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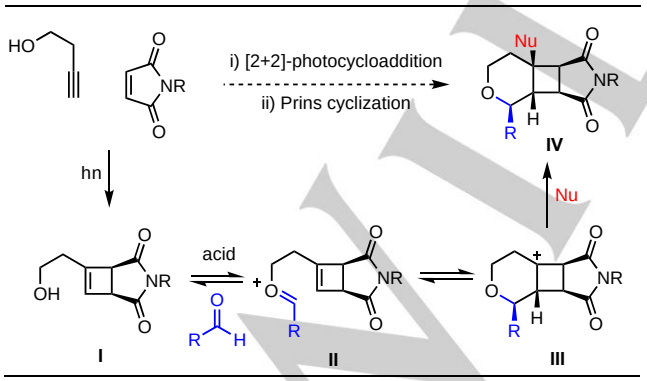
Sequential Photochemical and Prins Reactions for the Diastereoselective Synthesis of Tricyclic Scaffolds

Bethan L. Donnelly, Luke D. Elliott, Christine L. Willis and Kevin I. Booker-Milburn*

Abstract: Cyclobutene alcohols undergo Prins cyclizations to generate single diastereomers of novel tricyclic heterocycles with five contiguous stereocenters. Reaction times are significantly shorter (~15 mins) than with traditional alkene substrates. Stereoselective aza-Prins cyclizations of cyclobutene amine derivatives give fused aza-heterocyclic scaffolds. Computational studies provide insight into the observed stereocontrol. The modular approach is flexible enabling the introduction of a variety of functionality (including amides, nitriles, alkynes and arenes) to the sp^3-rich heterocyclic scaffolds with scope.

There is debate within medicinal chemistry that sp^3-rich structures are under-represented in drug discovery and new methods for the synthesis of easily diversifiable, sp^3-rich scaffolds are desirable.[1–3] Multi-component reactions offer an elegant solution where simple starting materials can be used to quickly generate molecular complexity. Synthesis of novel fused cyclobutane ring systems in this way would access new areas of chemical space, whilst retaining some of the conformational restriction often associated with successful drug molecules. Similar cyclobutane fused ring systems have previously been shown to have potential as bioisosteres for common building blocks in drug discovery.[4]

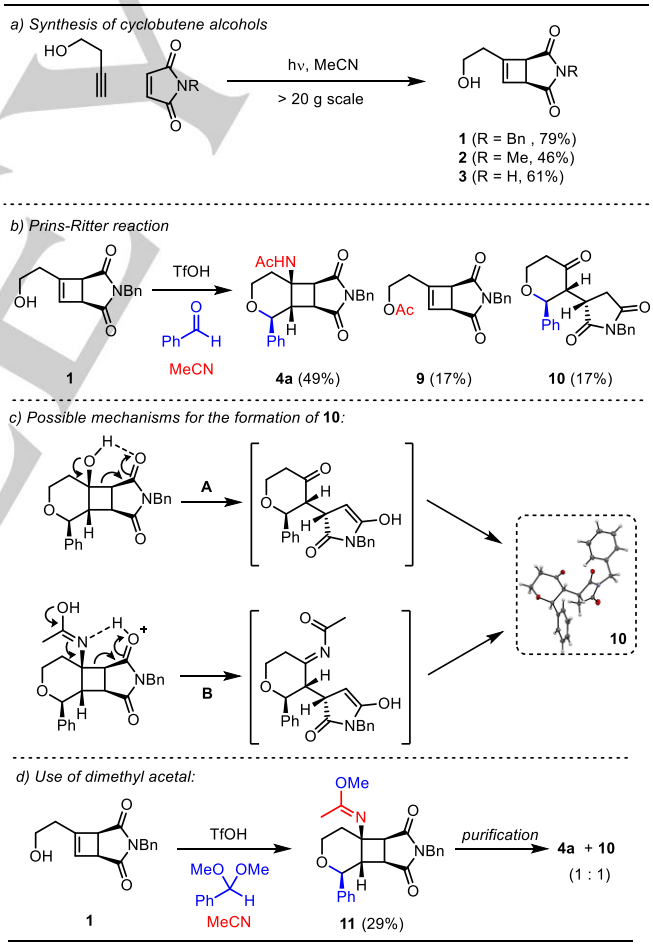
The Prins cyclization of an oxocarbenium ion generated *in situ*, for example from the acid-mediated reaction of a homoallylic alcohol and aldehyde, is a powerful method for the synthesis of functionalized tetrahydropyrans.[5,6] It has been used to good effect in natural product syntheses such as bryostatin[7], (+)-dactylolide[8] and (−)-blepharocalyxin D[9], however to the best of our knowledge, cyclobutene alcohols have not been reported as substrates in Prins cyclizations. This may reflect, in part, limited approaches for the synthesis of 2-cyclobutenylethanol and its derivatives compared to other substituted cyclobutenes.[10]



