and functional group tolerance of the reaction, (ii) develop a one-pot protocol for the in situ activation and cyclisation of free secondary amines to tertiary aryl amine products, and (iii) to develop continuous flow variants capable of delivering gram quantities of products.[5b] Direct amination of substituted benzenes and benzazoles under photocatalysis using in situ generated N-chloroamines has also been reported by Leonori[4b] and Xiao[5d] respectively. Although the photochemical/photocatalysed reactions deliver excellent results, the requirement for specialist equipment prompted us to re-investigate the application of metal-based catalysts as a complementary approach, with the aim that the organic media would also allow for a one-pot direct arylation of secondary amines. We report herein the outcome of these studies.

Results and Discussion

We began our studies by examining the intramolecular direct C-H amination using N-chloroamine **1a** as the substrate. Our starting point was the use of an excess of strong organic acids in dichloromethane (our optimized conditions for the photochemical variant) in conjunction with 10 mol% of iron additives (Table 1). The use of iron(II) sulfate heptahydrate in conjunction with TFA and p-toluenesulfonic acid were unsuccessful (entries 1, 2) returning only unreacted **1a**, but the use of methanesulfonic acid returned a 73% yield of tetrahydroquinoline **2a** (entry 3). The difference in reactivity between the p-toluenesulfonic and methanesulfonic acids may be due to the limited solubility of the former at the reaction concentration used (a heterogeneous mixture was observed). The importance of both additives was verified – omission of either acid or iron salt resulted in no observable reaction (entries 4, 5). A range of iron salts and complexes were screened (entries 6-11), but no improvement was seen. Support for the role of the iron salt in mediating radical-based processes (either through halide atom abstraction or SET) rather than as a Lewis acid was seen in the differing outcomes with iron(II) and iron(III) chlorides: the former led to efficient cyclisation, the latter to unreacted starting material. In the case of iron(II) acetate and iron(II) triflate, formation of the reduction product (amine **3a**) was the sole observable outcome. A range of solvents were also screened, but dichloromethane remained optimum: some cyclisation was seen in toluene (entry 12) but other solvents also favoured reduction to **3a**, possibly arising through hydride atom abstraction from the solvent itself. With the combination of iron(II) sulfate and methanesulfonic acid identified as optimal, an investigation of the effect of the stoichiometry of both additives was undertaken (see Supporting Information for details), but the use of 10 mol% iron salt with 10 equivalents of acid were the best performing conditions.



1a 2a 3a

Table 1. Optimisation of intramolecular amination

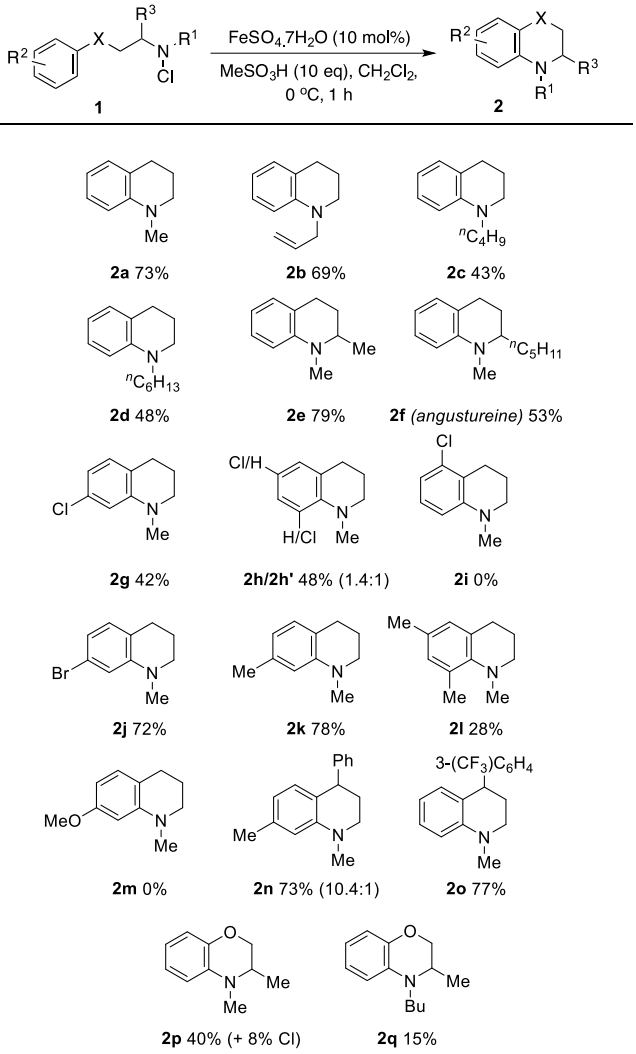
[a] Dr Gayle E. Douglas, Professor Stephen P. Marsden
School of Chemistry and Institute of Process Research and Development
University of Leeds
Leeds LS2 9JT (UK)
E-mail: s.p.marsden@leeds.ac.uk
Homepage: physicalsciences.leeds.ac.uk/staff/190/professor-steve-marsden
[b] Dr Steven A. Raw
Pharmaceutical Development
AstraZeneca
Macclesfield SK10 3RN (UK)

Supporting information for this article is given via a link at the end of the document.

Entry	Iron salt	Acid	Solvent	Product/Yield (%) [a]
1	$FeSO_4.7H_2O$	CF_3CO_2H	CH_2Cl_2	**1a** 100[b]
2	$FeSO_4.7H_2O$	p-TsOH	CH_2Cl_2	**1a** 100[b]
3	$FeSO_4.7H_2O$	$MeSO_3H$	CH_2Cl_2	**2a** 73
4	none	$MeSO_3H$	CH_2Cl_2	**1a** 100[b]
5	$FeSO_4.7H_2O$	none	CH_2Cl_2	**1a** 100[b]
6	$FeCl_2$	$MeSO_3H$	CH_2Cl_2	**2a** 63
7	$FeCl_3$	$MeSO_3H$	CH_2Cl_2	**1a** 90
8	Ferrocene	$MeSO_3H$	CH_2Cl_2	**2a** 20
9	$Fe(acac)_2$	$MeSO_3H$	CH_2Cl_2	**1a** 88
10	$Fe(OAc)_2$	$MeSO_3H$	CH_2Cl_2	**3a** 88
11	$Fe(OTf)_2$	$MeSO_3H$	CH_2Cl_2	**3a** 85
12	$FeSO_4.7H_2O$	$MeSO_3H$	Toluene	**2a** 45
13	$FeSO_4.7H_2O$	$MeSO_3H$	MeOH	**3a** 85
14	$FeSO_4.7H_2O$	$MeSO_3H$	2-MeTHF	**3a** 85
15	$FeSO_4.7H_2O$	$MeSO_3H$	Dioxane	**3a** 50

[a] Isolated yield. [b] Estimated by ^1H NMR.

