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A novel method for the synthesis of 1-aryltetrahydroisoquinolines.

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Abstract- Carbenium ions generated from substituted benzhydryls using acid catalysis undergo smooth intramolecular trapping by pendant sulfonamide groups to provide excellent yields of 1-aryltetrahydroisoquinolines.

Keywords: 1-Aryltetrahydroisoquinolines; carbenium ions; trapping; intramolecular; acid-catalysed.

The 1-aryltetrahydroisoquinoline nucleus **1** occupies an important position, both in natural product chemistry and in the design of many, highly active and vital pharmaceuticals. As well as being found in many, usually oxygenated alkaloids of varying complexity,¹ both natural and synthetic examples containing this residue have been found to possess a remarkable spectrum of bioactivities, ranging from antidiabetic activity, multidrug resistance reversal and serotonin reuptake inhibition to CNS activities offering prophylaxis against Huntington's, Alzheimer's and Parkinson's diseases, as well as acting as ligands in a class of novel anti-cancer compounds.² Therefore it is not surprising that many synthetic approaches to these compounds have been developed, the most prevalent of which are the closely related Pictet-Spengler³ and Bischler-Napieralski cyclisation, along with introduction of the 1-substituent onto a suitably functionalised parent heterocycles.⁴ Inevitably, asymmetric versions of such reactions have more recently been developed.^{2,4,5}

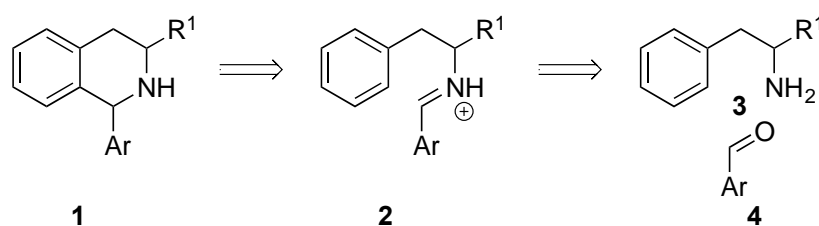
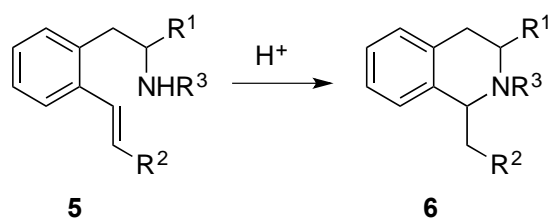


Figure 1. The 1-aryltetrahydroisoquinoline nucleus and its synthesis by a Pictet-Spengler reaction.

In the classical Pictet-Spengler method (Fig. 1), the key bond formation features electrophilic attack by an aryl group onto a pendant iminium species **2** derived *in situ* from a β-arylamine **3** and an aldehyde **4**. Despite being an intramolecular process, it is usually necessary for the nucleophilic aryl function to be activated by at least one methoxy group or a similar substituent. We have recently reported that, in general, tetrahydro-isoquinolines **6** can be efficiently prepared by acid-catalysed cyclisations of the corresponding β-(2-alkenylaryl)amines **5**, given the incorporation of a suitable *N*-protecting group, R³ (Scheme 1).⁶ This alternative procedure does not suffer from the limitation of requiring an electron rich aryl group and generally leads to a predominance of the 1,3-*cis*-stereoisomers but does require the use of strong acid catalyst such as trifluoromethanesulfonic (triflic) or concentrated sulfuric acid. Suitable protecting groups, R³, include tosyl, nosyl (nitrophenylsulfonyl) and

methoxycarbonyl. In favourable cases, even benzyloxycarbonyl (Z) groups can survive these relatively vigorous conditions.^{6,7}



Scheme 1. Acid-catalysed tetrahydroisoquinoline synthesis.

Clearly, such a disconnection featuring an alkene could not be used to form 1-aryl derivatives **1**. Instead, the necessary carbenium ions **7** should be available from the corresponding benzhydriyls **8**, given smooth, acid-catalysed water loss and subsequent trapping by the pendent amine function before rearrangement or some other undesired reaction (Fig. 2). The role of an equivalent of water, which is not generated during the related cyclisations onto alkenes (Scheme 1), was also an unknown factor.