Scheme 1. Proposed synthesis of tricyclic heterocycles

Recently Booker−Milburn *et al.* have developed an efficient photochemical synthesis of bicyclic cyclobutene alcohols **I** on multigram scales.[11–13] We envisaged that such compounds would undergo Prins cyclization *via* intermediates **II** and **III** to generate sp^3-rich polyheterocycles **IV** possessing several sites available for further library diversification (Scheme 1). Herein we report the results of studies leading to the selective synthesis of 6,4,5-tricyclic scaffolds with five contiguous stereocenters, decorated with a range of useful further functionality.

Succinimide **1** was synthesized *via* the [2+2]-cycloaddition of maleimide with homopropargyl alcohol in acetonitrile (MeCN). The imide can be subsequently *N*-benzyl- or methylated, or alternatively the photochemical reaction can be performed directly with *N*-methyl- or *N*-benzyl maleimide. These can all be performed on larger scale using flow photochemistry (Scheme 2a).



Scheme 2. Application of the Prins cyclization to cyclobutene alcohols and investigations into side product formation.

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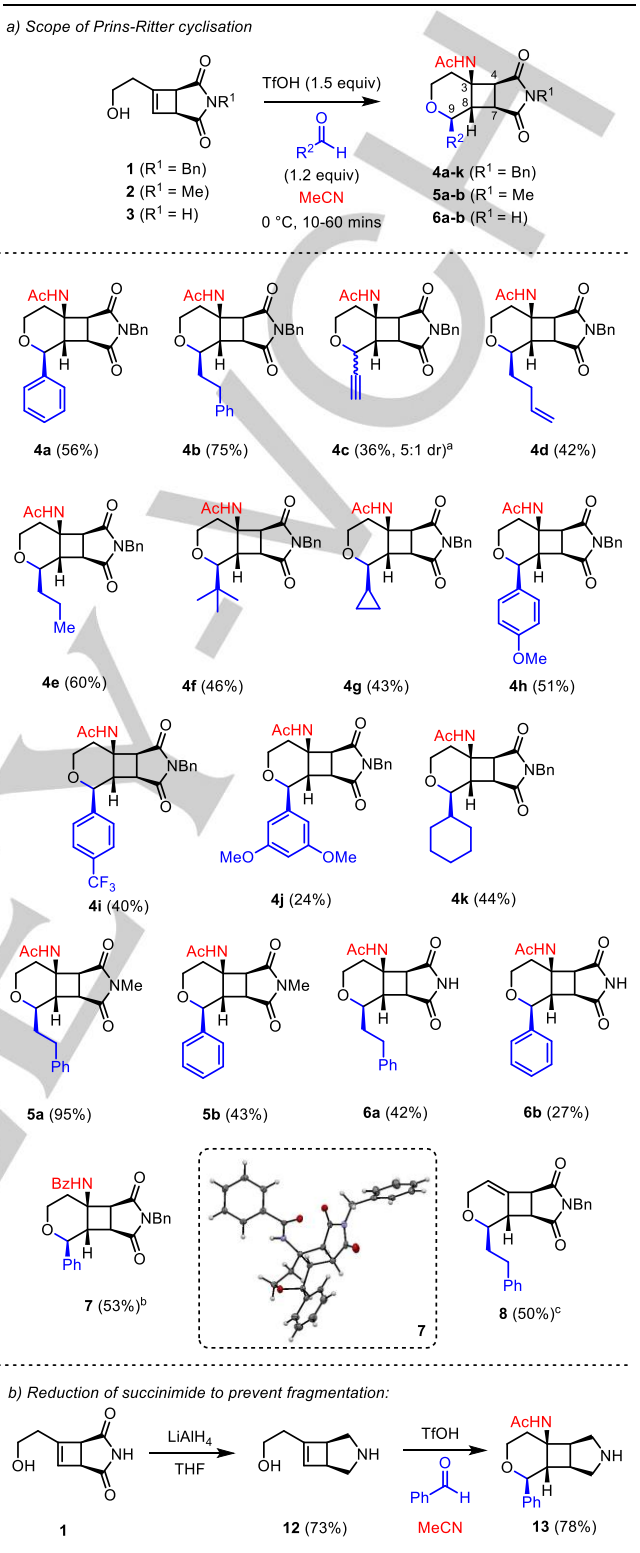
Initial investigations were based on tandem Prins−Ritter reaction conditions first reported by Willis *et al.* for the synthesis of 4-amidotetrahydropyrans.[14] Yadav *et al*. have used similar conditions for the formation of 4-amidopiperidine derivatives[15] and a Sakurai−Prins−Ritter reaction to prepare 2,6-disubstituted tetrahydropyrans has also been developed.[16–18] Thus, **1** was treated with benzaldehyde and triflic acid (TfOH) in acetonitrile at room temperature. After 30 minutes, the starting material had been completely consumed. Amide **4a** was isolated as a single diastereomer with creation of three new stereocenters (Scheme 2b). Substituting TfOH for other protic acids (HCl, H_2SO_4, AcOH) or Lewis acids (BF_3, $InCl_3$) returned only starting material in all cases. The reaction conditions employing TfOH were optimized for temperature (0 °C), concentration (0.2 M) and equivalents of aldehyde (1.2 eq.) and acid (1.5 eq.) with unusually short reaction (10-60 minutes).

