A Survey of the Borrowing Hydrogen Approach to the Synthesis of some Pharmaceutically Relevant Intermediates

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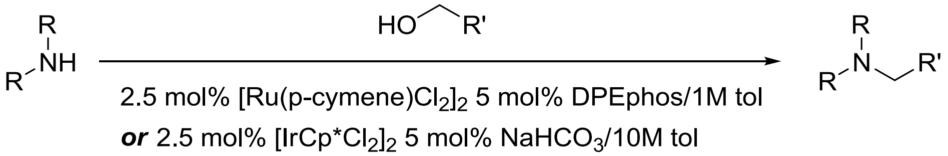
TOC Abstract



Commercial reagents and literature conditions used to evaluate “Borrowing hydrogen” methodology for pharmaceutical intermediates.

Yields are high for simple R/R’, but challenges identified for typical pharma substrates.

Abstract

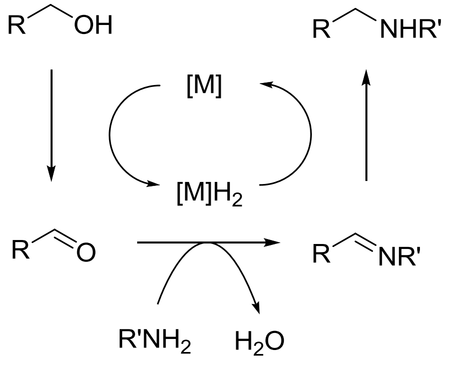
The use of the "borrowing hydrogen strategy" in the synthesis of a number of typical pharmaceutical intermediates has been investigated. The main aim of this work was to investigate the scope and limitations of current methodology using standard laboratory techniques in an industrial context. Some interesting and significant results were achieved across a diverse set of complex substrates; however several drawbacks with this approach were identified, such as the high loading, poor turnover and susceptibility to substrate inactivation of the catalysts. These are areas which are highlighted for future investigation and improvements.

Introduction

A cross-industry survey published in 2006 revealed that 'heteroatom alkylation and arylation' is the most common category of reaction used by process R&D functions in the preparation of drug candidate molecules.[1] Analysis showed that *N*-substitution accounts for 57% of such transformations, and of these 36% are achieved by the reaction of an amine with an alkylating agent and 20% by reductive amination. The ACS Green Chemistry Institute Pharmaceutical Roundtable has also published a perspective on key research areas.[2] Activation of alcohols for nucleophilic substitution was one of the most important areas in the category of 'currently used reactions that require improvement'.[2] These two papers highlight the fact that *N*-alkylation is one of the most commonly employed transformations in the pharmaceutical industry, even though these reactions are inherently inefficient. Whereas direct coupling of an amine with an alcohol would lead to water as the only by-product, conversion of an alcohol to an alkylhalide, or other activated form, adds at least one additional chemical step and leads to undesirable waste products. Reductive amination is a common alternative to alkylation but this may employ reagents that have poor atom economy (*e.g.* stoichiometric borohydride salts) and additional chemical steps are also required for alcohol oxidation and then reduction of an imine intermediate. Hydrogenation can sometimes be an atom efficient alternative for the reduction step, but the additional alcohol oxidation is still required and substrate scope is limited. Poor chemoselectivity is a general problem for reductive aminations and the risk of by-product formation through over-alkylation is also a limitation of both alkylation and reductive amination methodology, which can compromise yield and may lead to additional purification procedures. Alkylating reagents may also have genotoxic properties (PGIs), so in the preparation of pharmaceutical intermediates their use is stringently controlled to ensure that they are completely purged during the processes involved in active pharmaceutical ingredients (API) manufacture.[3] Any methodology that offers the complete avoidance of alkylating agents in pharmaceutical manufacture would therefore be beneficial, as the need for dedicated analytical and purging procedures would be circumvented.

Direct nucleophilic substitution of an alcohol by amine is an attractive alternative to alkylation, as water would be the only by-product and alcohols themselves are usually non-toxic, readily available and inexpensive. First reported in 1981,[4] in recent years there has been a resurgence of interest in using homogeneous catalysis to achieve direct *N*-alkylation of amines using alcohols as the formal electrophilic partner (Scheme 1).[5] This redox-neutral approach to alkylation belongs to the class of reactions termed ”borrowing hydrogen” and is potentially of significant interest to the pharmaceutical industry in that alkylating agents or the stoichiometric use of unstable aldehydes (in reductive aminations) might be avoidable.

Scheme 1**. “Borrowing Hydrogen” Approach to Alkylation of Amines with Alcohols**



While the “borrowing hydrogen” approach has been widely studied from an academic perspective, there are a number of challenges that need to be addressed before this reaches the status of a general technique which could be readily adopted by the pharmaceutical industry. The majority of "borrowing hydrogen" reactions are conducted at high temperatures, often with high loadings of precious metal catalysts, and high concentrations of reactants in relatively non-polar aromatic solvents such as toluene and xylene. Whilst this is satisfactory for small-scale reactions using simple, low molecular weight (often liquid) reagents, the technique may not necessarily transfer to large-scale reactions employing substrates of the type most commonly encountered in pharmaceutical development programme: high molecular weight, densely functionalised and often solid, with limited solubility. Some progress has been made in addressing the shortcomings, for example the use of water as a solvent has been successful in some reactions,[6] and more active catalysts enabling lower temperature reactions (down to room-temperature under solvent-free conditions) have been described.[7] Furthermore, a Pfizer research team have recently described the optimisation and scale-up of an iridium-catalysed alkylation of a benzylic amine with a primary alcohol.[8] This work identified an advantage in carrying out the reaction in pressure equipment to allow for heating above the azeotrope temperature of toluene/water, providing a higher and more consistent yield, and allowing catalyst loadings to be reduced to <0.05 mol% iridium. This groundbreaking application of the technology notwithstanding, the substrates for this specific reaction are not necessarily representative of the breadth of substrates likely to be encountered across the industry. The substrates used in this example are soluble to high concentrations in a non-polar solvent (toluene) and, unlike many pharmaceutical and agrochemical intermediates, they contain relatively little by way of functionality that might compete as metal binding sites. The current paper describes a programme of work aimed at evaluating the scope and performance of "borrowing hydrogen" chemistries with complex substrates from across a range of AstraZeneca development projects. We believe that the results of these broad scoping studies are complementary to those of the Pfizer group, and will both provide further support for the general applicability of a hydrogen borrowing approach to the synthesis of APIs, and also point out where limitations could benefit from more fundamental research.

Results and Discussion

A survey of the AstraZeneca portfolio of development compounds revealed a number of examples containing amines as structural sub-units which were constructed either by reaction of an amine with an alkylating agent or by reductive amination. Several of these examples appeared amenable to a borrowing hydrogen sequence as an alternative. These were considered for inclusion in the study on the basis of availability of appropriate substrates and an assessment of the apparent viability of the resulting alternative route to the API.

From the outset, in each case, we wished to assess quickly whether a 'borrowing hydrogen' approach would be viable using simple standard laboratory techniques, avoiding any requirement for sealed tube or pressure equipment where possible. If preliminary reactions proved successful, optimisation was considered on the basis of project priority; where unsuccessful, some investigation into possible causes was undertaken. The primary emphasis was to screen suitable examples against available catalyst systems rather than to develop bespoke conditions for each. In this way we hoped to gain further insight into the scope and limitations of this redox neutral methodology for amine synthesis in the context of typical API preparations.

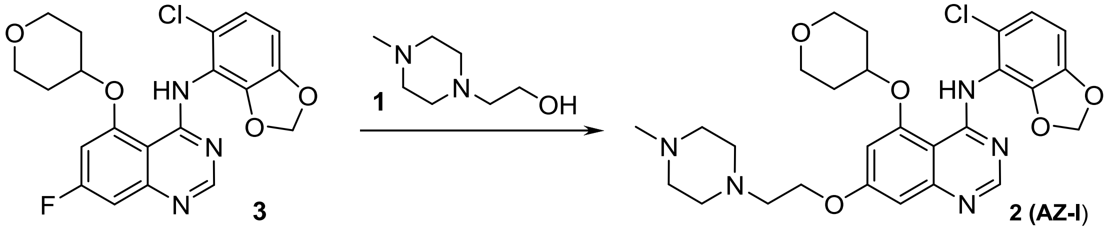
Our strategy was to focus mainly on the catalyst systems developed by Williams (2.5 mol% [Ru(*p*-cymene)Cl_2]$_2$/5 mol% DPEphos/1*M* in toluene – "Catalyst A")[9] and by Fujita and Yamaguchi (2.5 mol% [IrCp*Cl_2]$_2$/5 mol% $NaHCO_3$/10*M* in toluene – "Catalyst B")[10]. The rationale behind this was that a broad range of substrates have been shown to be compatible with both of these systems. Moreover, they are both appealing from a process development perspective: the catalyst/ligand combinations are available 'off-the-shelf', air-stable, and both protocols usually employ a 1:1 ratio of amine : alcohol. Exceptions to this were made where alternate catalyst systems had been reported to be applicable to closely-related substrates, in which case these were prioritised for investigation. In this work, both the amines and alcohols studied were often novel and therefore little was known about the likely compatibility of the substrates under the reaction conditions. Model reactions were often therefore employed in order to ascertain whether the coupling partner in question would undergo reaction with an amine or alcohol known to participate in ‘borrowing hydrogen’ type alkylations *e.g.* piperidine or benzyl alcohol, respectively.