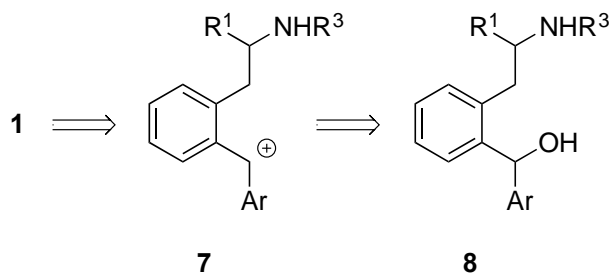


Figure 2. The retrosynthetic analysis for acid-catalysed 1-aryltetrahydroisoquinoline formation.

We chose to synthesise representative examples of the necessary benzhydriyls **8** starting from the readily available racemic amino alcohol **9**, which was first converted into the N-tosyl aziridine **10** as previously reported (Scheme 2).⁸ Subsequent copper-catalysed addition⁹ of the Grignard reagent derived from 2-bromobenzaldehyde diethyl acetal then gave the β -arylamine derivative **11**, which was protected on nitrogen by the addition of a Boc (*t*-butyloxycarbonyl) group in order to avoid a requirement for two equivalents of the next Grignard reagent. Selective hydrolysis of the acetal function in the resulting doubly-protected amine using iron(II) chloride¹⁰ then gave the aldehyde **12** in good overall yield.

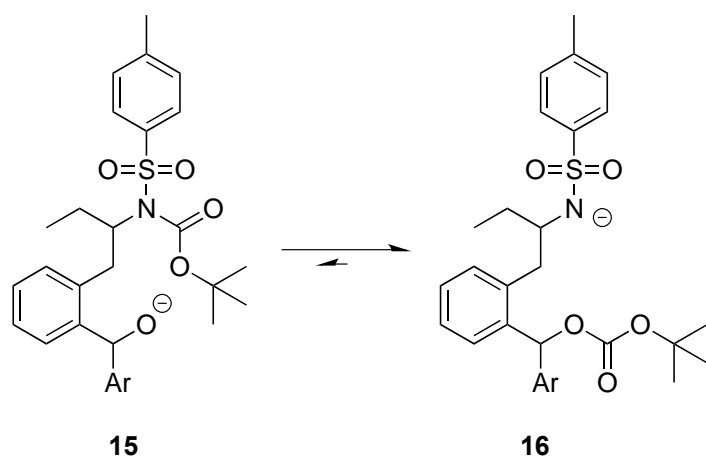
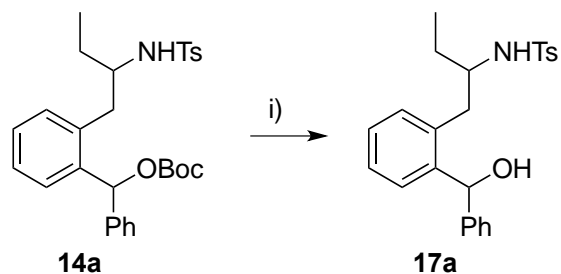


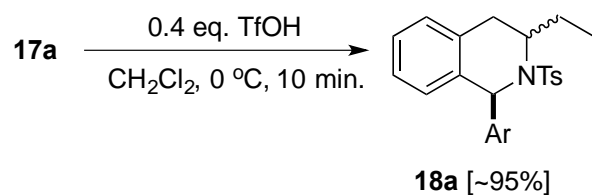
Figure 3. The two anions.

At this stage, we did not think that this would present a problem but, to keep to our original aims, the new carbonate function was removed by selective base-induced hydrolysis to give the corresponding free alcohol **17a**, in the case of the phenyl derivative **14a** (Scheme 3).



Scheme 3. Reagents and conditions: i) K₂CO₃, MeOH, reflux, 24 h (95%).