Further studies revealed acetate **9** and ketone **10** (Scheme 2b) as by-products of the reaction. Formation of **9** could be accounted for by reaction of the alcohol **1** with protonated acetonitrile, followed by hydrolysis on workup. The structure of **10** was confirmed by X-ray crystallography (Scheme 2c).[22] **4a** was re-subjected to the reaction conditions and found to be stable, confirming that **10** is formed during the reaction. The mechanism likely involves a Grob-like fragmentation of the central cyclobutane ring (Scheme 2c) by two possible mechanisms. Carbocation III (Scheme 1) is trapped by water, followed by retro-aldol (pathway A, Scheme 2c). Alternatively, fragmentation of the Ritter intermediate (pathway B, Scheme 2c) leads to **10**. The reaction was repeated with benzaldehyde dimethyl acetal in order to prevent formation of water on condensation with the alcohol **1**. In this case the acetimidate **11** was isolated through trituration of the crude reaction mixture, which during purification by column chromatography hydrolyzed to a 1:1 mixture of the desired product **4a** and the fragmented ketone **10** (Scheme 2d). Isolation of the acetimidate **11** is in accord with pathway B of the proposed mechanism.

The scope of the reaction of **1** with a series of aldehydes was explored (Scheme 3a). Substituted benzaldehydes, cyclic and straight chain aliphatics with a range of steric bulk, and unsaturated aldehydes gave the product as a single diastereomer in almost all cases. Aldehydes with longer aliphatic chains tended to give the highest yield; electron donating/withdrawing arenes did not show a clear trend.

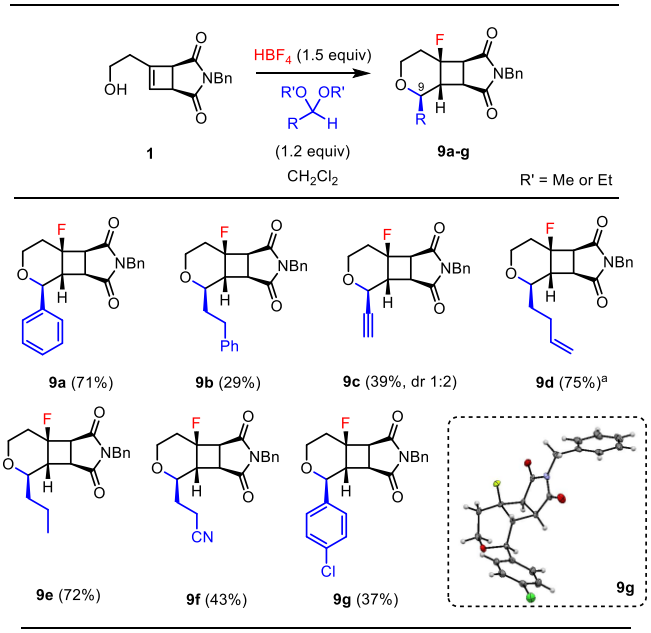
Prins cyclizations of the maleimides **2** and **3** were also investigated under the optimized reaction conditions. Although a 95% yield was achieved for the reaction of **2** with dihydrocinnammaldehyde to give **5a**, analogous reaction with benzaldehyde gave **5b** in only 43% yield. Reactions with **3** to give **6a** and **6b** gave significantly lower yields (42% and 27% respectively). Use of ketone electrophiles (acetone and cyclohexanone) gave no reaction.