We then examined the substrate scope of the intramolecular amination (Scheme 1). Variations in the N-substituent were tolerated, including the potentially removable[10] allyl-substituent in **2b**. As expected, longer N-alkyl chains gave lower yields (**2c**,**d**) owing to competing Hoffman-Loeffler-Freytag reactions of the aminium radicals. Substitution in the linking alkyl chain was tolerated, including a 2-pentyl substituent in **2f**, which corresponds to the naturally-occurring alkaloid angustereine.[11] Substituted aromatics also reacted: substrates with chloride substituents in the para- and meta-positions cyclized successfully (the latter giving a mixture of C6/C8-chlorotetrahydroquinolines **2h**), but the ortho-derivative failed to deliver **2i**. Bromide substitution was also tolerated in **2j**, and the availability of 7-halotetrahydroquinolines is noteworthy in the context of their potential utility in subsequent metal-catalysed cross-coupling chemistry along with the regiocomplementarity to products obtained by electrophilic halogenation of the parent tetrahydroquinolines.[12] Moderately electron-donating substituents such as para-methyl and meta,meta-dimethyl are also tolerated (**2k**,**l**), but as in the photochemical variants,[5a,b] more electron-rich arenes such as substituted anisoles are unsuccessful. The involvement of electrophilic aminating species was verified by competition experiments between differentially-substituted 3,3-diarylpropylamine substrates: cyclisation occurs predominantly (**2n**) or exclusively (**2o**) on the more electron-rich aromatic ring. This outcome matches previous observations in the photochemically-mediated aminations,[5a,b] and is consistent with the intermediacy of aminium radicals, potentially generated by single-electron transfer from iron(II) species. Our previous DFT work supports amination through a 6-exo addition to the arene.[5a] Rearomatisation could then be effected either by atom transfer/elimination or SET to generate a Wheland-type intermediate followed by proton loss.



Scheme 1. Substrate scope of the iron-catalysed direct aryl amination.

Overall, the average yield for the ten substrates which have been prepared by both the photochemical and iron-catalysed variants was broadly similar (ca. 6% higher in the former case), supporting the general interchangeability of the two practically complementary methods. We were also interested to see if the chemistry could be extended to other benzo-fused nitrogen heterocycles. Togo has previously demonstrated the synthesis of N-sulfonylated benzomorpholine derivatives through radical-mediated direct amination,[9h,i] and so we attempted the formation

of N-alkyl derivatives from readily-available β-aryloxyalkyl N-chloroamines. The N-methylbenzomorpholine **2p** was isolated as an inseparable mixture 5:1 mixture with a chlorinated derivative in 48% yield. Such over-chlorination has previously been seen with electron-rich products.[5a] Disappointingly, however, relatively minor changes in either N- or aryl substituents resulted in poor yields (e.g. 15% for the N-butyl analogue **2q**) and this series was discontinued.

Mindful of the success of our own group[5a,b] and others[4b,5d] in developing one-pot photochemical N-chlorination/amination procedures, we next investigated the development of a one-pot variant using iron-catalysis. N-Chlorination of amine **1a** was carried out using a molar equivalent of N-chlorosuccinimide before addition of methanesulfonic acid and the iron(II) sulfate. Disappointingly, only a trace of the product **2a** was observed (Table 2, entry 1). We eliminated the presence of the succinimide by-product of N-chlorination as the cause of this behavior by doping a reaction using pre-formed chloroamine with a molar equivalent of succinimide: an identical 73% yield of **2a** to that in Table 1, entry 3 was obtained. We therefore suspected that N-chlorosuccinimide was responsible for the issues. Although this reagent was charged in equimolar amounts to the amine and should be consumed in chloroamine formation, traces could be present either through incomplete chloroamine production or weighing errors. The reaction was therefore repeated with N-chlorosuccinimide as the limiting reagent (Table 2, entry 2), and a pleasing 65% yield of **2a** was observed. This yield compares well with the overall 48% yield for the two-step sequential chlorination (66%)/N-arylation (73%). Three other substrates were investigated and in each case the yield for the one-pot process was either comparable or superior to the two-step approach.

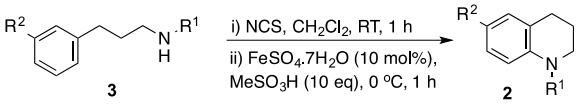


Table 2. One-pot amination

Entry	R^1	R^2	Equiv. NCS	Product, Yield (%)[a]
1	Me	H	1.0	**2a** <5[b]
2	Me	H	0.9	**2a** 65
3	Allyl	H	0.9	**2d** 45
4	Butyl	H	0.9	**2b** 57
5	Me	Cl	0.9	**2g** 42

[a] Isolated yield. [b] Estimated by ^{1}H NMR.

Minisci's initial work on direct aromatic amination focused on intermolecular reactions of N-chloroamines with arenes, the latter usually being present in a large excess,[5e] while Leonori's recent work demonstrates efficient photocatalysed couplings are possible.[4b] We wished to verify that intermolecular processes were also possible under our iron-catalysed conditions, and so investigated the coupling of two substituted piperidine derivatives **6a**,**b** with two substituted aromatics (tetralin **4** and toluene **5**). Using the arene in excess, moderate yields of aminated products were observed (Table 3, entries 1, 3, 4 and 6). The reactions with tetralin produced, in each case, a single regioisomer, with substitution being observed at the less-hindered 4-position. Reactions with toluene gave mixtures of ortho-, meta- and para-substitution, as anticipated by comparison with Minisci's earlier studies.[5e] Such reaction conditions (large excess of arene) would be appropriate for decoration of a valuable amine with a cheap/readily-available arene; however, more generally useful would be a process using only a modest excess of either reagent. After some optimization, we found that the use of a small excess (1.5 equivalents) of N-chloroamine gave reasonable yields of the aminated products (entries 2 and 5). The use of the N-chloroamine in larger excess (2-3 equivalents) gave lower isolated yields and was not pursued.

