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The silyl–Prins reaction: a novel method for the synthesis of dihydropyrans

Adrian P. Dobbs* and Saša Martinović

School of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK

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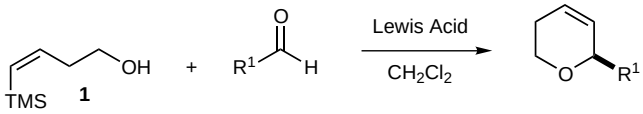
Abstract—Reaction of 4-trimethylsilyl-3-buten-1-ols with aldehydes under mild Lewis acid conditions gives substituted dihydropyrans in excellent yields and with good stereocontrol. © 2002 Published by Elsevier Science Ltd.

Substituted pyrans are a common structural motif of many natural products. The dihydropyran skeleton is a particularly attractive target since it both occurs in many natural products and furthermore the olefin function is a synthetically useful handle for further functionalisation, making it a key intermediate to many polysubstituted tetrahydropyrans. The literature now contains many versatile methods for the synthesis of dihydropyrans,[1] such as the hetero-Diels–Alder reaction, the intramolecular Sakurai reaction and ring-closing olefin metathesis. Unfortunately, the Sakurai reaction approach involves a lengthy synthesis of a bis-silylated homoallylic alcohol precursor, while the metathesis approach often requires the synthesis of complex precursors. Speckamp[1b] has also utilised vinylsilane chemistry in an approach to this structural motif, but this method requires extra steps in the formation of a hemiacetal intermediate and always gives an ester as one of two substituents in the products. By contrast, the Prins cyclisation, which involves treatment of a homoallylic alcohol with a carbonyl compound and usually a Brønsted acid, is a powerful methodology for the synthesis of tetrahydropyrans, although it often leads to complex mixtures of products.[2] Li has recently reported a Lewis acid mediated synthesis of dihydropyrans using a novel carbonyl allylation–Prins cyclisation method, using 3-trimethylsilylallyltributylstannane as the cyclisation precursor.[3] However, there are two drawbacks associated with this process: the use of tin, which is undesirable due to the associated separation and toxicity problems and the use of two equivalents of an aldehyde means that only identical substituents may be introduced in the product. Finally, Brimble has reported the synthesis of aryldihydropyrans using a Sonogashira-selenoetherification strategy.[4] However, a simple and general route to dihydropyrans, permitting the incorporation of varying substituents, is still a synthetic need. Herein we describe a novel method for the synthesis of dihydropyrans, using mild Lewis acids, which overcomes many of the drawbacks of the alternative methods.

The desired substrate for our initial studies was *Z*-4-trimethylsilyl-3-buten-1-ol **1**. This was easily prepared in two steps using literature methods[1c] (silylation using

Table 1. The synthesis of simple dihydropyrans[6]



Entry	R^1	Lewis acid	Conditions	% Yield[a]
1	$PhCH_2$	$InCl_3$	Rt	88
2	$PhCH_2$	TMSOTf	−78°C	86
3	$PhCH_2$	$BF_3{\cdot}OEt_2$	−78°C	90
4	n-C_5H_{11}	$InCl_3$	Rt	65
5	Cyclohexyl	$InCl_3$	Rt	72
6	Ph_2CH	$InCl_3$	Rt	85
7	Ph	$InCl_3$	Rt	39
8	4-NO_2-Ph	$InCl_3$	Rt	86
9	4-CF_3-Ph	$InCl_3$	Rt	54
10	$PhCH_2$	$InCl_3$	0.5 equiv. $InCl_3$; rt	80
11	$PhCH_2$	$InCl_3$	0.1 equiv. $InCl_3$; rt	63

[a] All reactions were performed with alcohol:aldehyde:Lewis acid in a 1:1:1 ratio in dichloromethane unless otherwise stated.

* Corresponding author. Tel.: +44 1392 263410; fax: +44 1392 263434; e-mail: a.dobbs@exeter.ac.uk

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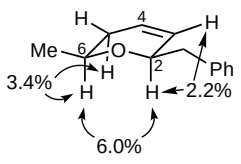
n-butyllithium/trimethylsilyl chloride followed by D*i*BAL reduction) from 3-butyn-1-ol in 74% overall yield.

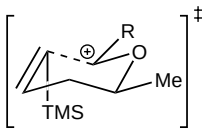
In order to test the feasibility of **1** as a precursor for a silyl-Prins type reaction, initial cyclisation studies were performed using **1** with phenylacetaldehyde with a range of Lewis acids (Table 1). Of the Lewis acids screened, indium trichloride (Table 1 entry 1), trimethylsilyltriflate (entry 2) and boron trifluoride etherate (entry 3) were the most successful. Pleasingly, all three gave a single dihydropyran product and in comparable yields. Therefore, indium trichloride was the Lewis acid of choice for further studies, since it is both a mild, crystalline Lewis acid (that does not require rigorously anhydrous reaction conditions) and the reaction could be performed at room temperature, compared to the low temperature (−78°C) required for the two alternative Lewis acids. Excellent yields were obtained for the indium trichloride mediated reaction using a range of different aldehydes (Table 1, entries 4–9). The use of various benzaldehydes in this reaction is particularly interesting (Table 1, entries 7–9). Benzaldehyde is surprisingly low yielding, but this is in keeping with related methods that have also reported lower[1c] or no[3] products with aromatic aldehydes. Both *p*-NO_2 and *p*-CF_3 substituted benzaldehydes gave significantly enhanced yields of dihydropyran product, compared to benzaldehyde, with the *p*-NO_2 benzaldehyde proving particularly reactive in this method. This presumably results from an electronic effect from the nitro group.