Other nitrile-based solvents could also be incorporated *e.g.* **1** was reacted with benzaldehyde in benzonitrile giving tricyclic amide **7** as a single diastereomer (by NMR). The structure was confirmed by X-ray crystallography[22] (Scheme 3a). Use of five equivalents of acetonitrile in dichloromethane gave the eliminated product **8**. Alkene **8** can also be formed by conducting the reaction in dichloromethane.



Scheme 3. Scope of the Prins-Ritter reaction. [a] Reaction carried out with 3,3-diethoxy-1-propyne. [b] Reaction carried out with benzonitrile solvent. [c] Reaction carried out in dichloromethane solvent.

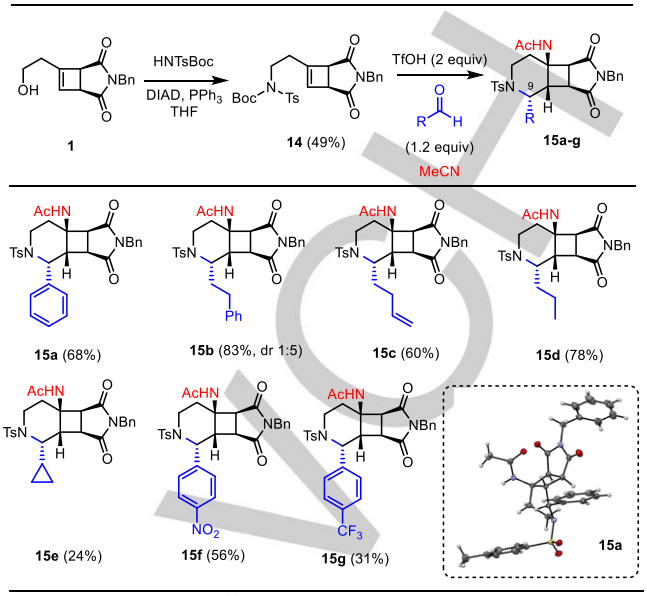
As imide functionality is implicated in formation of **10**, **1** was reduced with $LiAlH_4$ to amine **12** (Scheme 3b). Prins cyclization of cyclobutene alcohol **12** with benzaldehyde gave the anticipated tricyclic product **13** in 78% yield, with no ketonic by-product detected, also demonstrating the tolerance of the reaction to free amines.



Scheme 4. Scope of the Prins reaction for the synthesis of tertiary fluorides **9a-g**. [a] Reaction carried out with 4-pentenal.

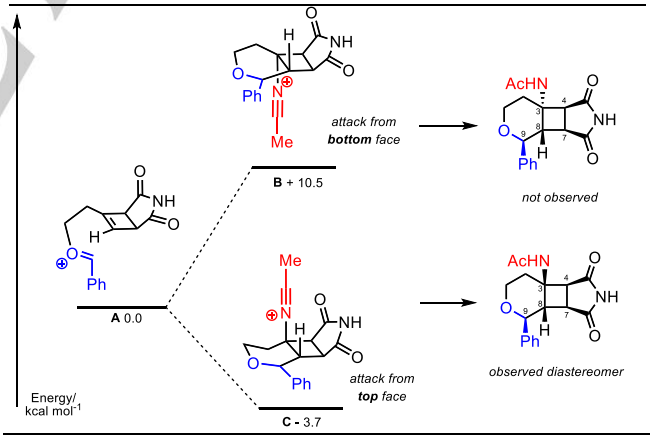
As well as the Prins−Ritter reaction, it was found that **1** reacts with a series of acetals catalysed by HBF_4 in dichloromethane to yield products with a tertiary fluoride moiety (Scheme 4). The analogous reaction with aldehydes leads to the predominant formation of ketone **10**, likely due to liberation of water. Various substituted acetals were all converted to the desired tricyclic products **9a-9g**. As with the Prins−Ritter reaction, the stereocontrol was found to be excellent in all cases (X-ray crystallography of **9g**).[22]