We were delighted to find that brief exposure of the benzhydryl alcohol **17a** to 0.4 equivalents of triflic acid in dichloromethane at 0 °C gave an essentially quantitative return of the desired 1-phenyltetrahydroisoquinoline **18a** (Scheme 4). Evidently, formation of an equivalent amount of water did not have a deleterious effect.



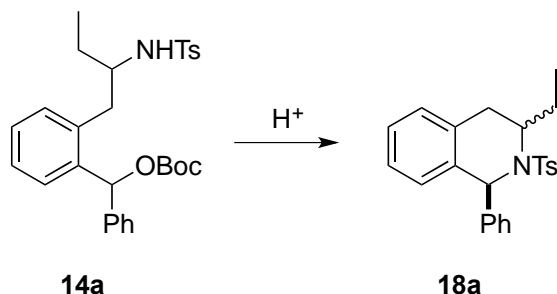
Scheme 4. The first successful cyclisation.

The product **18a** was isolated in a very clean state after a simple work-up consisting of neutralisation of the triflic acid using aqueous potassium carbonate and separation of the organic layer, which was then washed once with water, dried (MgSO₄) and filtered through a short silica gel plug. Additional chromatographic purification was unnecessary. However, the product was obtained as a 3:1 mixture of *cis*- and *trans*- isomers; fortunately, the stereochemistry of this and many structurally related tetrahydroisoquinolines has been determined by a combination of NMR and X-ray analyses.¹² It turns out that there were usually insufficient differences between the two sets of ¹³C NMR data to allow for reliable assignments to be made in the case of such 1-aryl derivatives. In contrast, ¹H NMR data could be used to secure such assignments using clear differences in chemical shifts, δ_{H} in CDCl₃, between the following protons: the benzylic methine singlets (*cis*, ~ 6.2; *trans*, ~6.1), the benzylic methylene double doublets [*cis*, ~2.95 (*J* = 16.2 and 4.7 Hz) and ~2.75 (16.2 and 6.9 Hz); *trans*, ~2.81 (*J* = 15.9 and 4.5 Hz) and 2.30 (15.9 and 6.8 Hz)] and the non-benzylic (3-) protons α - to nitrogen (*cis*, m, ~ 4.0; *trans*, m, ~3.7).

Given the relative facility of this conversion, we wondered if separate removal of the Boc group was actually necessary. Mechanistically, protonation of this group should lead either to rapid formation of the corresponding alcohol **17a** or to direct formation of the required carbenium ion derived from it. In the event, the presence of the Boc group had very little effect on the progress of the cyclisation (Table 1, first entry), producing essentially the same result to that obtained using the free alcohol (Scheme 3). We then examined the reactivity of the OBoc derivative **14a** with a variety of weaker acids; the results are collected in Table 1. Trifluoroacetic (TFA) and concentrated sulfuric acid were equally effective in producing the desired product **18a**, with similar isomeric ratios, although the required reaction times were longer while *p*-toluenesulfonic acid was only successful when the reaction was carried out in toluene at reflux. Silica gel was ineffective even after prolonged exposure at ambient temperature, in contrast to the corresponding *p*-methoxy derivative (*vide infra*). Of particular interest was the increased stereoselectivity in favour of the *cis*-isomer of product **18a** when the reaction time using triflic acid was increased (second entry), suggesting that a ring opening and re-closure equilibration was in operation and that, as expected, the 1,3-*cis* isomer was the thermodynamic product. This idea is also consistent with the observation that the much weaker acid, *p*-TSA, led to formation of predominantly the *trans*-isomer, evidently the

kinetic isomer, despite the reaction requiring a much higher temperature when using this reagent. This led us to carry out similar tests with the alternative substrates described below.