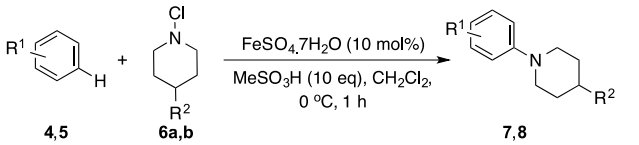
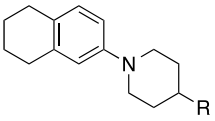
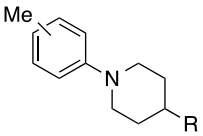


Table 3. Intermolecular amination

Entry	Product	R	Ratio **4** or **5**:**6**	Product, Yield (%)[a]
1		COPh	10:1	**7a** 33
2		COPh	1:1.5	**7a** 78
3		Ph	10:1	**7b** 28
4		COPh	10:1	**8a** 29[b]
5		COPh	1:1.5	**8a** 28[c]
6		Ph	10:1	**8b** 39[d]

[a] Isolated yield. [b] Mixture of o:m:p isomers in 3.6:7.2:5.5 ratio by ^{1}H NMR. [c] Mixture of o:m:p isomers in 3.6:7.2:5.5 ratio by ^{1}H NMR. [b] Mixture of o:m:p isomers in 3.5:4.7:5.0 ratio by ^{1}H NMR.

Conclusions

In conclusion, we have optimized the iron-catalysed direct C-H amination of arenes from N-chloroamines in organic media, a development which enables a direct one-pot formal oxidative coupling to generate tetrahydroquinolines and derivatives. The yields of this operationally simple process are comparable to our previously-developed photochemical aminations, and obviate the need for specialized photochemical reactors. While this work further demonstrates the utility of electrophilic nitrogen-centred radicals in organic synthesis, it is important to acknowledge some limitations: both highly electron-rich and electron-deficient substrates are problematic using this technique (the latter complication is common to a nearly all radical-mediated aminations, as noted and overcome in the specific instance of primary amine synthesis by Ritter[3a]). Nevertheless, the simplicity, cost-effectiveness and convenience of (particularly) the one-pot variant offers attractive alternatives to processes involving more complex pre-activated nitrogen species for appropriate substrates. Our ongoing work in the applications of aminium radical-mediated direct C-H aminations will be reported in due course.

Experimental Section

General procedure for the Intramolecular N-Arylation using Pre-Formed N-Chloroamines: To a stirred solution of the N-chloroamine **1** (1.0 eq) in DCM (0.2 M) at 0 °C was added $MeSO_3H$ (10 eq) and $FeSO_4.7H_2O$ (10 mol%). The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted three times with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography yielded the desired product **2**.

General Procedure for the Direct One-pot N-Arylation of Free Amines: To a stirred solution of the amine **3** (1.0 eq) in DCM (0.5 M) in the dark was added NCS (0.9 eq) portionwise over 10 min at RT. The reaction mixture was stirred for 1 h at RT then cooled to 0 °C. $MeSO_3H$ (10 eq) and $FeSO_4.7H_2O$ (10 mol%) were added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted three times with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography yielded the desired product **2**.

1-Methyl-1,2,3,4-tetrahydroquinoline (2a): The general procedure was followed, using chloroamine **1a** (100 mg, 0.54 mmol), $MeSO_3H$ (350 µL, 5.40 mmol) and $FeSO_4.7H_2O$ (15 mg, 0.050 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2a** (58 mg, 0.39 mmol, 73%) as a colourless oil. The data was in accordance with the literature.[5a] . (ii) One-pot synthesis from amine: the general procedure was followed using amine **1a** (100 mg, 0.67 mmol), NCS (80 mg, 0.60 mmol), $MeSO_3H$ (435 µL, 6.70 mmol) and $FeSO_4.7H_2O$ (19 mg, 0.07 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2a** (57 mg, 0.39 mmol, 65%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.11 (1H, t, J = 7.7, ArCH), 6.99 (1H, d, J = 7.1, ArCH), 6.65 – 6.62 (2H, m, 2 × ArCH), 3.28 – 3.24 (2H, m, NCH_2), 2.92 (3H, s, CH_3), 2.81 (2H, t, J = 6.4, $ArCH_2$), 2.05 – 2.00 (2H, m, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.8, 128.8, 127.0, 122.9, 116.2, 110.9, 51.3, 39.1, 27.8, 22.5; IR υ_{max} (neat) / cm^{-1} 3075, 3032, 2998, 2931, 2834, 1639, 1611, 1583; HRMS (ESI^+): $C_{10}H_{14}N$ $[M+H^+]$: calculated 148.1121, found 148.1118.

1-(Prop-2-en-1-yl)-1,2,3,4-tetrahydroquinoline (2b): (i) From chloroamine: the general procedure was followed, using chloroamine **2b** (100 mg, 0.48 mmol), $MeSO_3H$ (315 µL, 4.80 mmol) and $FeSO_4.7H_2O$ (13 mg, 0.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2b** (57 mg, 0.33 mmol, 69%) as a colourless oil. (ii) One-pot synthesis from amine: the general procedure was followed using amine **3b** (100 mg, 0.57 mmol), NCS (68 mg, 0.51 mmol), $MeSO_3H$ (331 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the **2b** (40 mg, 0.23 mmol, 45%) as a colourless oil. The data was in accordance with the literature.[5a] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.02 (1H, t, J = 7.8, ArCH), 6.94 (1H, d, J = 7.5, ArCH), 6.58 – 6.54 (2H, m, 2 × ArCH), 5.89 – 5.80 (1H, m, $CHCH_2$), 5.24 – 5.10 (2H, m, $CHCH_2$), 3.89 – 3.82 (2H, m, NCH_2CH), 3.31 – 3.23 (2H, m, NCH_2), 2.76 (2H, t, J = 6.3, $ArCH_2$), 2.02 – 1.90 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.4, 133.6, 129.0, 127.1, 122.4, 115.9, 115.7, 111.0, 53.9, 49.2, 28.2, 22.4; IR υ_{max} (neat) / cm^{-1} 3065, 3022, 2928, 2841, 1725, 1675, 1642, 1601; HRMS (ESI^+): $C_{12}H_{16}N$ $[M + H]^+$: calculated 174.1277, found 174.1272.