As well as tricyclic tetrahydropyranyl fused rings, the corresponding piperidines were prepared *via* aza-Prins cyclization (Scheme 5). Protected homoallylic amine **14** was prepared from **1** under Mitsunobu conditions. Addition of triflic acid to **14** promotes *in situ* deprotection of the carbamate protecting group, subsequent addition of aldehyde yielding tricyclic products **15a-g**. X-ray crystallography confirmed[22] the major diastereomer **15a** as having opposite stereochemistry at C-9 to the oxo-Prins reaction, likely due to steric interaction caused by the nitrogen protecting group in the iminium transition state.[19] This aza-Prins sequence is notable for the stereoselective and rapid generation of tricyclic systems containing three orthogonally protected nitrogen atoms.



Scheme 5. Synthesis of the homoallylic amine **14** and scope of the aza-Prins-Ritter reaction to give amides **15a-g**. DIAD = diisopropyl azadicarboxylate; THF = tetrahydrofuran

Density functional theory (DFT) calculations (B3LYP/6-31+G(d), see SI for details) were undertaken to explain C-3 and C-8 stereochemistry (Scheme 6). The difference in stereochemistry at C-9 between oxo- and aza-Prins cyclizations has been previously rationalized.[19,20,21] By considering the optimized geometries for the intermediates **A**, **B** and **C,** conformational searches and energy minimization showed that the lowest energy conformation of **A** required the oxocarbenium ion to be positioned on the opposite face to the maleimide, thus avoiding steric clash (Scheme 6).



Scheme 6. Calculated ground state energies of intermediates **A**, **B** and **C** (B3LYP/6-31+G(d), gas phase potential energies relative to **A**, see SI for details).

Facially selective cyclization accounts for the observed stereochemistry at C-8. By modelling the intermediates for nucleophilic attack from both the top (**B**) and bottom (**C**) face, the stereochemistry at C-3 can also be explained. Approach of the nucleophile from the bottom face (intermediate **B**) was found to be 14.2 kcal mol^{-1} higher in energy relative to the alternative mode

of attack (**C**). This is strongly supportive of the *cis*-relationship of C-3 and C-8 as observed experimentally (Scheme 6).

A novel application of the Prins reaction has allowed a facile synthesis of complex tricyclic sp^3 rich scaffolds in 2-steps. To the best of our knowledge this is the first reported study of cyclobutenes in Prins cyclisations. Reaction times are significantly shorter (~15 mins) compared to traditional alkene substrates. The reaction is diastereoselective, giving products with up to five contiguous stereocenters. The modular nature of this reaction allows for the incorporation of groups for further derivatization through use of different aldehydes. Use of reaction conditions, which alter the nucleophile incorporated, leads to the installation of both amide and fluoride quaternary centres. Finally, an aza-Prins cyclization gives tricyclic heterocyclic scaffolds containing three orthogonally protected nitrogens.

Acknowledgements

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Keywords: Prins cyclization • Ritter reaction • photochemistry • cyclobutene • fluorination • cyclization

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[22] Ellipsoids set at 50% probability for the molecular structures of **7**, **9g**, **10** and **15a.** CCDC 1897232 (**7**), CCDC 1897233 (**9g**), CCDC 1897234 (**10**) and CCDC 1897232 (**15a**) contain supplementary crystallographic data, which can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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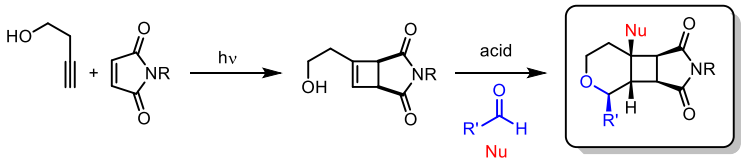
COMMUNICATION



2 steps • single diastereomer • 5 contiguous stereocentres • >30 examples

Strained cyclobutenes have proved to be highly reactive partners in multi-component Prins cyclizations, delivering highly functionalised polycyclic structures with a high degree of stereocontrol. Reaction times were considerably shorter compared to traditional Prins alkene substrates.

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