Table 1: The reactivity of various acids with the OBoc derivative **14a**

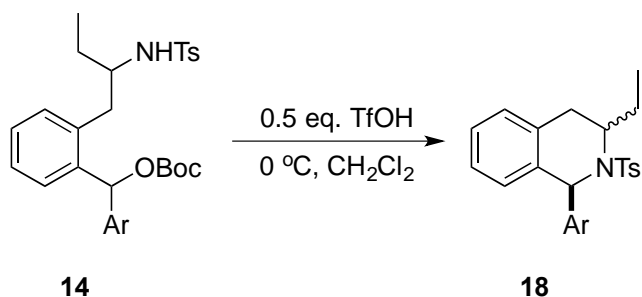


Acid ^a	Equiv.	Solvent	Temp.	Time	Yield (18a ; %)	c/ ^b ratio
TfOH	0.5	CH ₂ Cl ₂	0 °C	10 min.	95	3.5:1
TfOH	0.5	CH ₂ Cl ₂	0 °C	0.5 h	91	~95:5
TFA	1.0	CH ₂ Cl ₂	0 °C	1 h	90	3:1
c.H ₂ SO ₄	0.5	CH ₂ Cl ₂	0 °C	1 h	90	3:1
<i>p</i> -TSA	1.0	Toluene	110 °C	20 min.	85	1:3
SiO ₂	2.0	CH ₂ Cl ₂	20 °C	24 h	0 ^c	-

^a) TfOH = trifluoromethanesulfonic acid, CF₃SO₃H; TFA = trifluoroacetic acid; *p*-TSA = 4-toluenesulfonic acid; SiO₂ = Merck Kieselgel 60H silica gel; ^b) *cis* to *trans* ratio determined by ¹H NMR integration; ^c) *cf.* cyclisation of *p*-methoxy derivative **14d** during chromatography.

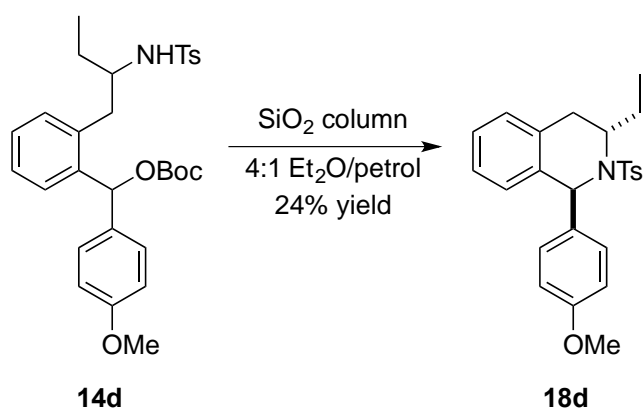
For this brief scope and limitations study, we chose to use triflic acid as the catalyst, in view of both the high yields obtained and the speed of reaction although, no doubt, other acids such as TFA and c.H₂SO₄ might well have been equally effective. The results obtained are collected in Table 2. As already discussed, the phenyl-substituted product **18a** underwent isomerisation during prolonged reaction (Entries 1 and 2). Similarly, brief exposure of the 4-chlorophenyl example **14b** gave an excellent yield of the tetrahydroisoquinoline **18b** in a 2:1 *cis-trans* ratio (Entry 3). Although not attempted with this derivative, the isomerisation towards the *cis*-diastereoisomer was again observed with the *p*-fluoro derivative **14c**, where a similar pattern of change was observed (Entries 4-6).

Table 2: The reactivity of various acids with the OBoc derivatives **14**



Entry	Ar	Time (min.)	Yield (18 ; %)	c/t ratio
1	Ph	10	95	3.5:1
2	Ph	30	91	all <i>cis</i>
3	<i>p</i> -ClC ₆ H ₄	10	93	2:1
4	<i>p</i> -FC ₆ H ₄	1	90	4:1
5	<i>p</i> -FC ₆ H ₄	10	97	3:1
6	<i>p</i> -FC ₆ H ₄	30	93	all <i>cis</i>
7	<i>p</i> -MeOC ₆ H ₄	5	91	12:1
8	<i>p</i> -MeOC ₆ H ₄	60	94	all <i>cis</i>
9	-naphthyl	15	79	3:1
10	-naphthyl	40	91	10:1
11	2-thienyl	5	94	10:1
12	2-thienyl	40	98	all <i>cis</i>