For clarity of presentation, the various case studies are collated according to the type of alcohol being used as the alkylating agent.

Case Study 1 – Methanol

Amino alcohol **1** is a final intermediate in the synthesis of potent SRC kinase inhibitor AZ-I **2** and is introduced via base-mediated displacement of the aryl fluoride **3** prior to formation of the difumarate salt of the API (Scheme 2).[11]

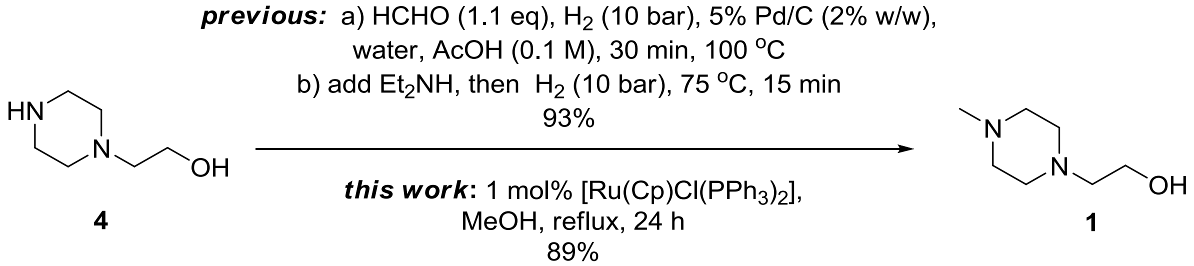
***Scheme 2.* Role of Piperazinyl Alcohol 1 in the Synthesis of AZ-I (2)**



Amine **1** had previously been prepared by one of two conventional approaches: alkylation of *N*-methylpiperazinewith 2-chloroethanol or reductive methylation of piperazine **4** with formaldehyde (Scheme 3). The reductive amination approach was eventually optimised to provide the product in high yield (93%), under carefully controlled conditions, involving removal of excess formaldehyde by conversion to volatile diethylmethylamine, by a sequential reductive amination with diethylamine. An alternative approach to the latter transformation based upon borrowing hydrogen reactions of methanol was therefore investigated.

There are relatively few examples of *N*-methylations using methanol under borrowing hydrogen conditions using homogeneous metal catalysts, and relatively forcing conditions are usually required, presumably reflecting the less favourable oxidation of methanol relative to higher alcohols.[4a,12,13] However, Del Zotto has reported that ruthenium(II) cyclopentadienyl complexes promote *N*-methylation of amines in methanol solvent in a sealed vessel at 100 °C.[14] Applying modified conditions (reaction carried out in an open vessel at reflux) to piperazine **4** resulted in smooth conversion of starting material to product, allowing straightforward isolation by distillation in excellent yield (89% on 60 mmol scale). Reducing the catalyst charge from 1 mol% led to unacceptably long reaction times (incomplete after 24 hours at reflux). Interestingly, no alkylation was observed if alcohols other than methanol were used (*e.g.* ethanol, isopropanol, benzyl alcohol) which may explain why no self-condensation of the hydroxyl-bearing piperazine **4** was observed. Use of this catalyst may be generally applicable to methylation of secondary amines and provide a useful alternative to methods using potentially carcinogenic formaldehyde. It is noteworthy that Del Zotto also reports that primary amines bis-methylate but that anilines are unreactive.[14]

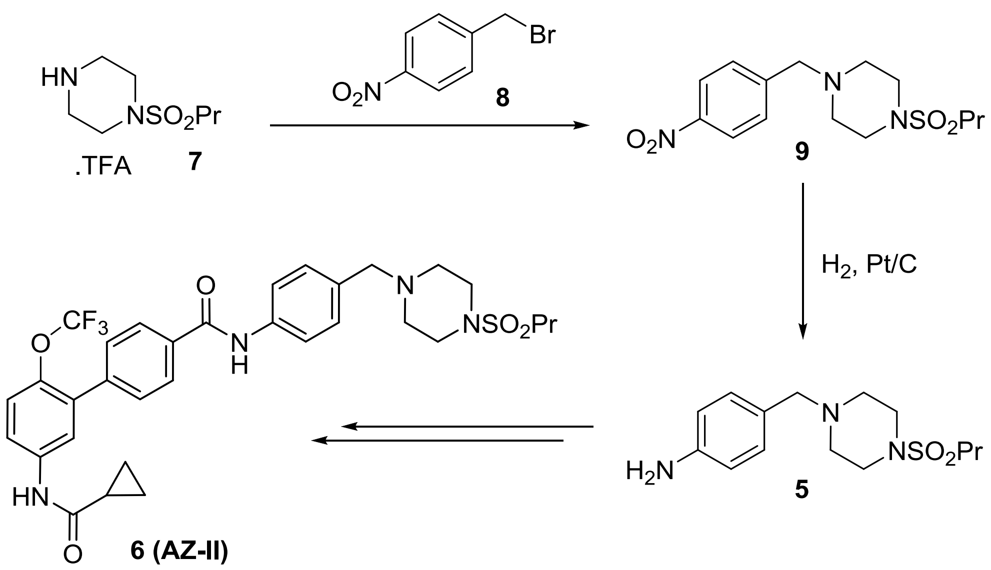
***Scheme 3.* *N*-Methylation Routes to Amino Alcohol 1**



Case Study 2 – Primary Alcohols

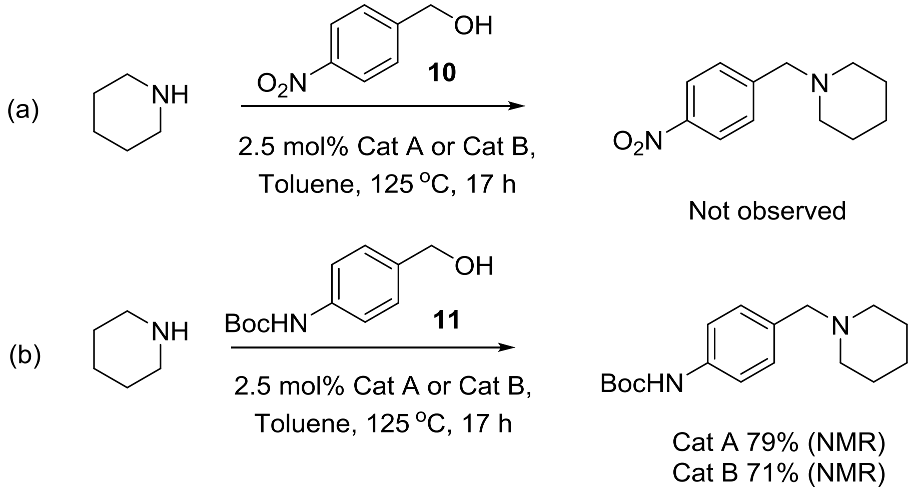
Aniline **5** is a significant sub-unit of anti-hepatitis candidate AZ-II **6,** a potent inhibitor of hepatitis C virus replication. Compound **5** is currently prepared by alkylation of sulfonamide **7** (Scheme 4)[15] with *p*-nitrobenzyl bromide **8**. Reduction of the nitro group in the product **9** then furnishes the corresponding aniline **5**, ready for acylation to assemble the drug substance.

