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Aminomethylhydroxylation of alkenes: Exploitation in the synthesis of scaffolds for small molecule libraries

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ABSTRACT

The application of [4+2] cycloadditions between alkenes and an *N*-benzoyl iminium species, generated in situ under acidic conditions, is described in the synthesis of diverse molecular scaffolds. The key reaction led to the formation of cyclic imidates in good yield and with high regioselectivity. It was demonstrated that the cyclic imidates may be readily converted into 1,3-amino alcohols. Incorporation of orthogonally-reactive functionality, such as aryl and alkyl bromides, into the cycloaddition substrates enabled the synthesis of additional scaffolds. For one scaffold, the synthesis of exemplar screening compounds was undertaken to demonstrate potential value in small molecule library production.

1. Introduction

Reactions that enable the difunctionalisation of alkenes are key tools in synthetic organic chemistry. For example, alkene epoxidation,[1] dihydroxylation[2] and aminohydroxylation[3] are highly general, and have been widely exploited in the synthesis of biologically-active molecules. In contrast, reactions that enable the overall aminomethylhydroxylation of alkenes are much less well developed. Such processes would have significant strategic value since there is a wide range of biologically active 1,3-amino alcohols. Examples of bioactive 1,3-amino alcohol derivatives include (−)-sedamine, a potential treatment for cognitive disorders;[4] (+)-negamycin, which may have value as a treatment for muscular dystrophy;[5] and fluoxetine, a major antidepressant drug (Fig. 1).[6]

In this paper, we describe the scope and limitations of an efficient process for the overall aminomethylhydroxylation of alkenes (Scheme 1). Specifically, it was proposed to exploit [4+2] cycloaddition reactions between alkenes **1** and an in situ-generated *N*-benzoyl iminium ion **3** to yield 5,6-dihydro-4*H*-oxazines **4**;[7–9] hydrolysis would then yield 1,3-amino alcohols **2**. The value of this process in the synthesis of a range of diverse small molecule scaffolds was demonstrated. Finally, for one of the small molecule scaffolds, it was shown that decoration was possible to give a wide range of exemplar screening compounds.

2. Results and discussion

2.1. Identification of optimal conditions for the [4+2] cycloaddition

Initially, we investigated a range of conditions for in situ *N*-benzoyl iminium ion generation, and subsequent [4+2] cycloaddition with alkenes. For this study, two alkenes—cyclohexene (**1b**) and *trans*-stilbene (**1a**)—were chosen on the basis of their contrasting steric and electronic properties. The alkenes and *N*-hydroxymethyl benzamide were treated with concentrated sulfuric acid in a range of solvents at elevated temperature. Our results are summarized in Table 1. Good yields of the required products **4a** and **4b** were obtained (as single diastereomers) when acetic acid was used as solvent (entries 3a and 3b). In contrast, more modest yields were obtained in either toluene at 90 °C (entries 1a and 1b) or 1,2-dichloroethane at 80 °C (entries 2a and 2b).

2.2. Investigation of the scope of the [4+2] cycloaddition

A broad range of substrates was selected to investigate the scope and limitations of the [4+2] cycloaddition (Scheme 2). In each case, the reaction was initially performed at room temperature

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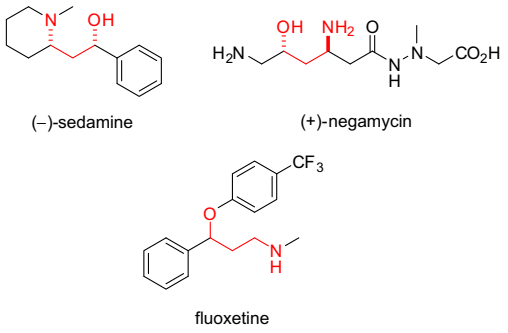
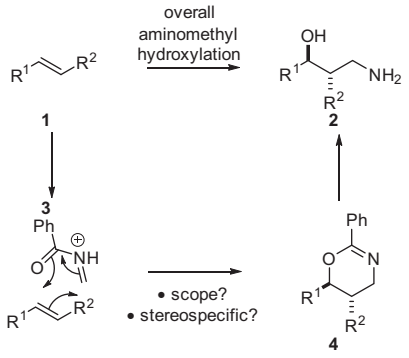
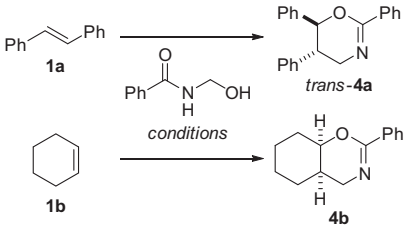


Figure 1. Examples of bioactive 1,3-amino alcohols.



