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


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 sp3-rich heterocyclic scaffolds with scope.

There is debate within medicinal chemistry that sp3-rich structures are under-represented in drug discovery and new methods for the synthesis of easily diversifiable sp3-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 cyclobutene 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]

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 sp3-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 1. Proposed synthesis of tricyclic heterocycles](image)

![Scheme 2. Application of the Prins cyclization to cyclobutene alcohols and investigations into side product formation.](image)
Initial investigations were based on tandem Prins–Ritter reaction conditions first reported by Willis et al. for the synthesis of 4-aminotetraydropryans.[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 tetraydropryans 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, H₂SO₄, AcOH) or Lewis acids (BF₃ or InCl₃) 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 equivalents of ketone (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. Carboclication III (Scheme 1) is trapped by water, followed by retroaldol (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 acetamide 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 acetamide 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 dihydrocinnamaldehyde 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[25] (Scheme 3a). Use of five equivalents of acetobenzone 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 LiAlH₄ 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.

As well as the Prins–Ritter reaction, it was found that 1 reacts with a series of acetals catalysed by HBF₄ 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-g. As with the Prins–Ritter reaction, the stereocontrol was found to be excellent in all cases (X-ray crystallography of 9g).

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-3 and C-8. By modelling the intermediates for nucleophilic attack from both the top (B) and bottom (C) face, the stereoselective face of the nucleophile was found to be 14.2 kcal mol⁻¹ higher in energy relative to the alternative mode.

Facially selective cyclization accounts for the observed stereoselectivity at C-8. By modelling the intermediates for nucleophilic attack from both the top (B) and bottom (C) face, the stereoselectivity 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.

Density functional theory (DFT) calculations (B3LYP/6-31+G(d), see SI for details) were undertaken to explain C-3 and C-8 stereoselectivity (Scheme 5). The difference in stereoselectivity 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 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).
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.

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


[22] Ellipsoid 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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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.