Scheme 4. **Role of Aniline 5 in the Synthesis of AZ-II (6)**



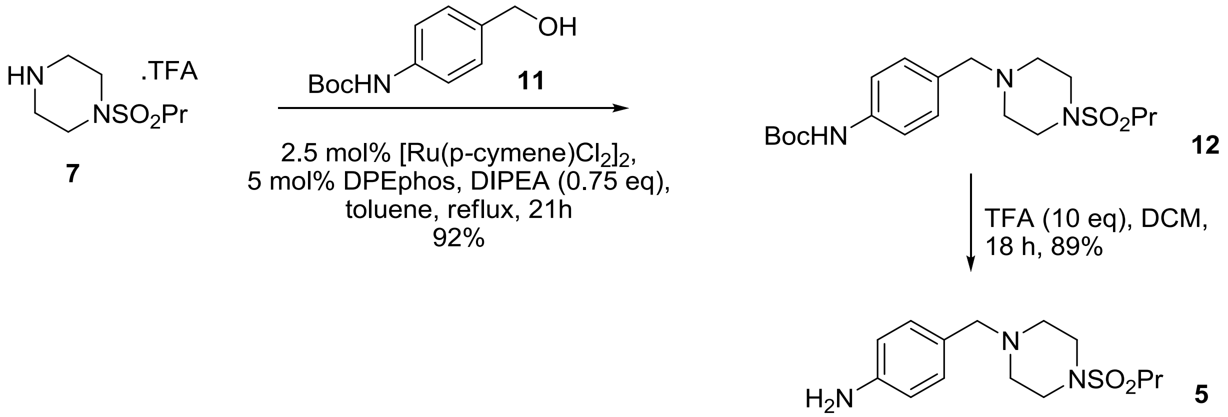
The amination of *p*-nitrobenzyl alcohol **10** with aniline under borrowing hydrogen conditions has been reported using iridium catalysts,[6d,10,16] but initial investigations aimed at a potential borrowing hydrogen approach towards aniline **5**, using **10** with piperidine as a model amine, were not encouraging (Scheme 5a). Very little reaction was observed with Catalyst A and although some reaction occurred with Catalyst B there was also evidence for reduction of the nitro group: the use of ruthenium[17] and iridium-based[18] catalysts to effect tandem nitroarene reduction/alkylation using alcohols as both the terminal reductant and alkylating agent is documented. However, we were unable to achieve clean reduction of the nitro group in this reaction. An alternative strategy based upon alkylation of a pre-formed aniline was therefore sought to circumvent the incompatibility of the reactive nitro function with the catalyst system. Direct alkylation of *p*-aminobenzyl alcohol was discounted on the basis that competing alkylation of the unprotected amine may occur but pleasingly, the Boc-protected analogue **11** performed well in model studies in the alkylation of piperidine, using either Catalyst A or B. Each catalyst (2.5 mol%) was trialled in toluene at 125 °C (sealed tube) for 17 h, after which time no starting alcohol was apparent, and both catalysts gave satisfactory levels of conversion (79% and 71% respectively) as assayed by NMR analysis using TCNB (1,2,4,5-tetrachloro-3-nitrobenzene) as an internal standard (Scheme 5b). We were therefore encouraged to examine the behaviour of the monosulfonyl piperazine **7** found in the real system.

Scheme 5. Model Alkylations of *p*-Nitrogen-substituted Benzylic Alcohols with Piperidine



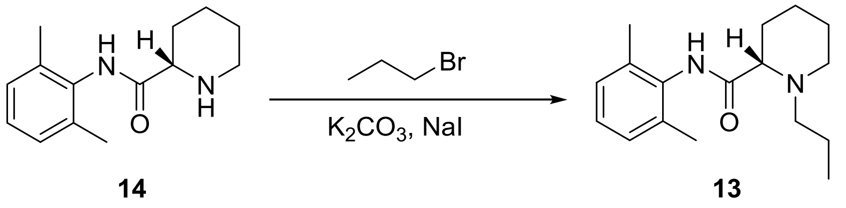
Initial experiments assessing the alkylation involved separate preparation of the free base of **7** prior to use in model alkylation reactions with benzyl alcohol. However, results with either Catalyst A or B were capricious. This led to speculation that residual TFA (as a result of the free-basing procedure) or another trace impurity in sulfonamide **7** may be influencing the outcome of the reaction. Williams has reported the direct use of dimethylammonium acetate as a substrate in borrowing hydrogen alkylations[9] so attempts were made to use the TFA salt **7** directly. Pleasingly, it was shown that **7** could be alkylated efficiently with benzyl alcohol in the presence of 0.75 eq DIPEA when using Catalyst A. The same conditions were then applied to effect alkylation of TFA salt **7** with alcohol **11** in excellent yield (92% on a 10 mmol scale); deprotection of intermediate **12** using TFA in dichloromethane then returned the required aniline **5** (89%, Scheme 6). This represents an important proof-of-principle for the application of borrowing hydrogen methodology in the synthesis of polyfunctional drug intermediates. Additionally, the ability to use amine salts directly in a borrowing hydrogen approach is very attractive given that amine intermediates are frequently isolated as salts. A further important observation from a process development perspective is that significant coloration is observed during the course of these reactions. In this example, dark brown coloration remained in the product even after silica gel chromatography. This may have implications with regard to both metal contamination and carry-through of colour to API.

Scheme 6. Borrowing Hydrogen Approach to Intermediate 5.



We next examined the alkylation of a more highly functionalized amine with a simple aliphatic primary alcohol. Anaesthetic Ropivacaine (**13**) may be prepared by alkylation of piperidine **14** with bromopropane (Scheme 7).[19] Replacement of the alkylating agent at this late stage of the synthesis would be attractive and we therefore investigated the use of a borrowing hydrogen reaction with propanol.

***Scheme 7. N*-Alkylation Route to Ropivacaine (13)**



However, attempts to effect this transformation were unsuccessful using either Catalyst A or B. In all cases, analysis by GC/GCMS revealed essentially unreacted starting materials. However, trace levels of two components were also observed, each with MH^+ 273 *i.e.* 2 less than that required for piperidine **13**

(MW = 274). We therefore suspected that the initial alcohol oxidation step had occurred but that an alternative pathway was preventing return of the hydrogen back to the desired iminium intermediate, thus stalling the reaction. We therefore investigated the reaction of **14** with propanal, and observed clean conversion to the two products with $MH^+ = 273$ that had been observed as the minor components above. Subsequent treatment with sodium triacetoxyborohydride failed to effect conversion to the desired product, supporting the notion that the resistance of this intermediate towards reduction was responsible for the borrowing hydrogen reaction stalling. The structure of the major component was shown to be aminal **15**, as confirmed by single crystal x-ray diffraction (Figure 1 – enantiomer shown). The minor component was not isolated but was presumed to be the diastereomeric aminal **16**, given the similarity between its ^{1}H NMR spectrum and that of aminal **15** (Scheme 8). It therefore seems that in the catalyzed process, nucleophilic capture of the iminium ion derived from reaction of **14** with propanal by the pendant amide to form the mixture of aminals was faster than intermolecular reduction by the relatively low concentration of metal hydride species in solution, and that once formed the aminals are resistant to ring-opening. To probe this further, piperidine **14** was treated with propanal in a 'direct' reductive amination using sodium triacetoxyborohydride,[20] *i.e.* with all components mixed without prior formation of the iminium ion. In this case, Ropivacaine **13** was returned quantitatively: evidently, the relatively high concentration of the active hydride reducing agent in this case can compete effectively with capture by the amide group. The results obtained suggest that borrowing hydrogen approaches may not be applicable to certain substrates bearing nucleophilic functionality close to the intermediate iminium ion, although the possibility remains that catalyst tuning to find a species more active in the reduction of iminium ions than systems A or B might lead to success.