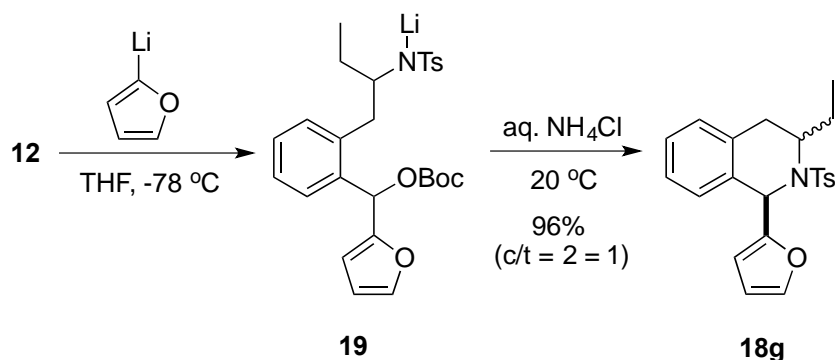
The 4-methoxy analogue **14d** was evidently much more reactive, as expected, which is presumably reflected in the isomer ratio of 12:1, obtained even after a brief five minute exposure to the acidic conditions (Entry 7). A longer reaction time gave essentially pure *cis*-isomer (Entry 8). That this substrate was much more reactive was also indicated by the isolation of a 24% yield of cyclised material, as very largely the *cis*-isomer, when the precursor **14d** was purified by column chromatography (Scheme 5)!



Scheme 5. Unexpected cyclisation of derivative **14d**.

Much the same pattern of cyclisation, relative to the phenyl derivative, was found for the naphthyl analogue **14e**, which underwent the same type of isomerisation (Entries 9 and 10), while the results obtained from the 2-thienyl derivative **14f** (Entries 11 and 12) were consistent with a relatively highly activated system, again as expected.

The 2-furyl analogue showed exceptionally high reactivity, such that we were unable to isolate the intermediate OBoc derivative **14g** after a routine work up using aqueous ammonium chloride as a quench; the only product was the cyclised material **18g** (Scheme 6). Thus, addition of 2-furyl lithium to the aldehyde **12** at low temperature presumably gave the rearranged OBoc intermediate **19**. However, upon quenching the reaction mixture with saturated aqueous ammonium chloride, only the desired cyclised product **18g** was isolated in 96% yield, in a 2:1 ratio of stereoisomers (Scheme 6).



Scheme 6. Unexpectedly facile cyclisation of the furyl derivative

Overall, this approach offers an efficient and relatively brief route to 1-aryltetrahydroisoquinolines. The precursor synthesis used in the present work consists of five efficient steps but could be modified using many alternatives, thereby providing additional flexibility. For example, routes to arylacetic acids could be used in combination with Curtius degradations to introduce the amine function, while a combination of a nitroaldol and reduction would achieve the same end. Nitrile chemistry could also be exploited along with a number of directed metalation strategies using β -arylamine derivatives¹³ or arylacetaldehydes.¹⁴ Finally, it may also be possible to use the present precursor synthesis to obtain enantiopure products, by starting with an optically pure amino alcohol (Scheme 2), given that the later *trans-cis* isomerizations occur solely by regeneration and trapping of benzylic carbenium ions, as seems likely given that the alternative would require a secondary alkyl-substituted carbenium ion. Future work will address this feature.

Acknowledgements.

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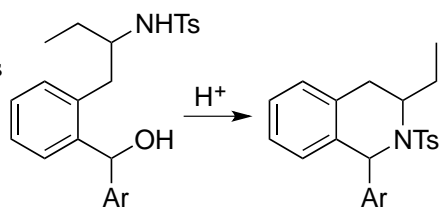
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[Graphic abstract]

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1-Aryltetrahydroisoquinolines are formed in excellent yields when suitably substituted benzhydryls are exposed to an acid catalyst.



Keywords: 1-Aryltetrahydroisoquinolines; synthesis; acid-catalysed; cyclisation; carbenium ions.