1-Butyl-1,2,3,4-tetrahydroquinoline (2c): (i) From chloroamine: The general procedure was followed, using chloroamine **1c** (100 mg, 0.44 mmol), $MeSO_3H$ (285 µL, 4.40 mmol) and $FeSO_4.7H_2O$ (12 mg, 0.04 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2c** (36 mg, 0.19 mmol, 43%) as a pale yellow oil. (ii) One-pot synthesis from amine: the general procedure was followed using amine **3c** (100 mg, 0.52 mmol), NCS (63 mg, 0.47 mmol), $MeSO_3H$ (305 µL, 4.70 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2c** (51 mg, 0.27 mmol, 57%) as a colourless oil. The data was in accordance with the literature.[5a] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.08 – 6.98 (1H, m, ArCH), 6.98 – 6.86 (1H, m, ArCH), 6.60 – 6.49 (2H, m, 2 × ArCH), 3.34 – 3.15 (4H, m, C_bH_2 and C_cH_2), 2.80 – 2.68 (2H, m, $ArCH_2$), 2.02 – 1.86 (2H, m, C_aH_2), 1.64 – 1.48 (2H, m, C_dH_2), 1.42 – 1.26 (2H, m, CH_2CH_3), 0.95 (3H, t, J = 7.3, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.4, 129.1, 127.0, 122.1, 115.1, 110.5, 51.2, 49.5, 28.4, 28.2, 22.3, 20.5, 14.1; IR υ_{max} (neat) / cm^{-1} 3064, 3020, 2954, 2929, 2860, 1676, 1601, 1503; HRMS (ESI^+): $C_{13}H_{20}N$ $[M + H]^+$: calculated 190.1590, calculated 190.1593.

1-Hexyl-1,2,3,4-tetrahydroquinoline (2d): The general procedure was followed, using chloroamine **1d** (100 mg, 0.39 mmol), $MeSO_3H$ (255 µL, 3.90 mmol) and $FeSO_4.7H_2O$ (11 mg, 0.04 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2d** (41 mg, 0.19 mmol, 48%) as a colourless oil. The data was in accordance with the literature.[5a] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.09-6.99 (1H, m, ArCH), 6.97-6.89 (1H, m, ArCH), 6.63-6.47 (2H, m, includes 2 × ArCH), 3.34-3.15 (4H, m, includes CH_{2c} and CH_{2b}), 2.75 (2H, t, J = 6.4, $ArCH_2$), 2.02-1.88 (2H, m, CH_{2a}), 1.66-1.51 (2H, m, CH_{2d}), 1.40-1.24 (6H, m, includes $CH_{2e,}$ CH_{2f} and CH_2CH_3), 0.98-0.81 (3H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.5, 129.3, 127.2, 122.3, 115.3, 110.6, 51.7, 49.6, 31.9, 28.4, 27.1, 26.3, 22.8, 22.4, 14.2; IR υ_{max} (neat)/cm^{-1}: 3066, 2925, 2855, 1601, 1574, 1504, 1456, 1369; HRMS (ESI): $C_{15}H_{24}N$ $[M+H]^+$: calculated 218.1903, found 218.1902.

1,2-Dimethyl-1,2,3,4-tetrahydroquinoline (2e): The general procedure was followed, using chloroamine **1e** (100 mg, 0.50 mmol), $MeSO_3H$ (330 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.051 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2e** (65 mg, 0.40 mmol, 79%) as a colourless oil. The NMR data is in accordance with literature.[5a] ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.13 (1H, t, J = 7.7, ArCH), 7.02 (1H, d, J = 7.3, ArCH), 6.64 (1H, t, J = 7.3, ArCH), 6.60 (1H, d, J = 8.2, ArCH), 3.52 – 3.44 (1H, m, CH), 2.94 (3H, s, NCH_3),

2.93 – 2.84 (1H, m, $ArCH_2$), 2.75 – 2.72 (1H, m, $ArCH_2$) 2.07 – 1.99 (1H, m, CH_2), 1.84 – 1.76 (1H, m, CH_2), 1.18 (3H, d, J = 6.5, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.4, 128.5, 127.1, 122.1, 115.4, 110.6, 53.8, 37.0, 28.1, 23.8, 17.6; IR υ_{max} (neat)/cm^{-1}: 3068, 3021, 2962, 2925, 2843, 2790, 1603, 1575; HRMS (ESI^+):$C_{11}H_{16}N$ $[M + H]^+$: calculated 162.1277, found 162.1273.

1-Methyl-2-hexyl-1,2,3,4-tetrahydroquinoline (angustureine, 2f): The general procedure was followed, using chloroamine **1f** (100 mg, 0.39 mmol), $MeSO_3H$ (260 µL, 3.90 mmol) and $FeSO_4.7H_2O$ (11 mg, 0.039 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2f** (45 mg, 0.21 mmol, 53%) as a colourless oil. The NMR data is in accordance with literature.[5a] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.07 (1H, t, J = 7.7, ArCH), 6.96 (1H, d, J = 7.3, ArCH), 6.57 (1H, t, J = 7.3, ArCH), 6.51 (1H, d, J = 8.2, ArCH), 3.29 – 3.17 (1H, m, CH), 2.92 (3H, s, CH_3), 2.86 – 2.73 (1H, m, $ArCH_2$), 2.71 – 2.58 (1H, m, $ArCH_2$) 1.94 – 1.82 (2H, m, CH_2), 1.65 – 1.53 (1H, m, C_aH_2), 1.44 – 1.19 (7H, m, includes C_aH_2, C_bH_2, C_cH_2 and C_dH_2) 0.98 – 0.81 (3H, m, CH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.7, 128.8, 127.2, 122.0, 115.3, 110.5, 59.1, 38.1, 32.2, 31.3, 25.9, 24.6, 23.7, 22.8, 14.2; IR υ_{max} (neat)/cm^{-1}: 3020, 2926, 2856, 1602, 1575, 1498, 1479, 1455; HRMS (ESI^+):$C_{15}H_{24}N$ $[M + H]^+$: calculated 218.1903, found 218.1903.

7-Chloro-1-methyl-1,2,3,4-tetrahydroquinoline (2g): The general procedure was followed, using chloroamine **1g** (100 mg, 0.46 mmol), $MeSO_3H$ (300 µL, 4.40 mmol) and $FeSO_4.7H_2O$ (13 mg, 0.046 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2g** (37 mg, 0.20 mmol, 42%) as a colourless oil. The data was in accordance with the literature.[5a] . (ii) One-pot synthesis from amine: the general procedure was followed using amine **1g** (100 mg, 0.54 mmol), $MeSO_3H$ (318 µL, 4.90 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.05 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2g** (37 mg, 0.20 mmol, 42%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.83 (1H, d, J = 7.8, ArCH), 6.56 – 6.49 (2H, m, 2 × ArCH), 3.25 – 3.19 (2H, m, NCH_3CH_2), 2.86 (3H, s, CH_3), 2.70 (2H, t, J = 6.4, $ArCH_2$), 1.99 – 1.90 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.5, 132.5, 129.5, 121.0, 115.5, 110.5, 50.9, 38.9, 27.3, 22.2; IR υ_{max} (neat) / cm^{-1} 3022, 2929, 2890, 2840, 1599, 1564, 1502, 1466; HRMS (ESI^+): $C_{10}H_{13}{}^{35}ClN$ $[M+H]^+$: calculated 182.0731, found 182.0723.