Scheme 8. **Iminium Generation and Competing Internal Nucleophilic Capture vs Reduction**

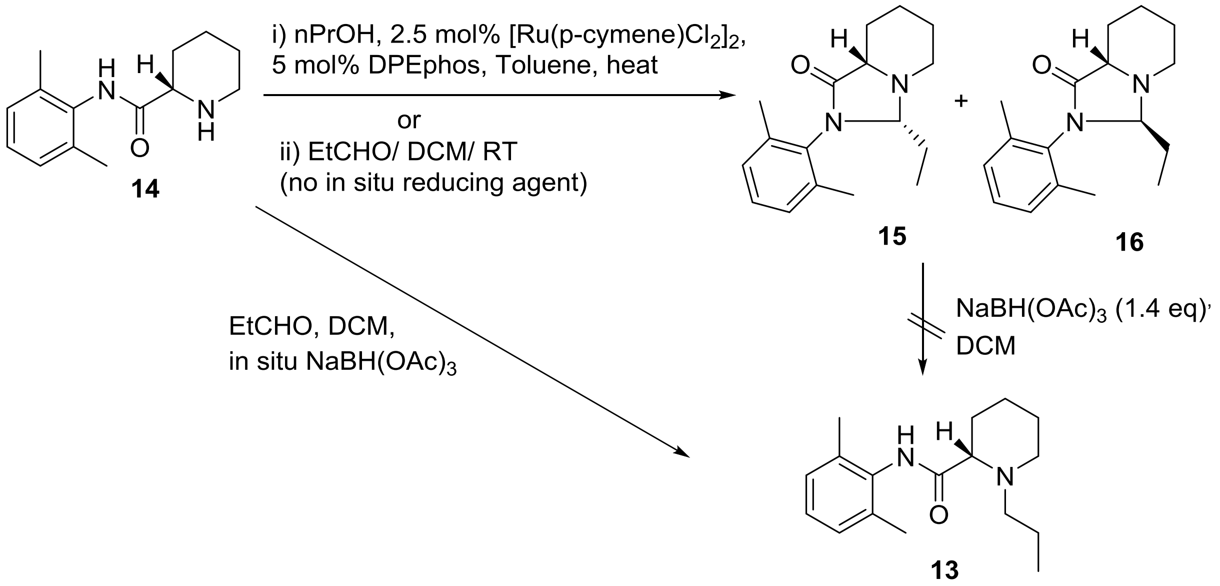
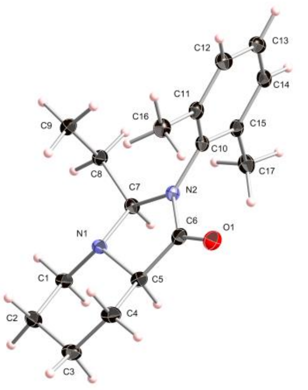


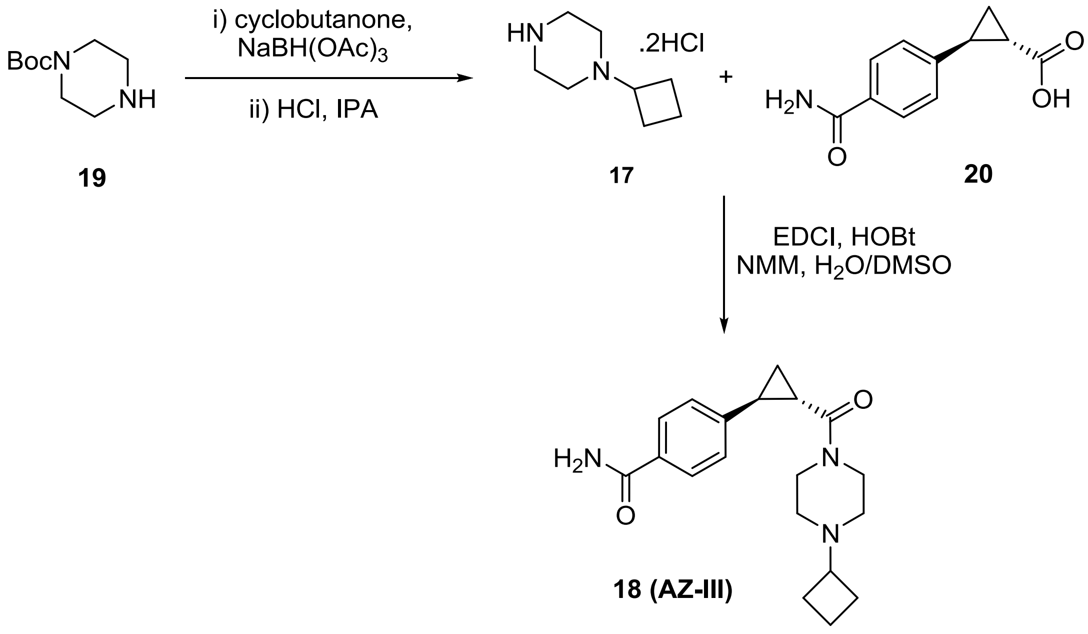
Figure 1. **X-Ray Crystal Structure of Aminal 15**



Case Study 3 – Secondary Alcohols

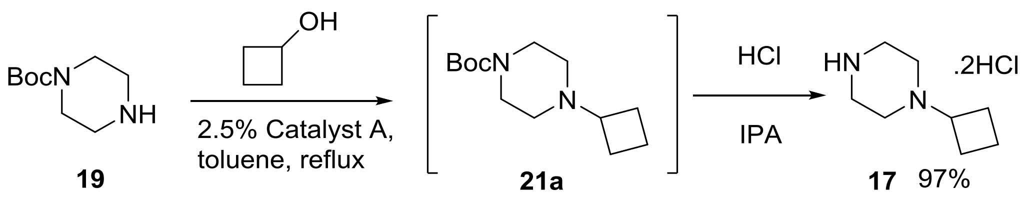
We next examined the applicability of borrowing hydrogen reactions of secondary alcohols, proceeding *via* the generally less electrophilic ketones. Piperazine dihydrochloride salt **17** is a key intermediate in the preparation of the histamine H3 receptor antagonist AZ-III **18** (Scheme 9). It is generated by reductive amination of *N*-Boc piperazine **19** with cyclobutanone, followed by deprotection; acylation with acid **20** using EDCI gives **18**.[21]

Scheme 9: **Synthesis of AZ-III (18)**



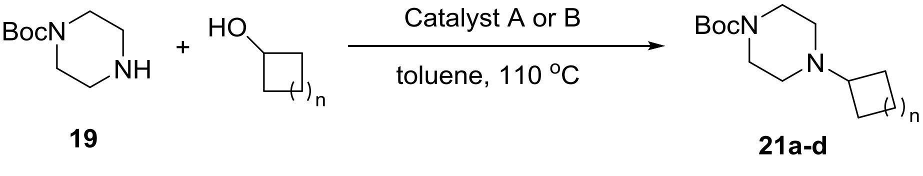
We therefore elected to examine the behaviour of **19** in a borrowing hydrogen alkylation with cyclobutanol. Pleasingly, good conversion was observed by GC analysis, with catalyst A giving superior performance over catalyst B (Table 1). These initial screening experiments were run at a loading of 2.5 mol%: attempts to reduce the catalyst loading gave unreliable results. In line with the current route, the intermediate Boc-protected amine **21a** was not isolated; addition of HCl/IPA to the reaction mixture effected deprotection and precipitation of the dihydrochloride salt **17** in near quantitative yield (Scheme 10). Coloration of the product, presumably due to residual metal, was observed to be a problem in this unoptimised procedure, but it was considered that this reaction would have been a viable alternative for scale-up and manufacture of intermediate **17.**

Scheme 10. **Borrowing hydrogen route to piperazine 17**



This facile combination of a secondary amine and secondary alcohol was very pleasing but unexpected, so we decided to explore the breadth of the reaction by studying the reaction of Boc-piperazine **19** with other cyclic secondary alcohols The use of secondary alcohols with Catalyst A is reported to be more challenging than when using primary alcohols and requires more forcing conditions (refluxing xylene).[9] We therefore investigated the reaction of **19** with a range of cyclic alcohols, analysing for conversion by GC (Table 1). For catalyst A, cyclobutanol was found to be a markedly better substrate than higher homologues, while for catalyst B cyclopentanol performed best. It can be anticipated that the oxidation of cyclobutanol is more challenging than for higher cyclic alcohols owing to the ring strain associated with introducing an sp^2 centre into a small ring. The resulting ketone will be notably more electrophilic than less strained congeners, and thus hemiaminal formation would be favoured, but elimination to form the iminium ion (frequently the rate-limiting step in imine formation[22]) would again be more difficult than for higher alcohols. Finally, reduction of the cyclobutanone-derived iminium would be expected to be more facile owing to relief of ring strain. These results suggest that for Catalyst A at least the latter step is significant in the overall rate of the reaction, and cyclobutanol can perhaps be regarded as an 'outlier' in terms of secondary alcohol performance. Indeed, the very clean reaction observed here between a secondary amine and cyclobutanol may provide a useful approach for preparation of cyclobutylamines.