Scheme 1. Overall process for the aminomethylhydroxylation of alkenes. A [4+2] cycloaddition reaction between an alkene **1** and an *N*-benzoyl iminium ion **3** would yield a 5,6-dihydro-4*H*-1,3-oxazine **4**; hydrolysis would then yield the corresponding 1,3-amino alcohol **2**.

Table 1
Investigation of conditions for [4+2] cycloaddition reactions

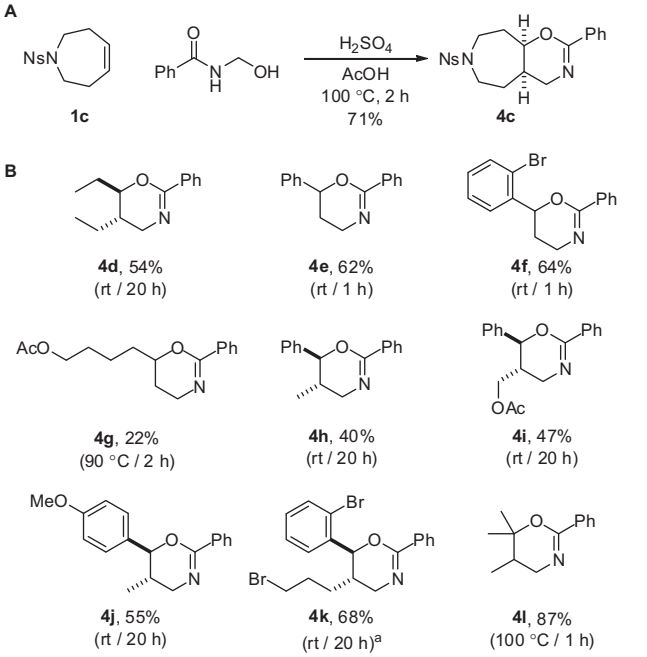


Entry	Substrate	Solvent	Temp (°C)/time (h)	Product (yield, %)
1a	**1a**[a,b]	Toluene	90/4	*trans*-**4a**, 14
1b	**1b**[a,b]	Toluene	90/4	**4b**, 8
2a	**1a**	1,2-DCE	80/3	*trans*-**4a**, 49
2b	**1b**	1,2-DCE	80/3	**4b**, 28
3a	**1a**	AcOH	90/2	*trans*-**4a**, 51
3b	**1b**	AcOH	70/2	**4b**, 61

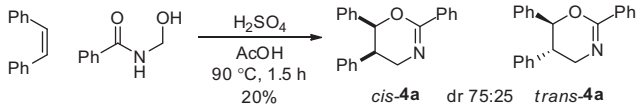
[a] No reaction was observed in DMF at 90 °C; $(BzNH)_2CH_2$ was observed as a by-product.
[b] No reaction was observed in TBME at reflux (97 °C). 1,2-DCE, 1,2-dichloroethane; TBME, *tert*-butyl methyl ether.

overnight, and if significant conversion was not observed, reaction at higher temperature was investigated.

Initially, the reaction of symmetrical alkenes was investigated. The heterocyclic alkene **1c**, prepared by ring-closing metathesis,[10] reacted smoothly upon treatment with *N*-hydroxymethyl benzamide and sulfuric acid in acetic acid at 100 °C to give the 5,6-dihydro-4*H*-oxazine **4c** in 88% yield. After reaction at room temperature overnight, *trans*-hex-3-ene yielded the 5,6-dihydro-4*H*-oxazine **4d** in 54% yield as a single (*trans*) diastereomer.



Scheme 2. Scope of the [4+2] cycloaddition. Panel A: exploitation of a cyclic alkene in the synthesis of the 5,6-dihydro-4*H*-oxazine **4c**. Panel B: Synthesis of a diverse range of 5,6-dihydro-4*H*-oxazines. The time and temperature of individual reactions is noted in parentheses. [a] Reaction performed in 1,2-dichloroethane. Ns, *p*-nitrophenylsulfonyl.