6-Chloro-1-methyl-1,2,3,4-tetrahydroquinoline (2h) and 8-chloro-1-methyl-1,2,3,4-tetrahydroquinoline (2h'): (i) From chloroamine: the general procedure was followed, using chloroamine **1h** (100 mg, 0.46 mmol), $MeSO_3H$ (300 µL, 4.60 mmol) and $FeSO_4.7H_2O$ (13 mg, 0.046 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded the regioisomers of **2h/2h'** as an inseparable mixture of isomers (1.4 : 1, 40 mg, 0.22 mmol, 48%) as a colourless oil. The NMR data for the 6-chloro product was in accordance with the literature.[13] ^1H NMR (400 MHz, $CDCl_3$, peaks for **2h**) δ = 7.02 (1H, dd, J = 8.7, 2.6, ArCH), 6.93 (1H, d, J = 2.6, ArCH), 6.50 (1H, d, J = 8.7, ArCH), 3.25 – 3.19 (2H, m, CH_2NMe), 2.88 (3H, s, CH_3), 2.75 (2H, t, J = 6.5, $ArCH_2$), 1.99 (2H, m, CH_2), ^{13}C NMR (101 MHz, $CDCl_3$, peaks for **2h**) δ = 145.3, 131.2, 128.4, 126.6, 124.4, 111.9, 51.1, 39.2, 27.7, 22.2; ^1H NMR (400 MHz, $CDCl_3$, peaks for **2h'**) δ = 7.19 (1H, d, J = 7.8, ArCH), 6.97 (1H, d, J = 7.8), 6.85 (1 H, t, J = 7.8, ArCH), 3.19 – 3.14 (2H, m, CH_2NMe), 2.91 (3H, s, CH_3), 2.82 (2H, t, J = 6.7, $ArCH_2$), 1.91 – 1.85 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for **2h'**) δ = 146.0, 128.3, 128.2, 127.5, 122.0, 120.7, 52.0, 42.8, 27.9, 17.2; IR υ_{max} (neat) / cm^{-1} 3040, 2934, 2861, 2841, 1596, 1560, 1499, 1463; HRMS (ESI^+): $C_{10}H_{13}{}^{35}ClN$ $[M+H]^+$: calculated 182.0731, found 182.0727.

7-Bromo-1-methyl-1,2,3,4-tetrahydroquinoline (2j): The general procedure was followed, using chloroamine **1j** (100 mg, 0.38 mmol), $MeSO_3H$ (250 µL, 3.80 mmol) and $FeSO_4.7H_2O$ (11 mg, 0.038 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2j** (62 mg, 0.27 mmol, 72%) as a colourless oil. The NMR data is in accordance with literature.[14] ^1H NMR (300 MHz, $CDCl_3$) δ = 6.78 (1H, d, J = 7.7, ArCH), 6.70 – 6.65 (2H, m, 2 × ArCH), 3.26 – 3.18 (2H, m, CH_2NMe), 2.86 (3H, s, CH_3), 2.68 (2H, t, J = 6.4, $ArCH_2$), 2.00 – 1.88 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.7 (C_q), 129.8 (ArCH), 121.5 (C_q), 120.6 (C_q), 118.5 (ArCH), 113.2 (ArCH), 50.9 (CH_2NMe), 38.9 (CH_3), 27.4 ($ArCH_2$), 22.1 (CH_2); IR υ_{max} (neat) / cm^{-1} 3015, 2928, 2886, 2837, 1593, 1557, 1497, 1464; HRMS (ESI^+): $C_{10}H_{13}{}^{79}Br{}^{35}ClN$ $[M + H]^+$ calculated 226.1583, found 226.1583.

1,7-Dimethyl-1,2,3,4-tetrahydroquinoline (2k): The general procedure was followed, using chloroamine **1k** (100 mg, 0.51 mmol), $MeSO_3H$ (335 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.051 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2k** (64 mg, 0.40 mmol, 78%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.76 (1H, d, J = 7.3, ArCH), 6.36 (2H, m, 2 × ArCH), 3.16 – 3.08 (2H, m, NCH_2), 2.80 (3H, s, NCH_3), 2.65 (2H, t, J = 6.5, $ArCH_2$), 2.20 (3H, s, $ArCH_3$), 1.93 – 1.84 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.6, 136.6, 128.7, 112.0, 117.0, 111.8, 51.4, 39.2, 27.5, 22.7, 21.6; IR υ_{max} (neat) / cm^{-1} 3041, 3022, 2924, 2856, 2839, 2812, 1611, 1575; HRMS (ESI^+): $C_{11}H_{16}N$ $[M + H]^+$: calculated 162.1277, found 162.1280.

1,6,8-Trimethyl-1,2,3,4-tetrahydroquinoline (2l): The general procedure was followed, using chloroamine **1l** (100 mg, 0.47 mmol), $MeSO_3H$ (305 mL, 4.70 mmol) and $FeSO_4.7H_2O$ (13 mg, 0.047 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2l** (22 mg, 0.13 mmol, 28%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.81 (1H, s, ArCH), 6.72 (1H, s, ArCH), 3.14 – 3.06 (2H, m, NCH_2), 2.75 (2H, t, J = 6.7, $ArCH_2$), 2.68 (3H, s, CH_3), 2.27 (3H, s, $ArCH_3$), 2.22 (3H, s, $ArCH_3$), 1.88 – 1.78 (2H, m,CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 131.3, 131.1, 130.5, 129.7, 128.8, 127.9, 52.2, 43.0, 27.7, 20.6, 18.4, 16.7; IR υ_{max} (neat) / cm^{-1} 2997, 2933, 2853, 1722, 1678, 1605, 1479. 1439; HRMS (ESI^+): $C_{12}H_{18}N$ $[M + H]^+$: calculated 176.1453, found 176.1455.

1,7-Dimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline (2n): The general procedure was followed, using chloroamine **1n** (100 mg, 0.37 mmol), $MeSO_3H$ (240 µL, 3.70 mmol) and $FeSO_4.7H_2O$ (10 mg, 0.037 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **1n** as an inseperable mixture 10.4:1 mixture with the isomeric product 1-methyl-4-(4-methylphenyl)-1,2,3,4-tetrahydroquinoline (64 mg, 0.27 mmol, 73%) as a colourless oil. The data is in accordance with the literature.[5a] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.25 (2H, m, 2 × ArCH), 7.21 – 7.17 (1H, m, ArCH), 7.12 – 7.09 (2H, m, 2 × ArCH), 6.62 (1H, d, J = 7.6, ArCH), 6.49 (1H, s, ArCH), 6.39 (1H, d, J = 7.6, ArCH), 4.09 (1H, t, J = 6.2, $CHCH_2$), 3.23 – 3.11 (2H, m, NCH_2), 2.93 (3H, s, NCH_3), 2.29 (3H, s, $ArCH_3$), 2.26 – 2.19 (1H, m, $CHCH_2$), 2.12 – 2.02 (1H, m, $CHCH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.8 (2 × C_q), 137.2, 129.8, 128.7, 128.3, 126.1, 122.1, 117.1, 111.8, 48.7, 43.2, 39.3, 31.3, 21.7; IR υ_{max} (neat) / cm^{-1} 3076, 3063, 2975, 2950, 1640, 1568, 1452, 1415; HRMS (ESI^+): $C_{17}H_{20}N$ $[M + H]^+$: calculated 238.1590, found 238.1585.