Table 1. **Alkylation of Piperazine 19 with Cyclic Alcohols**



Alcohol	n	Product	Cat A (1M) % Conversion[a]	Cat B (10M) % Conversion[a]
Cycobutanol	1	**21a**	100	44

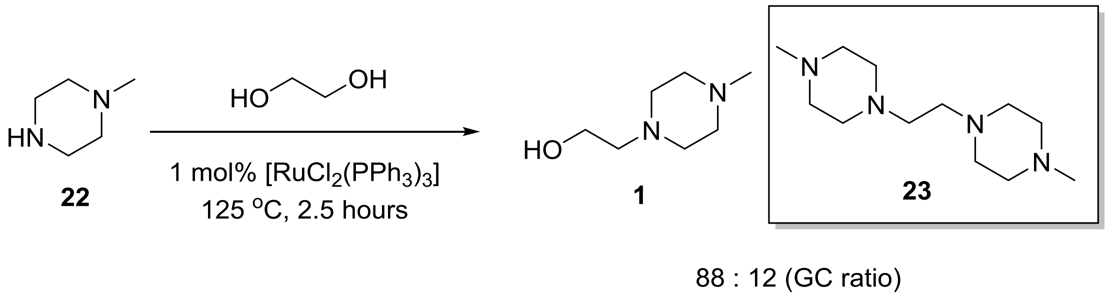
Cyclopentanol	2	**21b**	54	84
Cyclohexanol	3	**21c**	8	57
Cycloheptanol	4	**21d**	35	70

[a] Determined by GC Area

Case Study 4 – 1,n-Diols

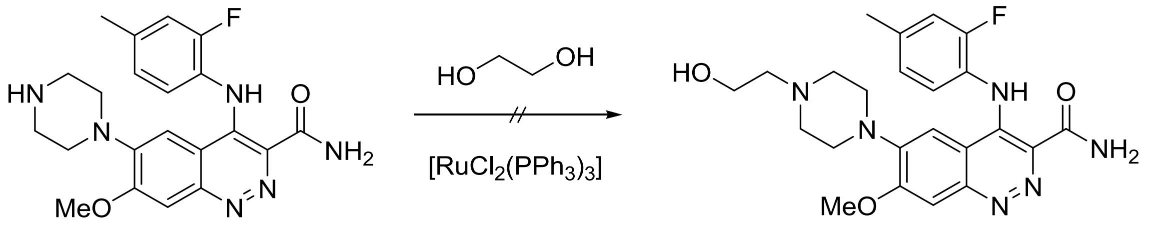
As detailed above, amino alcohol **1** is an intermediate in the synthesis of AZ-I (**2**).[11] It has previously been prepared by alkylation of *N*-methylpiperazine with 2-chloroethanol. Given the prevalence of beta-amino alcohols as targets or intermediates in pharmaceutical synthesis, we were interested to investigate whether *N*-alkylation of amines with ethylene glycol under borrowing hydrogen conditions[9,12c,f,23] was a viable alternative to the use of 2-haloethanols. We therefore attempted to aminate ethylene glycol with *N*-methylpiperazine **22** using a modified literature procedure.[23a] Piperazine **22** was rapidly consumed to return an 88:12 ratio (as determined by GC) of the desired amino alcohol **1** and the unwanted tetramine **23** arising from amination of both alcohols of the ethylene glycol (Scheme 11). It is possible that the ratio could have been improved with further optimisation but this approach was not pursued with this particular substrate as the alternative methylation approach described in Scheme 3 appeared more promising in terms of ease of purification.

Scheme 11. **Amination of Piperazine 22 with Ethylene Glycol**



Given this encouraging result, the same approach was investigated towards the synthesis of investigational compound AZ-IV (**24**) by amination of ethylene glycol with the advanced piperazine intermediate **25**, but in this instance we were disappointed to find that no trace of product was observed (Scheme 12). It was postulated that the prevalence of potential bidentate metal binding sites in piperazine **25** might deactivate the catalyst. This was supported by a spiking experiment where it was shown that the reaction of piperazine **22** and ethylene glycol no longer proceeded in the presence of piperazine **25**. This highlights a general problem area when considering a borrowing hydrogen strategy: catalyst poisoning is more likely when using densely functionalised intermediates.

Scheme 12. **Failed Borrowing Hydrogen Approach to AZ-IV (24)**

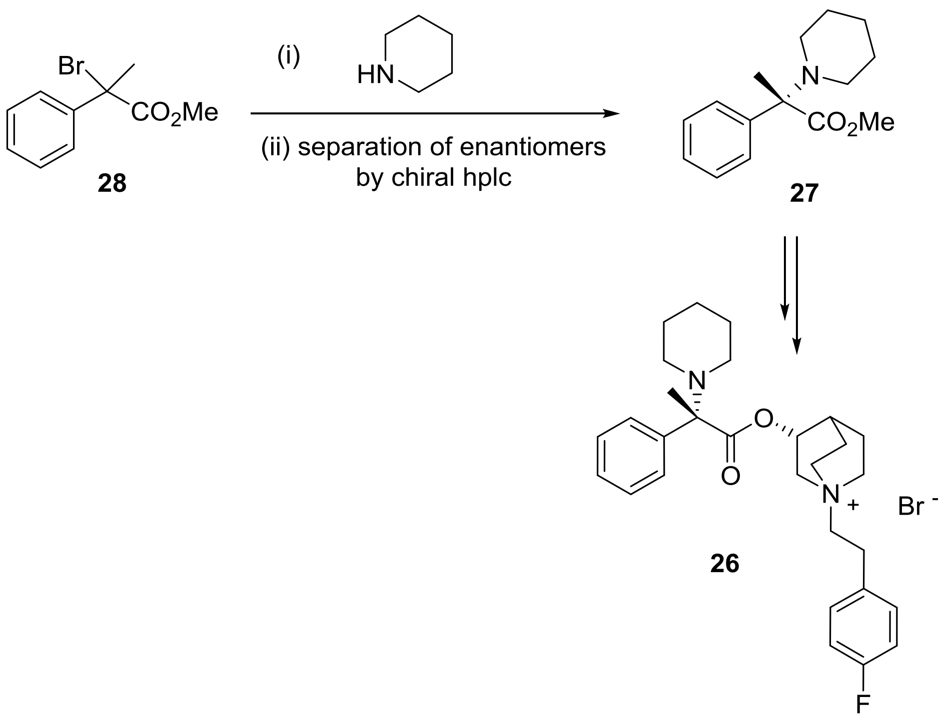


25

24 (AZ-IV)

We next investigated the use of higher diols in amine alkylation chemistry. The use of 1,n-diols to effect cyclative dialkylation of primary amines has been well documented, [6,7b,9,24] and we were keen to investigate whether this would be efficient in the context of an advanced pharmaceutical intermediate. (*S*)-Aminoester AZ-V (**26**) is an investigational muscarinic antagonist which is prepared from enantiomerically pure piperidine **27**, itself prepared as a racemate by substitution of methyl 2-bromo-2-phenylpropionate **28** with piperidine, followed by chromatographic resolution of the enantiomers (Scheme 13).[25]

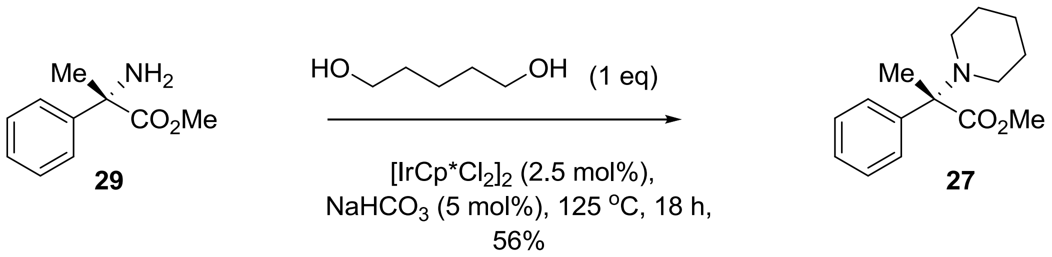
Scheme 13. **Current Route to AZ-V (26)**



Given the availability of enantiomerically pure (*S*)-amino ester **29**, we were intrigued to see whether cyclative double alkylation could be effected under borrowing hydrogen conditions to give **27**. The formation of benzyl piperidine by reaction of benzylamine with 1,5-pentanediol is known using catalyst B,[6] and we verified that this reaction was successful in our hands (89% benzyl piperidine by GC area, unoptimised) before examining the hindered quaternary amino ester **29**. As expected, the cyclisation is adversely affected by increased steric bulk around the amine, returning only traces of the desired (*S*)-piperidine **27** (5% by GC area) (Scheme 14).