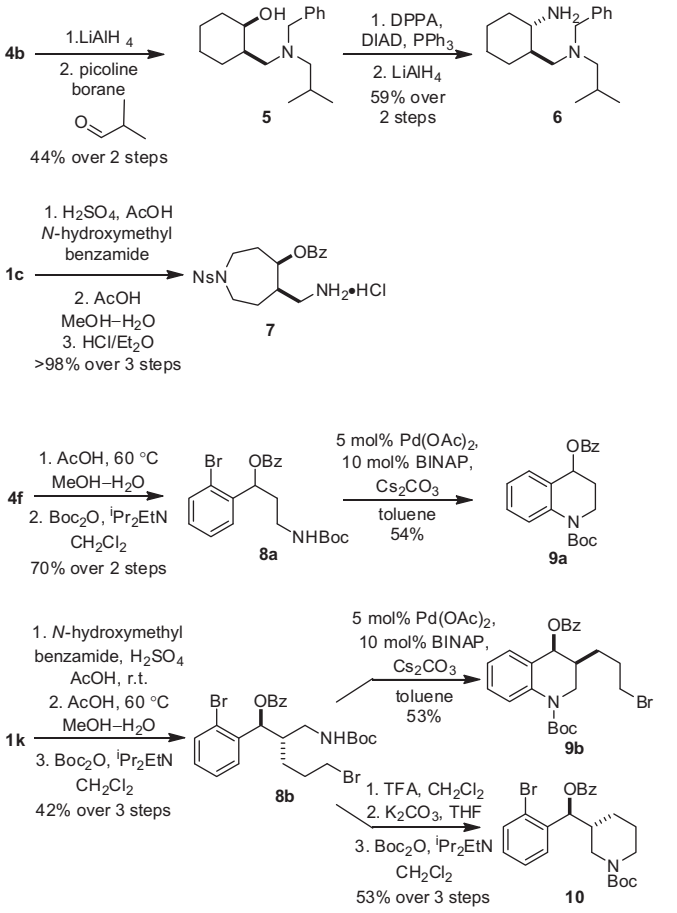
Scheme 3. Investigation of the cycloaddition reaction of *cis*-stilbene.

The regioselectivity of the cycloaddition was investigated with a range of unsymmetrical alkene substrates. Thus, mono-substituted alkenes reacted to yield the corresponding 6-aryl- (**4e** and **4f**) or 6-alkyl- (**4g**) substituted 5,6-dihydro-4*H*-oxazines as single regioisomers. Similarly, a range of *trans*-1,2-disubstituted alkenes yielded the corresponding *trans*-5,6-disubstituted 5,6-dihydro-4*H*-oxazines (**4h**-**4k**) as single regio- and diastereoisomers. In addition, 2-methyl-but-2-ene gave the 5,6-dihydro-4*H*-oxazine **4l** as a single regioisomer. These results are consistent with a concerted, but asynchronous, cycloaddition reaction in which the new C–C bond is formed in advance of the new C–O bond.

To further probe the stereospecificity of the cycloaddition, we investigated *cis*-stilbene as a substrate (Scheme 3). Surprisingly, treatment of *cis*-stilbene with *N*-hydroxymethyl benzamide and sulfuric acid in acetic acid at 70 °C gave a low yield of a 75:25 mixture of *cis* and *trans*-diasteroisomers (*cis*- and *trans*-**4a**). This reaction contrasted strongly with that of *trans*-stilbene in which *trans*-**4a** was obtained as a single diastereoisomer (entry 3b, Table 1). We subsequently demonstrated that *cis*-**4a** does epimerise upon treatment with sulfuric acid in acetic acid; we therefore hypothesise that the cycloaddition is stereospecific, but that *cis*-**4a** begins to equilibrate under the reaction conditions to give the thermodynamically more stable diastereomer, *trans*-**4a**.

2.3. Synthesis of diverse small molecule scaffolds

We demonstrated the value of several of the 5,6-dihydro-4*H*-oxazines **4** in the synthesis of a range of diverse small molecule

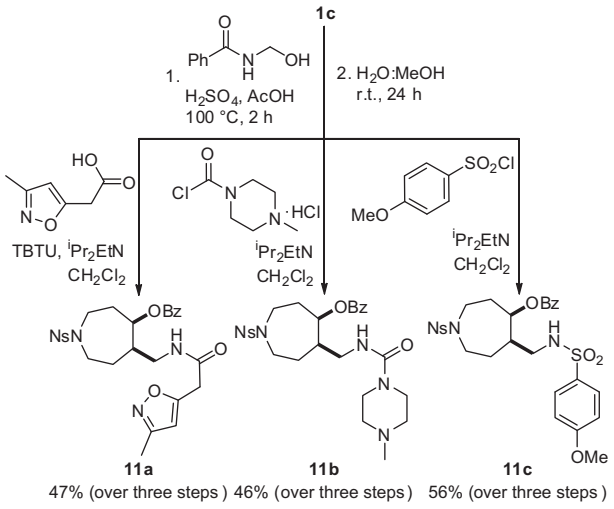


Scheme 4. Synthesis of scaffolds from 5,6-dihydro-4*H*-oxazines. DPPA, diphenylphosphoryl azide; DIAD, diethyl azodicarboxylate; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