1-Methyl-4-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroquinoline 2o: The general procedure was followed, using chloroamine **1o** (100 mg, 0.31 mmol), $MeSO_3H$ (200 µL, 3.10 mmol) and $FeSO_4.7H_2O$ (9 mg, 0.031 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2o** (69 mg, 0.24 mmol, 77%) as a colourless oil. The data is in accordance with the literature.[5a] ^1H NMR (300 MHz, $CDCl_3$) δ = 7.50 – 7.35 (3H, m, 3 × ArCH), 7.25 (1H, d, J = 7.6, ArCH), 7.18 – 7.10 (1H, m, ArCH), 6.70 – 6.67 (2H, m, 2 × ArCH), 6.57 (1H, td, J =7.3, 1.1, ArCH), 4.24 – 4.15 (1H, m, $CHCH_2$), 3.31 – 3.07 (2H, m, CH_2N), 2.94 (3H, s, CH_3), 2.35 – 2.01 (2H, m, $CHCH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.5, 146.8, 132.2, 130.7 (q, J = 32.0), 129.8, 128.8, 128.0, 125.3 (q, J = 3.8), 124.3 (q,

J = 272.3), 123.8, 123.1 (q, J = 3.8), 116.5, 111.3, 48.4, 43.4, 39.2, 31.1; IR υ_{max} (neat) / cm^{-1} 3066, 3026 2945, 2927, 1602, 1503, 1444, 1322; HRMS (ESI^+): $C_{17}H_{17}F_3N$ $[M + H]^+$: calculated 292.1308, found 292.1313.

3,4-Dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine 2p: The general procedure was followed, using chloroamine **1p** (150 mg, 0.75 mmol), $MeSO_3H$ (490 µL, 7.50 mmol) and $FeSO_4.7H_2O$ (21 mg, 0.075 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2p** (25 mg, 0.15 mmol, 20%) as a colourless oil. The NMR data is in accordance with the literature.[15] ^1H NMR signals for the major product reported (300 MHz, $CDCl_3$) δ = 6.92 – 6.84 (1H, m, ArCH), 6.83 – 6.77 (1H, m, ArCH), 6.69 – 6.61 (2H, m, 2 × ArCH), 4.21 (1H, dd, J = 10.5, 2.6, CH_2), 4.04 (1H, dd, J = 10.5, 2.6, CH_2), 3.44 – 3.33 (1H, m, CH), 2.89 (3H, s, NCH_3), 1.22 (3H, d, J = 6.5, CH_3); ^{13}C NMR signals for the major product reported (101 MHz, $CDCl_3$) δ = 144.2, 126.6, 121.8, 116.6, 116.4, 111.7, 69.2, 52.1, 36.1, 14.1; **IR** υ_{max} (neat) / cm^{-1} 3065, 3039, 2972, 2929, 2875, 2820, 1604, 1499; LCMS (ESI^+): $C_{19}H_{22}NO$ $[M + H]^+$: calculated 164.2, found 164.4

4-Butyl-3-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine 2q: The general procedure was followed, using chloroamine **1q** (100 mg, 0.41 mmol), $MeSO_3H$ (270 µL, 4.10 mmol) and $FeSO_4.7H_2O$ (11 mg, 0.04 mmol). Purification by column chromatography, eluting with 10% EtOAc in hexane afforded **2q** (13 mg, 0.06 mmol, 15%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 6.93 – 6.77 (2H, m, 2 × ArCH), 6.68 – 6.55 (2H, m, 2 × ArCH), 4.13 – 3.97 (2H, m, OCH_2), 3.54 – 3.41 (1H, m, CH), 3.40 – 3.27 (1H, m, CH_2), 3.21 – 3.04 (1H, m, CH_2), 1.71 – 1.52 (2H, m, CH_2), 1.47 – 1.32 (2H, m, CH_2), 1.22 (3H, d, J = 6.5, $CHCH_3$), 1.04 – 0.94 (3H, m, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.4, 134.5, 121.8, 116.3, 116.1, 111.8, 69.1, 50.9, 48.7, 29.5, 20.4, 15.9, 14.0; IR υ_{max} (neat) / cm^{-1} 3065, 3039, 2958, 2930, 2872, 1605, 1578, 1502; HRMS (ESI^+): $C_{13}H_{20}NO$ $[M + H]^+$: calculated 206.1539, found 206.1538.

Synthesis of 4-benzoyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)piperidine 7a: To a stirred solution of the chloroamine **6a** (100 mg, 0.45 mmol) in DCM (0.45 mL) at 0 °C was added tetralin (610 µL, 4.50 mmol) $MeSO_3H$ (295 µL, 4.50 mmol) and $FeSO_4.7H_2O$ (12 mg, 0.045). The RM was stirred at 0 °C for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography, eluting with DCM in hexane afforded **7a** (48 mg, 0.15 mmol, 33%) as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$) δ = 8.00 – 7.93 (2H, m, 2 × ArCH), 7.60 – 7.54 (1H, m, ArCH), 7.48 (2H, t, J = 7.6, 2 × ArCH), 6.97 (1H, d, J = 8.3, ArCH), 6.76 (1H, d, J = 7.7, ArCH), 6.68 (1H, s, ArCH), 3.69 (2H, dt, J = 6.1, 2.8, NCH_2), 3.42 – 3.31 (1H, m, CHCO), 2.88 – 2.77 (2H, m, NCH_2), 2.73 – 2.68 (4H, m, 2 × C_bH_2), 2.04 – 1.91 (4H, m, 2 × CH_2CH), 1.82 – 1.74 (4H, m, 2 × C_aH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 202.5, 137.6, 136.1, 133.0, 129.7, 128.9, 128.8, 128.3, 117.4, 115.1, 50.2, 43.6, 29.9, 28.7, 28.6, 23.5, 23.4; IR υ_{max} (neat) / cm^{-1} 3057, 3013, 2854, 2834, 2801, 1679, 1609, 1597; HRMS (ESI^+): $C_{22}H_{25}NNaO$ $[M + Na]^+$: calculated 342.1828, found 342.1825.