These reactions were all performed in toluene at 1*M* concentration whereas many reactions using Catalyst B are run under much more concentrated conditions *e.g.* 10*M*. Therefore, the reaction was repeated at 10*M* concentration and also in the absence of solvent which greatly improved the conversion to (*S*)-piperidine **27** (87% by GC area for neat reaction; incomplete at 10*M*). However, the isolated yield from the neat reaction was disappointing (56%) based on the apparent conversion. Analysis of the crude product by ^{1}H nmr was not informative due to a number of over-lapping signals. The reaction was repeated with an internal standard present and the GC yield was determined to be 68%, whereas the profile seemed much better (92% by GC area). This led to speculation that involatile by-products, not detectable by GC, were being formed. This is perhaps not surprising since the reaction is performed neat: at higher concentrations undesired intermolecular alkylations are more likely to compete with the desired intramolecular cyclisation step. The reaction was scaled to 20 mmol and subjected to an extractive work-up to return (*S*)-piperidine **27** (3.67 g, 87% GC area; theoretical yield 4.94 g). Clearly, additional optimisation is required but this is a very encouraging result given the steric demands of the substrate.

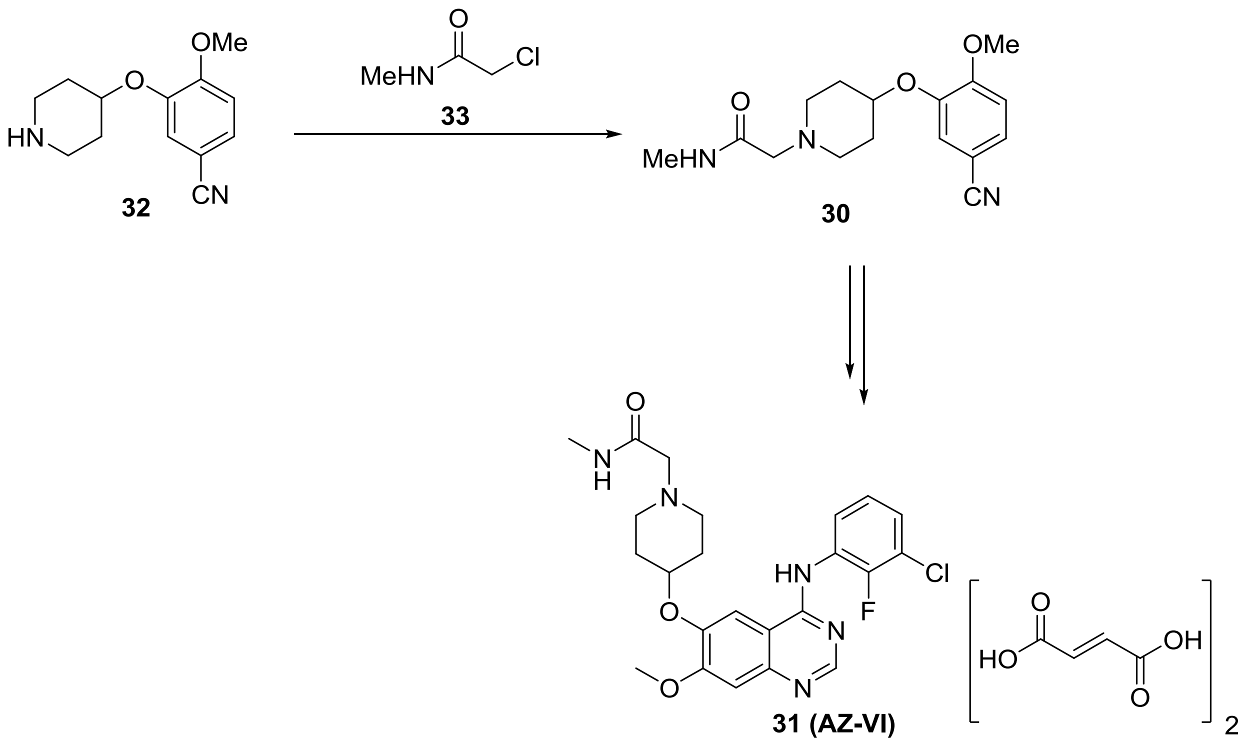
Scheme 14. **Borrowing Hydrogen Approach to (*S*)-Piperidine 27**



Case Study 5 – Glycolic Acid Derivatives

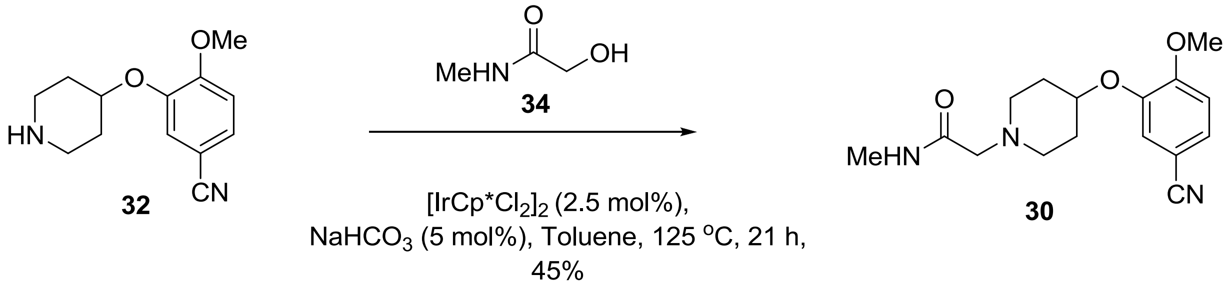
Access to 2-substituted acetamide **30** was required as part of an investigation into alternative synthetic routes to the orally active anti-proliferative agent AZ-VI difumarate (**31**). Compound **30** is currently obtained by alkylation of 4-aryloxypiperidine **32** with chloroacetamide **33** (Scheme 15).[26]

Scheme 15. **Current Route to AZ-VI (31)**



The replacement of the chloroacetamide **33** with the glycolic amide **34** was therefore examined. This is a challenging substrate for borrowing hydrogen alkylation, given the likely difficulties in the oxidation of glycolic derivatives to the highly reactive glyoxylic derivatives, and indeed there is only one report of a method for such transformations in the literature.[27] In fact, no reaction at all was observed when using Catalyst A with alcohol **34**. Some reaction was observed using Catalyst B, however, and the best conditions (Scheme 16) returned the desired acetamide **30** in 45% yield, after purification by chromatography (on 2 mmol scale). While clearly still requiring some optimization, this is a highly challenging transformation and illustrates further the potential for replacement of highly reactive halides.

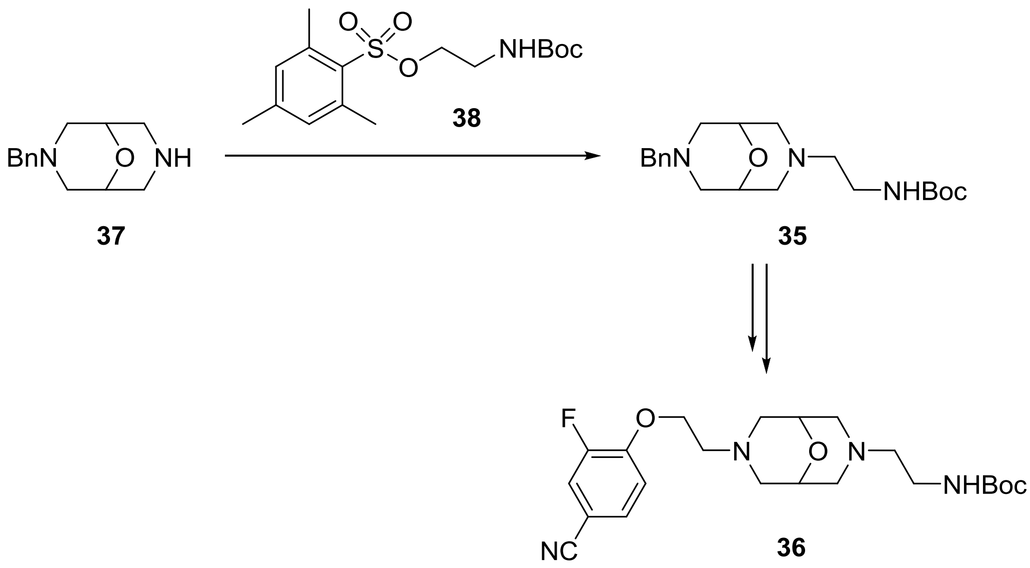
Scheme 16. **Amination of Glycolic Amide 34**



Case Study 6 – Amino Alcohols

Triamine **35** is an intermediate in the synthesis of novel antiarrhythmic agent AZ-VII (**36**), and is currently prepared by alkylation of monoprotected diamine **37** with mesitylsulfonate ester **38** (Scheme 17).[28] Replacing the mesitylsulfonate with a direct alkylation using *N*-Boc ethanolamine **39** would therefore save a synthetic operation (sulfonate ester formation) and we therefore investigated the feasibility of the transformation. This example is also a key exercise to challenge the scope of the hydrogen borrowing catalyst systems, which appear to be compromised by substrates containing multiple heteroatoms (nitrogen and/or oxygen), particularly when they are separated by 2 carbon atoms. Such substrates can potentially chelate the metal centre of the catalyst, leading to catalyst ‘poisoning’, as well as suffering from potential side-reactions associated with tautomerisation of α-heterosubstituted aldehydes and imines.[9]

