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# Highly diastereoselective Prins-type cyclisation of cyclopropylvinylic aldehydes mediated by $TiCl_4$†

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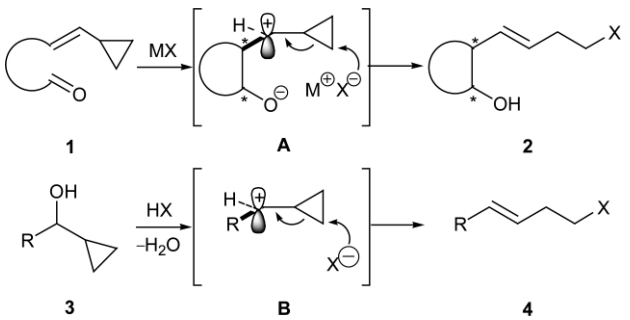
***Received (in Cambridge, UK) 29th April 2004, Accepted 23rd June 2004***
***First published as an Advance Article on the web 23rd July 2004***

**A novel intramolecular Prins type cyclisation of cyclopropylvinylic aldehydes 1 promoted by $TiCl_4$ under mild reaction conditions to form *cis*-cyclic products 2 in high yields has been accomplished.**

The development of efficient synthetic methods for achieving stereocontrol in the construction of cyclic systems is of considerable current interest in synthetic chemistry.[1] During the past decades, substantial progress has been made, and as a result, many stereoselective synthetic routes have been extensively explored.[2] In this regard, the intramolecular Prins cyclisation has proved to be a useful transformation in the construction of five, six, and even larger membered rings for the synthesis of carbocyclic and heterocyclic biofunctional molecules.[3] Notable methods have been developed in recent years for accessing stereocontrol through the Prins type reaction, the vast majority of which involve construction of the oxacyclic ring by carbon–carbon bond formation from an oxocarbonium intermediate *via* electrophilic cyclisation.[4] In the course of our research program aimed at finding new synthetic methods for the stereoselective construction of pyran units,[5] we became quite interested in the reaction of cyclopropylvinylic aldehyde **1** in the presence of promoter MX to form cyclic compound **2** through the Lewis acid catalyzed Prins procedure as depicted in Scheme 1.

It was envisaged that the cyclisation of **1** with proper promoter MX for the diastereoselective synthesis of **2** through a carbocationic intermediate **A** could be realized in a predictable fashion. The background to this prediction was the known reaction pathway for the formation of homoallylic halide **4** from cyclopropyl alcohol **3** in acidic media through intermediate **B**.[6] To the best of our knowledge, the use of the cyclopropylvinyl moiety as an electrophile for capturing an incoming nucleophile has not been reported, even though this functionality has been often employed as a substrate for transition metal catalysed cycloadditions.[7,8] The realization of an efficient method in this reaction should also be valuable because synthetic applications can be foreseen for homoallylic chloride.[9] This research led to the discovery of a new type of Prins cyclisation of **1** under mild reaction conditions with remarkably high diastereoselectivity. The starting point of this investigation was the availability of cyclopropylvinylic aldehydes **1**: these compounds were readily prepared by the modification of known procedures as described in the literature.[10,11] The stage was thus set for the Prins cyclisation of cyclopropylvinylic aldehydes **1** mediated by a Lewis acid.



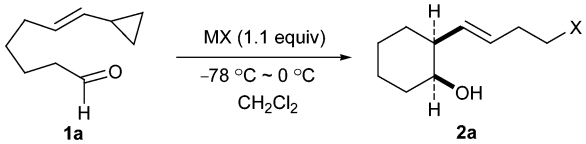

**Scheme 1** Proposed reaction pathway.

To find optimum conditions a series of experiments was performed with cyclopropylvinylic aldehyde **1a** as a model substrate. Preliminary investigations on the transformation of **1a** indicated that the conversion to the corresponding **2a** could not be achieved satisfactorily with $SnCl_4$ and $InCl_3$ under various conditions mainly due to decomposition of substrate as shown in Table 1.

Fortunately, we found that $TiCl_4$ was able to promote the reaction process; $TiCl_4$ was generally superior and was chosen for systematic studies. After surveying numerous conditions for orienting experiments, several key findings emerged: i) 1.1 equivalents of $TiCl_4$ were required for optimal conditions in terms of chemical yields and reaction rates; ii) reaction performed at −78 °C to 0 °C in $CH_2Cl_2$ resulted in the best chemical yields in comparison with other solvents such as toluene, $CH_3CH_2CN$, and THF; iii) reaction produced the (*E*)-vinylic product as a sole isomer according to the analysis of 500 MHz $^1$H NMR spectra; iv) only *cis*-isomer **2a** was formed as determined by the analysis of 500 MHz $^1$H NMR spectra of crude products. Under optimal conditions, the reaction was performed by addition of $TiCl_4$ (1.1 equiv.) to a solution of **1a** (1 equiv.) in $CH_2Cl_2$ at −78 °C. After 2 h at −78 °C, the reaction mixture was allowed to warm to 0 °C and then the reaction was quenched by addition of aqueous $NaHCO_3$. The crude product was purified by $SiO_2$ column chromatography to give **2a** in 74% yield as a colorless oil. With the notion that this approach might lead to a general and efficient method for the new type of Prins cyclisation, we set out to determine the scope of reaction with several cyclopropylvinylic aldehydes **1** as listed in Table 2. Indeed, the method is successful with a variety of cyclopropylvinylic aldehydes **1** and affords products of high diastereomeric purity as can be seen in Table 2. It is worthy of note that the reaction produced no or only trace amounts of minor products according to the analysis of 500 MHz $^1$H NMR spectra of the crude products.