scaffolds (Scheme 4). Thus, treatment[7e] of **4b** with $LiAlH_4$ yielded an *N*-benzyl 1,3-amino alcohol which was directly reductively aminated to yield the 1,3-aminoalcohol **5**. Treatment of **5** with DPPA, DIAD and PPh_3,[11] followed by reduction of the intermediate azide with $LiAlH_4$ gave the 1,3-diamine **6**.

Cycloaddition of the alkene **1c**, followed by treatment with acetic acid in MeOH–H_2O,[7a] and subsequent salt exchange with HCl/Et_2O, gave the *O*-benzoylated 1,3-amino alcohol derivative **7** as a hydrochloride salt. In a similar vein, hydrolysis of the 5,6-dihydro-4*H*-oxazines **4f** and **4k**, followed by Boc protection, gave the *O*-benzoyl *N*-Boc 1,3-amino alcohol derivatives **8a** and **8b**, respectively. In the case of **4k**, the cycloadduct was not purified, and was immediately hydrolysed and protected to yield the *O*-benzoyl *N*-Boc 1,3-amino alcohol derivative **8b** (in 42% yield over 3 steps from **1k**). Treatment of **8a** and **8b**, which each bear a suitably positioned *o*-bromophenyl substituent, with 5 mol% $Pd(OAc)_2$ and 10 mol% BINAP[12] gave the corresponding 4-benzoyloxy tetrahydroquinolines **9a** and **9b**, respectively. With **8b**, an alternative cyclisation was possible: removal of the Boc protecting group from the primary aliphatic amine, followed by neutralization of the resulting ammonium salt and finally reprotection, gave the Boc-protected piperidine **10**.

Thus, it was possible to prepare a range of molecular scaffolds that may have value in the synthesis of small molecule libraries. Crucially, all of these scaffolds—**6**, **7**, **9a**, **9b** and **10**—have (at least) two differentially-protected sites that may be suitable for subsequent decoration.



Scheme 5. Formation and decoration of the scaffold **4c**. TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

2.4. Decoration of scaffold and library production

To demonstrate the potential for exploitation in library synthesis, a range of analogues was prepared from the 1,3-amino alcohol derivative **7**. Thus, the cyclic alkene **1c** was converted into **7** which was then directly derivatised to yield the amide **11a**, the urea **11b** and the sulfonamide **11c** (Scheme 5).

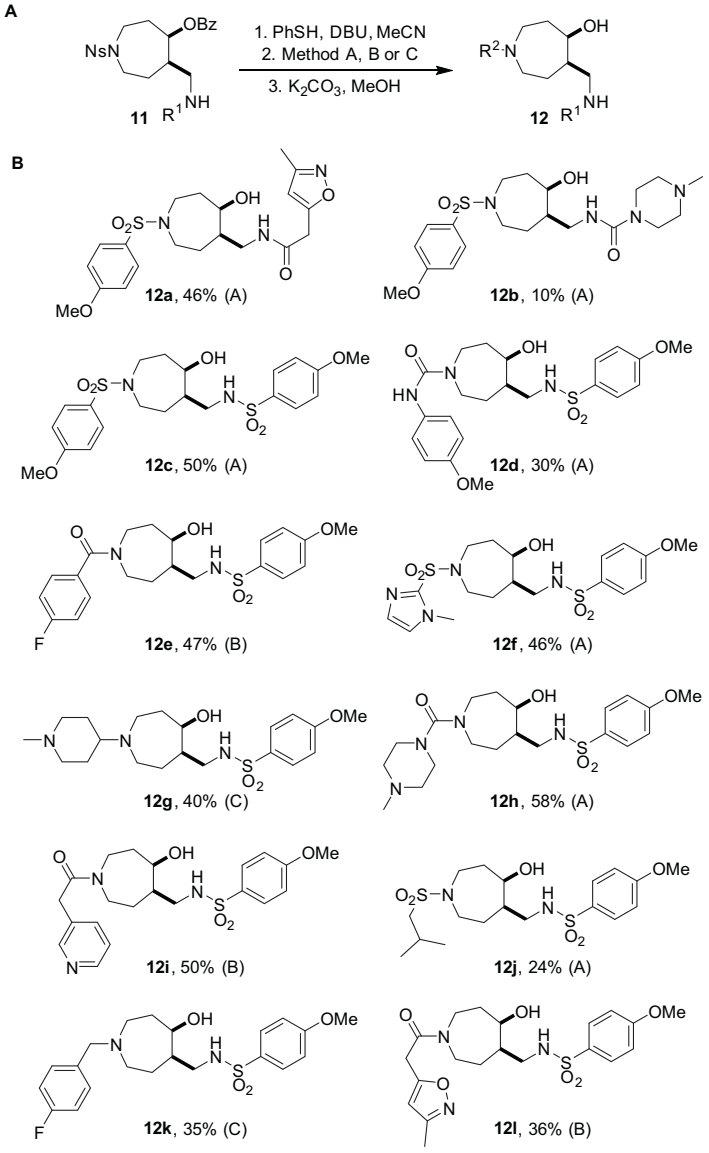
Subsequently, it was demonstrated that a second decoration reaction was also possible (Scheme 6). Thus, the *p*-nitrophenylsulfonyl group was removed from each of the derivatives **11a-c**, which were then decorated and debenzoylated to yield a range of exemplar screening compounds. Specifically, it was shown that decoration was possible by sulfonylation (→ **12a**, **12b**, **12c**, **12f** and **12j**), urea formation (→ **12d** and **12h**), amide formation (→ **12e**, **12i** and **12l**) and reductive amination (→ **12g** and **12k**).