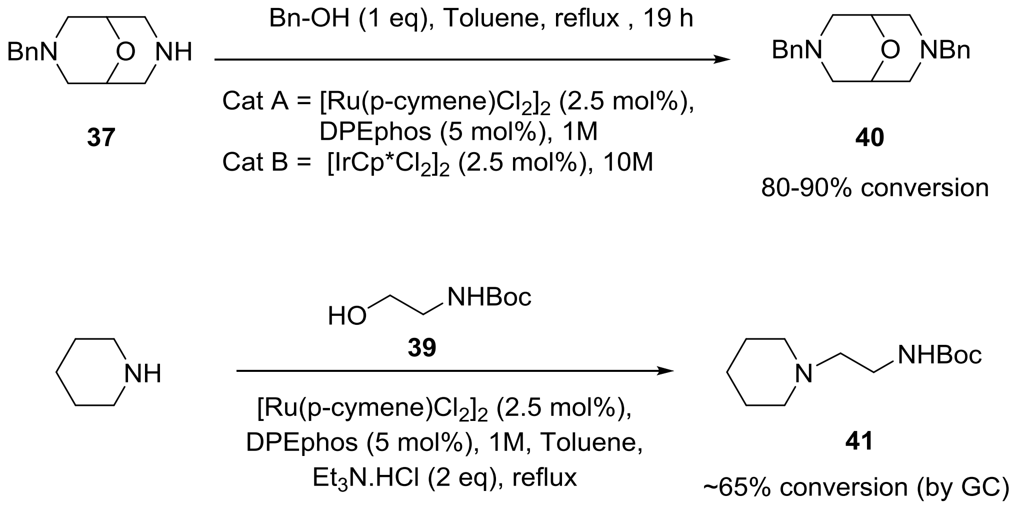
Scheme 17. **Current Route to AZ-VII (36)**



For the preparation of our desired intermediate **35** we required to react together substrates **37** and **39**; however, since each of these compounds, as well as the product **35**, have the potential to compromise the catalysts, we decided to carry out model studies to test the viability of each substrate separately in hydrogen borrowing reactions (Scheme 18). In the first instance we examined the reaction of diamine **37** with benzyl alcohol, which is known to be a good substrate in redox-neutral alkylations. Both the ruthenium system (Catalyst A) and the iridium system (Catalyst B) performed well, providing almost complete conversion to dibenzylated product **40** after 19 h at reflux in toluene. As noted for previous reactions, a higher concentration of the reaction with the iridium catalyst (10*M*) was required to give a similar rate as to the ruthenium catalyst at 1*M* concentration. The conversions for this reaction were estimated to be between 80-90% based on GC/GCMS and on NMR analysis of the crude reaction products and we judged that amine **37** is a suitable substrate for hydrogen borrowing alkylation with simple alcohols, even though it contains 3 heteroatoms conformationally disposed towards bidentate coordination modes.

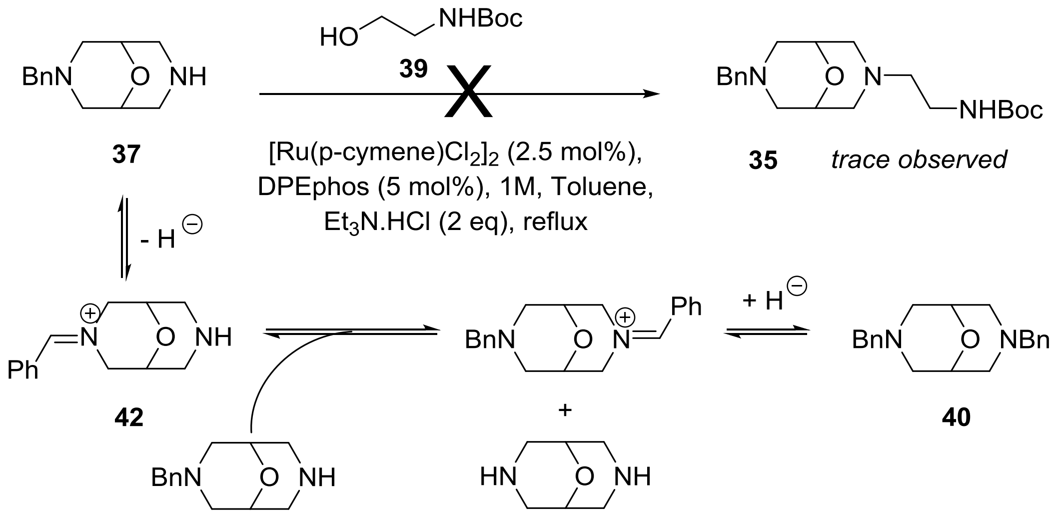
In a second model reaction we tested the viability of *N*-Boc-ethanolamine **39** as an alcoholic substrate for hydrogen borrowing alkylation. Using piperidine as a simple model amine substrate, no significant reaction was observed using iridium-based Catalyst B, but some conversion to the desired **41** was observed with ruthenium-based Catalyst A, estimated to be about 65% conversion by GC. This suggests that protected ethanolamine **39** is a more problematic substrate than standard aliphatic alcohols.

Scheme 18. **Model Alkylation Reactions with Amine 37 and Alcohol 39**



Following this modest success with model studies, the best conditions identified were applied to the desired reaction of **37** with **39**. The reaction mixture was complex and contained only trace quantities of a compound identified as the desired protected triamine **35** by GC/MS comparison with an authentic sample (Scheme 19). The main new product in the reaction mixture was identified as dibenzylamine **40** by comparison of GCMS data and NMR signals in the crude reaction mixture to data from a sample produced from the previous model reaction between diamine **37** and benzyl alcohol. The formation of diamine **40** is informative. From the previous model study, using piperidine, it is clear that *N*-Boc - ethanolamine **39** is not a particularly good borrowing hydrogen substrate and it seems that the dehydrogenation of benzylamine **37** occurs in preference to (or competition with) oxidation of the alcohol. Iminium ion **42** might then act as an alkyating agent for **37**, to provide dibenzylamine **40** following hydride transfer. Dehydrogenation and subsequent dimerisation has previously been demonstrated for primary and secondary amines.[16] The potential for amine dehydrogenation to compete (particularly with activated benzylic amines) when alcohol dehydrogenation is problematic and may be a general issue that needs to be considered in planning borrowing hydrogen alkylations of polyfunctional substrates.

Scheme 19. **Attempted Synthesis of Amine 35**



Conclusions

In this broad scoping study, we hope to have demonstrated some of the opportunities and current limitations of borrowing hydrogen chemistry for the alkylation of amines avoiding potentially genotoxic alkyl halide or sulfonate intermediates. The impressive application of this technology by Pfizer in the synthesis of PF-03463275 notwithstanding,[8] it appears that the demands of complex, polar polyfunctional intermediates common to pharmaceutical targets do still impose some limitations on the broad applicability of the chemistry. Nevertheless, we have found significant encouragement from some key examples that this technology has the potential to deliver improved processes for pharmaceutical manufacture. The method still offers good opportunities for avoiding alkylating agents as intermediates and works relatively reliably for simple aliphatic alcohols (MeOH, 1ry and 2ry). Structural incompatibilities with the chemistry are more obviously visible, however, in complex polyfunctional molecules typified by pharmaceutical intermediates rather than the relatively simple lipophilic substrates typically examined in methodological development studies. The catalyst incompatibilities with heteroatom rich heterocyclic structures were demonstrated eg by spiking experiments that show catalyst poisoning by **25** in the otherwise successful alkylation of piperazine 2**2** by ethylene glycol. Additionally, neighbouring group participation in polyfunctional molecules can lead to interception of reactive intermediates, as in the case of formation of the stable imidazolidinone **15**. Finally, the reaction conditions employed in this scoping study highlight the need for more active and tolerant catalysts, capable of operating at low loadings (from the standpoints of both economics and metal residue issues –as highlighted here by colouration issues), and across a broad range of solvents (such as those often required for relatively insoluble advanced intermediates) and process-relevant concentrations. We hope that this study will serve to encourage others in the process chemistry community to investigate the adoption of this technology, and to challenge those engaged in catalyst development to investigate the next generation of hopefully more active and robust catalysts that can tolerate the demands of the molecules outlined herein.