Synthesis of 4-phenyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)piperidine 7b: To a stirred solution of the chloroamine **6b** (100 mg, 0.51 mmol) in DCM (0.51 mL) at 0 °C was added tetralin (695 µL, 5.10 mmol) $MeSO_3H$ (330 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.051). The RM was stirred at 0 °C for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography, eluting with DCM in hexane afforded **7b** (39 mg, 0.13 mmol, 26%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.15 (5H, m, 5 × ArCH), 6.97 (1H, d, J = 8.1, ArCH), 6.78 (1H, d, J = 8.1, ArCH), 6.70 (1H, s, ArCH), 3.72 (2H, d, J = 11.4, 2 × NCH_2), 2.79 – 2.66 (7H, m, includes CH, 2 × C_bH_2, 2 CH_2CH), 1.92 (4 H, s, 2 × $CHCH_2$), 1.77 (4H, s, J = 2.0, 2 × C_aH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.9, 146.3, 137.6, 129.7, 128.7, 128.5, 126.9, 126.3, 117.4, 115.1, 51.3, 42.6, 33.5, 29.9, 28.6, 23.6, 23.4; IR υ_{max} (neat) / cm^{-1} 3058, 3025, 2923, 2852, 2798, 1736, 1681, 1609; LCMS (ESI^+): 292.2 $[M+H]^+$. Accurate mass data could not be obtained.

[1-(Methylphenyl)-4-piperidinyl]phenylmethanone 8a To a stirred solution of the chloroamine **6a** (100 mg, 0.45 mmol) in DCM (0.45 mL) at 0 °C was added toluene (480 µL, 4.50 mmol) $MeSO_3H$ (295 µL, 4.50 mmol) and $FeSO_4.7H_2O$ (12 mg, 0.045). The RM was stirred at 0 °C for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography, eluting with DCM in hexane afforded **8a** as inseparable regioisomers, o:m:p, 3.6:7.2:5.5 (42 mg, 0.13 mmol, 29%) as a colourless oil. NMRs reported as a mixture of the three regioisomers. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.99 – 7.93 (2H, m), 7.57 (1H, ddd, J = 7.9, 2.3, 1.1), 7.48 (2H, dd, J 11.6, 4.2), 7.18 (0.22H, d, J = 8.8, ArCH, o), 7.15 (0.44H, t, J = 7.7, ArCH, m), 7.07 (0.68H, d, J = 8.2, 2 × ArCH, p), 6.88 (0.68H, d, J = 8.2, 2 × ArCH,p), 6.83 – 6.65 (1.98H, m, 6 ArCH, o and m), 3.79 – 3.65 (2H, m, NCH_2), 3.43 – 3.32 (1H, m, CH), 2.85 (2H, m, NCH_2), 2.33 (0.66H, s, CH_3, o), 2.32 (1.32H, s, CH_3, m), 2.27 (1.02H, s, CH_3, p), 2.01 – 1.92 (4H, m, 2 × CH_2CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.5, 151.7, 150.3, 149.6, 138.8, 136.3, 136.1, 136.0, 133.1, 133.0, 129.7, 129.4, 129.0, 128.8, 128.3, 120.6, 119.2, 117.6, 117.1, 115.5, 113.8, 50.1, 49.6, 43.6, 28.7, 28.7, 28.5, 21.8, 20.5; IR υ_{max} (neat) / cm^{-1} 3057, 3026, 2948, 2921, 2807, 2748, 1678, 1595; LCMS (ESI^+) 280.4 $[M + H]^+$. Accurate mass data could not be obtained.

1-Methylphenyl-4-phenylpiperidine 8b To a stirred solution of the chloroamine **6b** (100 mg, 0.51 mmol) in DCM (0.45 mL) at 0 °C was added toluene (545 µL, 5.10 mmol) $MeSO_3H$ (330 µL, 5.10 mmol) and $FeSO_4.7H_2O$ (14 mg, 0.051). The RM was stirred at 0 °C for 1 h. The RM was basified using 2 M NaOH (pH 9). The two phases were separated and the aqueous phase was extracted with DCM (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography, eluting with DCM in hexane afforded **8b** as inseperable regioisomers, o:m:p, 3.5:4.7:5.0 (39 mg, 0.14 mmol, 39%) as a colourless oil. All data reported as a mixture of the three regioisomers. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.23 – 7.07 (5H, m, 5 × ArCH), 7.08 – 7.01 (0.36H, m, ArCH, m), 6.99-6.95 (1.05H, m, 2 × ArCH, p), 6.82 – 6.77 (1.05H, m, 2 × ArCH, p), 6.72 – 6.67 (0.72H, m, includes o and m ArCH), 6.58-6.53 (0.26H, d, J = 7.4, ArCH, o), 3.71 – 3.56 (2H, m, NCH_2), 2.73 – 2.44 (3H, m, NCH_2, and CH), 2.22 (0.78H, s, CH_3, o), 2.21 (1.08H, s, CH_3, m), 2.16 (1.14H, s, CH_3, p); 1.94-1.76 (4H, m, include 2 × CH_2CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ =151.9, 149.7, 146.2, 138.8, 136.1, 131.0 129.6, 129.0, 128.5, 128.4, 127.0, 126.9, 126.8, 126.3, 126.2, 120.5, 119.0, 117.6, 117.1, 113.8, 51.3, 50.7 42.6, 42.5, 33.9, 29.7, 20.5; IR υ_{max} (neat) / cm^{-1} 3060, 3028, 2948, 2923, 2810, 2748, 1595, 1425; LCMS (ESI^+): 252.4 $[M + H]^+$. Accurate mass data could not be obtained.

Acknowledgments

We thank the EPSRC and AstraZeneca for a DTP CASE award to GED.

Keywords: amination • aryl amines • radical • iron catalysis • tetrahydroquinolines

[1] (a) The Chemistry of Anilines, Part 1, (Ed. Z. Rapoport), Wiley-VCH, ed. A. Ricci, Wiley VCH, 2008.**2007**; (b) P. F. Vogt and J. J. Gerulis, Amines, Aromatic, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH,

Weinheim, **2005**; (c) Amino Group Chemistry: From Synthesis to the Life Sciences, (Ed. A. Ricci), Wiley VCH, Weinheim, **2008**.