The stereochemical assignments were based on the magnitudes of the vicinal coupling constants of six-membered ring protons for compounds **2a**, **2d**, and **2e**. Small coupling constants for C*H*OH for all cases clearly indicated that the hydroxy group is located at the axial position. The *cis*-stereochemical relationship for **2a** and **2b**

**Table 1** Preliminary investigations[a]




| Entry | MX | *t*/h | Result[b] |
|---|---|---|---|
| 1 | $SnCl_4$ | 12 | 12% yield with decomposition |
| 2 | $InCl_3$ | 12 | Trace (decomposition) |
| 3 | TMSCl/LiBr | 12 | No reaction occurred |
| 4 | $TiCl_4$ | 2 | 74% yield |
| 5 | $TiBr_4$ | 4 | 37% yield with decomposition |

[a] Reactions were carried out with MX (1.1 equiv.) in $CH_2Cl_2$ at −78 °C and then warming to 0 °C. [b] Yields refer to isolated and purified products.

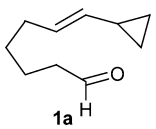
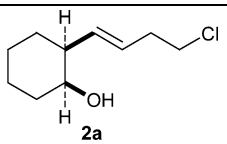
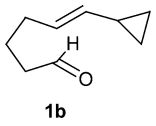
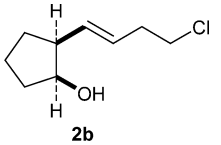
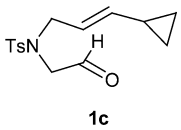
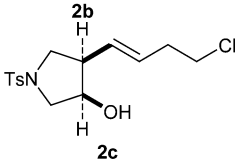
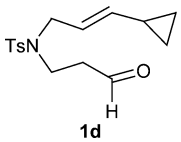
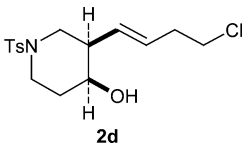
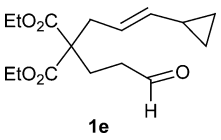
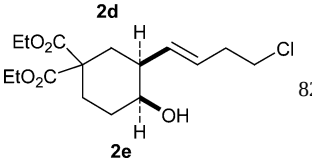
† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b406362g/

DOI: 10.1039/b406362g

was also confirmed by NOE experiments: we observed NOE enhancements between stereogenic vicinal protons.

Although the exact mechanistic aspects of this transformation have not been rigorously elucidated, the following pathway could be a probable chemical route on the basis of experimental results. Obtaining the *cis*-products from **1** under $TiCl_4$ promotion can be accounted for by the intervention of the pseudopericyclic stereochemical models **C** and **D** with minimum steric interactions and optimal orbital interactions, which lead to the major reaction pathway as illustrated in Fig. 1. Thus, we believe that the orientation between olefinic and carbonyl moieties offered by $TiCl_4$ could be more crucial for stereoselectivity.

**Table 2** Prins cyclization of **1** promoted by $TiCl_4$.[a]

| Entry | Substrate | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 74 |
| 2 |  **1b** |  **2b** | 79 |
| 3 |  **1c** |  **2c** | 82 |
| 4 |  **1d** |  **2d** | 76 |
| 5 |  **1e** |  **2e** | 82 |

[a] Reactions were carried out with $TiCl_4$ (1.1 equiv.) in $CH_2Cl_2$ at −78 °C for 2 h and then warming to 0 °C. [b] Yields refer to isolated and purified products.

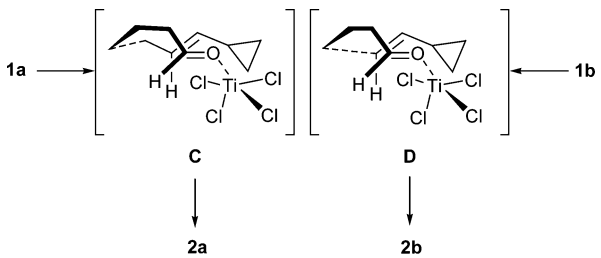



**Fig. 1** Proposed reaction pathway.

In summary, a new intramolecular Prins type cyclisation of cyclopropylvinylic aldehydes **1** promoted by $TiCl_4$ under mild reaction conditions to form *cis*-products **2** has been accomplished in a general and efficient way, which promises to be useful. Further studies including synthetic applications and extension of this method into enantiomeric pathways are in progress.

Generous financial support from grants from the Korea Ministry of Science and Technology through the National Research Laboratory program (NRL) and the Center for Molecular Design and Synthesis (CMDS: KOSEF SRC) at KAIST is gratefully acknowledged.

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