Experimental Section

General. Starting materials, reagents and solvents were obtained from commercial suppliers and used without further purification. NMR spectra were obtained using Bruker DPX 400, DRX 500 and Avance 600 instruments; ^{1}H spectra were measured with reference to an internal standard of tetramethylsilane at 0 ppm and ^{13}C spectra were measured with reference to the $CDCl_3$ signal at 77.0 ppm or the DMSO signal at 39.5 ppm. GC analyses were performed with an Agilent 6890N instrument and HPLC analyses with an Agilent 1100 instrument. High resolution mass spectra were run on a Bruker MicrOTOFQ LCMS instrument and the major ion was analysed using positive ion electrospray ionisation.

2-(4-Methylpiperazin-1-yl)ethanol (1) [RuCl(Cp)(PPh_3)$_2$] (436 mg, 0.6 mmol, 1 mol%) was added to a solution of piperazine **4** (7.81 g, 60.0 mmol) in methanol (240 ml) under N_2. The reaction was stirred at RT for 10 minutes, then heated to reflux (bath at 85 °C) for 24 hours. Methanol was removed on the rotary evaporator and the residue was then purified by bulb-to-bulb distillation under reduced pressure (oven at 110 °C; *ca* 2 mbar) to return amino alcohol **1** (7.68 g, 89% th) as a pale yellow oil. Spectroscopic analysis was in agreement with the reported data.[11]

4-((4-Propylsulfonyl)piperazin-1-yl)methyl)aniline (5) [Ru(*p*-cymene)Cl_2]$_2$ (156 mg, 0.25 mmol, 2.5 mol%), DPEphos (275 mg, 0.50 mmol, 5.0 mol%), sulphonamide trifluoroacetate salt **7** (3.06 g, 10.0 mmol), alcohol **11** (2.23 g, 10.0 mmol), diisopropylethylamine (0.70 g, 7.50 mmol) and PhMe (10 ml) were stirred under N_2 at RT for 10 minutes. The reaction was heated at reflux for 21 hours, then cooled to RT and concentrated under reduced pressure to return the crude product which was purified by flash column chromatography, eluting with 2% MeOH in DCM, to return intermediate **12** (3.67 g, 92% th) as a brown oil which slowly solidified. ^{1}H NMR (400 MHz, 300 K, $CDCl_3$) δ 1.05 (3H, t, *J*7.40), 1.52 (9H, s), 1.81-1.88 (2H, m), 2.48-2.51 (2H, m), 2.85-2.89 (2H, m), 3.26-3.29 (4H, m), 3.47 (2H, s), 6.47 (1H, Br s), 7.18-7.23 (2H, m), 7.30.7.36 (2H, m); ^{13}C (100 MHz, 300 K, $CDCl_3$), δ13.18, 16.80, 28.33, 45.75, 50.73, 52.54, 62.14, 80.57, 118.50, 129.75, 132.14, 137.54, 152.76; HRMS (electrospray +ve ion) calcd for $[M+H]^+$ $C_{19}H_{32}N_3O_4S$ 398.2108, found 398.2099.

TFA (7.65 mL, 100.0 mmol) was added to a solution of intermediate **12** (3.67 g, 9.23 mmol) in DCM (50 mL) at RT. The reaction was stirred overnight then concentrated under reduced pressure. The residue was redissolved in PhMe (50 mL), then extracted with 2M HCl (3 x 50 mL). The combined aqueous phases were washed with DCM (50 mL), then basified with 2M NaOH and extracted with DCM (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to return aniline **5** (2.45 g, 89% th) as a brown oil which slowly solidified. ^{1}H NMR (400 MHz, 300 K, d_6-DMSO) δ 1.04 (3H, t, *J*7.60), 1.74 2H, sex, *J*7.60), 2.39-2.48 (4H, m), 3.05 (2H, t *J*7.60), 3.14-3.26 (4H, m), 3.36 (2H, s), 5.04 (2H, s), 6.56 (2H, ~d, *J*8.20), 6.98 (2H, ~d, *J*8.20);

^{13}C (100 MHz, 300 K, $CDCl_3$) δ12.80, 16.30, 45.20, 48.95, 51.85, 61.45, 113.75, 124.20, 129.70, 147.65. Other data was also in agreement with the reported data.[15]

1-Cyclobutylpiperazine dihydrochloride (17) [Ru(*p*-cymene)Cl_2]$_2$ (383 mg, 0.63 mmol, 2.5 mol%), DPEphos (673 mg, 1.25 mmol, 5.0 mol%), *N*-Boc piperazine **12** (4.66 g, 25.0 mmol), cyclobutanol (1.98 g, 25.0 mmol) and PhMe (25 ml) were stirred under N_2 at RT for 10 minutes. The reaction was heated at reflux for 16 hours, then cooled to RT. IPA (42 ml) and 5-6N HCl in IPA (25 ml, 125-150 mmol) were added to the brown suspension which was then heated to 50 °C for 2.5 hours. The suspension was cooled to RT and stirred overnight (for convenience). The solid was isolated by filtration, displacement washed with IPA (50 ml), then dried under reduced pressure at 50 °C to return piperazine **14** (5.17 g, 97% th) as a light brown solid. Spectroscopic analysis was in agreement with the reported data.[20]

(3*S*,8a*S*)-2-(2,6-Dimethylphenyl)-3-ethylhexahydroimidazo[1,5-*a*]pyridine-1(*5H*)-one (15) Propanal (616 μL, 8.6 mmol) was added to a solution of piperidine **14** (2.00 g, 8.6 mmol) in DCM (30 mL) at RT and stirred overnight. The reaction mixture was concentrated under reduced pressure, then purified by flash column chromatography, eluting with 1:1 EtOAc:^{i}hexane, to provide an analytical sample. The cleanest fraction only was concentrated under reduced pressure to return aminal **15** (370 mg, 16% th) as a pale yellow solid which was recrystallised from EtOH. ^1H NMR (400 MHz, 300 K, $CDCl_3$) δ 0.66 (3H, t, *J*7.5), 1.30-1.76 (6H, m), 1.92 (1H, m), 2.12 (1H, m), 2.20 (3H, s), 2.25 (3H, s,), 2.26 (1H, m), 2.79 (1H,dt, *J*10.5, 2.5), 3.13 (1H,dt, *J*10.5, 3.5), 4.21 (1H, m), 7.04 (1H, m), 7.08-7.17 (2H, m); ^{13}C (100 MHz, 300 K, $CDCl_3$) δ 9.40, 18.80, 19.20, 23.60, 24.00, 25.05, 25.70, 48.70, 64.85, 80.40, 128.05, 128.45, 128.75, 133.80, 135.80, 138.15, 171.80; HRMS (electrospray +ve ion) calcd for $C_{17}H_{25}N_2O$, 273.1961, found 273.1965.

(*S*)-Methyl 2-phenyl-2-(piperdin-1-yl)propanoate (27) (*S*)-Methyl 2-amino-2-phenylpropanoate **29** (358 mg, 2 mmol), 1,5-pentanediol (210 μL, 2 mmol), [IrCp*Cl_2]$_2$ (40 mg, 0.05 mmol, 2.5 mol%) and

$NaHCO_3$ (9 mg, 0.1 mmol, 5.0 mol%) were stirred under N_2 at RT for 10 minutes in a carousel tube. The tube was then sealed and heated to 125 °C for 18 hours. The reaction was cooled to RT and the crude product was purified by flash column chromatography, eluting with 9:1 isohexane:EtOAc, to return piperidine **27** (276 mg, 56% th) as a colourless oil. Spectroscopic analysis was in agreement with the reported data.[25]

2-(4-(5-Cyano-2-methoxyphenoxy)piperidin-1-yl)-*N*-methylacetamide (30) $[IrCp^*Cl_2]_2$ (40 mg, 0.05 mmol, 2.5 mol%), $NaHCO_3$ (9 mg, 0.1 mmol, 5.0 mol%), piperidine **32** (465 mg, 2 mmol), alcohol **34** (178 mg, 2 mmol) and PhMe (2 ml) were stirred under N_2 at RT for 10 minutes in a carousel tube. The tube was then sealed and heated to 125 °C for 21 hours. The reaction was cooled to RT, then concentrated under reduced pressure to return the crude product which was purified by flash column chromatography, eluting with 2% MeOH in DCM, to return acetamide **30** (270 mg, 45% th) as a colourless solid. Spectroscopic analysis was in agreement with the reported data.[26]

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Supporting Information Available

X-Ray Crystal Structure data for Aminal 15 is available. This information is available free of charge *via* the internet at http://pubs.acs.org/.

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