[2] For recent reviews, see: a) T. Xiong, Q. Zhang Chem. Soc. Rev. **2016**, 45, 3069-3087; b) K. Murakami, G. J. P. Perry, K. Itami Org. Biomol. Chem. **2017**, 15, 6071-6075.

[3] (a) W. S. Ham, J. Hillenbrand, J. Jacq, C. Genicot, T. Ritter, Angew. Chem. Int. Ed. **2019**, 58, 532-536; (b) S. L. Roessler, B. J. Jelier, P. F. Tripet, A. Shemet, G. Jeschke, A. Togni, E. M. Carreira, Angew. Chem. Int. Ed. **2019**, 58, 526-531; (c) L. Legnani, G. Prina Cerai, B. Morandi, ACS Catal. **2016**, 6, 8162–8165; (d) J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, X. Li, N. Jiao, Chem. Eur. J. **2017**, 23, 563–567.

[4] (a) K. A. Margrey, A. Levens, D. A. Nicewicz Angew. Chem. Int. Ed. **2017**, 56, 15644–15648; (b) A. Ruffoni, F. Julia, T. D. Svejstrup, A. J. McMillan, J. J. Douglas, D. Leonori, Nature Chem. **2019**, 11, 426-433.

[5] (a) S. C. Cosgrove, J. M. C. Plane, S. P. Marsden Chem. Sci. **2018**, 9, 6647–6652; (b) S. C. Cosgrove, G. E. Douglas, S. A. Raw, S. P. Marsden, ChemPhotoChem **2018**, 2, 851-854; (c) T. D. Svejstrup, A. Ruffoni, F. Julia, V. M. Aubert, D. Leonori, Angew. Chem. Int. Ed. **2017**, 56, 14948–14952; (d) J.-D. Wang, Y.-X. Liu, D. Xue, C. Wang, J. Xiao, Synlett **2014**, 25, 2013–2018; (e) F. Minisci, Synthesis **1973**, 1-24; (f) H. Bock, K.-L. Kompa, Chem. Ber. **1966**, 99, 1357–1360; (g) H. Bock, K.-L. Kompa, Angew. Chem. Int. Ed. **1965**, 4, 783; (h) F. Minisci, R. Galli, Tetrahedron Lett. **1965**, 8, 433–6. See also reference 4b.

[6] J. Davies, T. D. Svejstrup, D. Fernandez Reina, N. S. Sheikh, D. Leonori, J. Am. Chem. Soc. **2016**, 138, 8092–8095.

[7] (a) N. Sabat, L Postova Slavetinska, B. Klepetarova, M. Hocek, ACS Omega **2018**, 3, 4674-4678; (b) T. W. Greulich, C. G. Daniliuc, A. Studer, Org. Lett. **2015**, 17, 254–257; (c) K. Foo, E. Sella, I. Thome, M. D. Eastgate, P. S. Baran, J. Am. Chem. Soc. **2014**, 136, 5279–5282; (d) L. J. Allen, P. J. Cabrera, M. Lee, M. S. Sanford, J. Am. Chem. Soc. **2014**, 136, 5607–5610; (e) H. Kim, T. Kim, D. G. Lee, S. W. Roh, C. Lee, Chem. Commun. **2014**, 50, 9273–9276.

[8] (a) Y.-N. Ma, M.-X. Cheng, S.-D. Yang, Org. Lett. **2017**, 19, 600–603; (b) Y.-N. Ma, X. Zhang, S.-D. Yang, Chem. Eur. J. **2017**, 23, 3007–3011

[9] (a) N. Lucchetti, A. Tkacheva, S. Fantasia, K. Muniz, Adv. Synth. Cat. **2018**, 360, 3889-3893; (b) S. J. Yip, T. Kawakimi, K. Murakami, K. Itami, Asian J. Org. Chem., **2018**, 7, 1372-1375; (c) X. Wang, B. Lei, L. Ma, H. Jiao, W. Xing, J. Chen, Z. Li, Adv. Synth. Cat., **2017**, 359, 4284-4288; (d) C. Martinez, A. E. Bosnidou, S. Allmedinger, K. Muniz, Chem. Eur. J. **2016**, 22, 9929–9932; (e) K. Tong, X. Liu, Y. Zhang, S. Yu, Chem. Eur. J. **2016**, 22, 15669–15673; (f) Q. Qin, S. Yu, Org. Lett. **2014**, 16, 3504; (g) L. Song, L. Zhang, S. Luo, J.-P. Cheng, Chem. Eur. J. **2014**, 20, 14231–14234; (h) H. Togo, Y. Harada, M. Yokoyama, J. Org. Chem. **2000**, 65, 926–929; (i) H. Togo, Y. Hoshina, T. Muraki, H. Nakayama, M. Yokoyama, J. Org. Chem. **1998**, 63, 5193–5200.

[10] (a) V. Cadierno, S. E. Garcia-Garrido, J. Gimeno, N. Nebra, Chem. Commun. **2005**, 41, 4086-4088; (b) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, Org. Lett. **2001**, 3, 3781-3784.

[11] I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, Phytochemistry **1999**, 51, 1167–1169.

[12] Although C6-bromination usually dominates, for approaches to C7-bromination of tetrahydroquinolines in superacids, see: C. Berrier, J. C. Jacquesy, M. P. Jouannetaud, A. Renoux, New. J. Chem. **1987**, 11, 605-609.

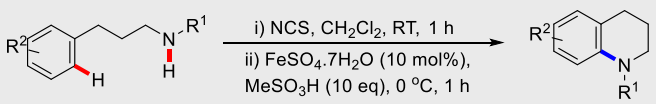
[13] M. Minakawa, K. Watanabe, S. Toyoda, Y. Uozomi, Synlett, **2018**, 29, 2385-2389.

[14] Y. Koide, Y. Urano, K. Hanaoka, W. Piao, M. Kusakabe, N. Saito, T. Terai, T. Okabe, T. Nagano, J. Am. Chem. Soc. **2012**, 134, 5029-5031.

[15] R. A. Bunce, D. M. Herron, L. Y. Hale, J. Heterocyclic Chem. **2003**, 40, 1031-1039.

Entry for the Table of Contents

FULL PAPER



An optimized procedure for the direct intra- and intermolecular amination of aromatic C-H bonds with aminium radicals generated from N-chloroamines under iron catalysis is reported. A range of substituted tetrahydroquinolines could be readily prepared, while extension to the synthesis of benzomorpholines was more limited in scope. A direct one-pot variant was developed, allowing direct formal oxidative N-H/C-H coupling.

Heterocyclic Synthesis

G. E. Douglas, S. A. Raw, S. P. Marsden

Page No. – Page No.

Iron-Catalysed Direct Aromatic Amination with N-Chloroamines