This validation work enabled the nomination of small molecule library for production for inclusion in the Joint European Compound Library (JECL) of the European Lead Factory (ELF). The library was nominated on the basis of the validation work, and the predicted molecular properties of the proposed compounds (Fig. 2).

3. Conclusion

In conclusion, we have demonstrated that the [4+2] cycloaddition between alkenes and an in situ generated *N*-benzoyl iminium ion can be exploited as a key step in the synthesis of 1,3-amino alcohol derivatives. The reaction was found to be highly regioselective with a wide range of unsymmetrical alkenes. The results were consistent with a concerted, stereospecific cycloaddition in which C–C bond formation is more advanced that C–O bond formation.

The value of the [4+2] cycloaddition reaction was demonstrated in the synthesis of a range of diverse scaffolds. Crucially, each of the scaffolds was differentially-protected with (at least) two possible sites for decoration. For one of the scaffolds, it was also demonstrated that decoration was possible to give exemplar screening compounds. On the basis of this validation work, a small molecule library was nominated for production, leading to the addition of over 500 novel compounds to the JECL.[13]



Scheme 6. Synthesis of exemplar screening compounds. Panel A: Overview of the final decoration step. Method A: sulfonyl chloride, isocyanate or acid chloride, $^{i}Pr_2EtN$, CH_2Cl_2. Method B: carboxylic acid, TBTU, $^{i}Pr_2EtN$, CH_2Cl_2. Method C: aldehyde or ketone, $NaBH(OAc)_3$, AcOH, THF, 60 °C. Panel B: Specific exemplar screening compounds prepared. Yields over three steps are indicated, together with the method used in the second step.

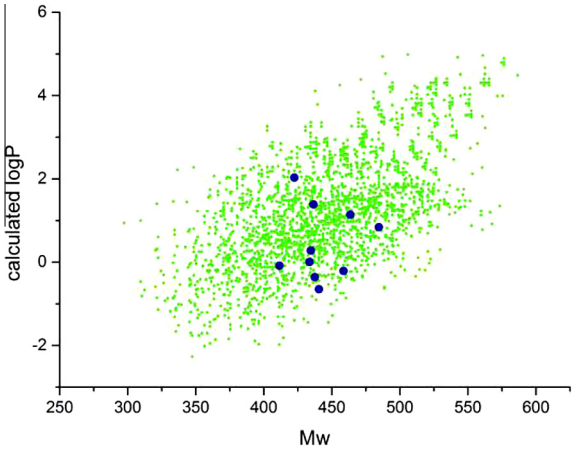


Figure 2. Molecular properties of exemplar screening compounds synthesised during validation work (blue, enlarged for clarity) and compounds nominated for library production (green).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2015.01.058.

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13. For the library production, the order of the synthetic steps was altered: (1) PhSH, DBU, MeCN; (2) K_2CO_3, MeOH; (3) Method A, B or C (Scheme 6).