When using catalytic amounts of indium trichloride, the desired dihydropyran was still obtained in good yields, although slightly lower than observed in the stoichiometric reaction (Table 1, entries 10 and 11). Nevertheless, the yields obtained suggest that the reaction is truly catalytic, albeit with low catalyst turnovers. This aspect of the chemistry is part of an ongoing study.

The methyl substituted version of **1** was prepared using an analogous route to that employed for **1** (71% overall yield from commercially available 2-methylpent-4-yn-1-ol) in order to investigate the synthesis of disubstituted dihydropyrans. Pleasingly, reaction of *Z*-5-trimethylsilylpent-4-en-2-ol **2** with a range of aldehydes gave dihydropyrans in good yields and with excellent stereoselectivity for the 2,6-*cis* derivatives, as determined by NOE studies.

A 6.0% NOE was observed between the two hydrogen atoms at C(2) and C(6)[7]. No evidence for the 2,6-*trans* product could be detected, even in the crude reaction mixtures.





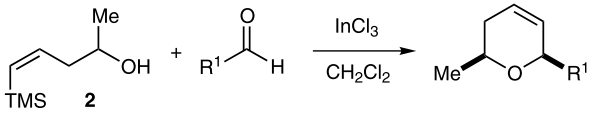
3

After Lewis acid activation of the aldehyde, the reaction is believed to proceed via nucleophilic attack from the alcohol, followed by cationic cyclisation to give a carbocation stabilised by the β-effect from silicon. Subsequent collapse and elimination of the silicon moiety gives the observed dihydropyran product. A chair-like transition state **3** with equatorial substituents in the developing six-membered ring could account for the stereoselective production of *cis*-2,6-disubstituted dihydropyrans.

It is not only simple substituted dihydropyrans that are of interest and a method towards trisubstituted and fused ring systems would also be of synthetic value. The combination of diethylaluminium chloride/lithium trimethylsilylacetylide is a powerful method for the opening of epoxides.[1c] This approach was utilised with cyclohexene and cyclopentene oxides to yield the corresponding silylhomopropargylic alcohols. Subsequent D*i*BAL reduction gave the silylhomoallylic alcohols **4** and **5** that were subjected to our standard cyclisation conditions (Scheme 1). Both 5,6- and 6,6-ring-fused dihydropyrans were obtained in good yields and excellent selectivity for the conformations shown. The stereochemistry observed is in accord with *anti*-opening of the epoxide precursor and *cis* selectivity in the dihydropyran ring closure. Relative stereochemistry was again established with the aid of NOE experiments.

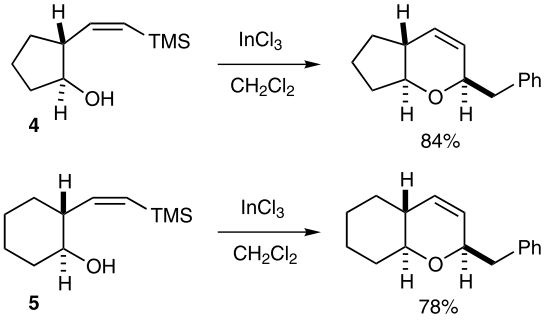
Finally, Li has reported that epoxides may also act as suitable precursors for the synthesis of aryl-substituted tetrahydropyrans, in a related Lewis acid mediated reaction.[5] Therefore we have initiated a programme of

Table 2. Synthesis of disubstituted dihydropyrans[6,7]

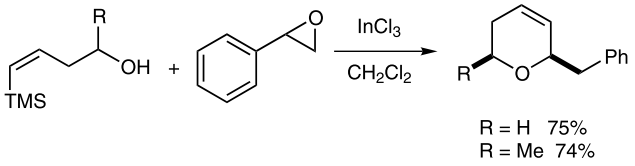


Entry	R^1	% Yield[a]
1	$PhCH_2$	50
2	*n*-C_5H_{11}	65
3	Cyclohexyl	69
4	Ph_2CH	78
5	4-NO_2-Ph	60

[a] All reactions were performed with alcohol:aldehyde:Lewis acid in a 1:1:1 ratio in dichloromethane unless otherwise stated.



Scheme 1. Synthesis of fused dihydropyrans.



Scheme 2. Synthesis of dihydropyrans from epoxide precursors.

study to investigate the use of epoxides in the synthesis of dihydropyrans. Treatment of styrene oxide with indium trichloride and either **1** or **2** generated the corresponding dihydropyran, in yields comparable to that obtained from phenylacetaldehyde and with similar levels of stereoselectivity (Scheme 2).

In conclusion, we have demonstrated a rapid and high yielding stereospecific synthesis of dihydropyrans from aldehydes and silylated homoallylic alcohols using mild Lewis acid reagents. It is also a useful route to trisubstituted dihydropyrans. Furthermore, epoxides may be employed as the reaction partners in place of aldehydes. The latter two areas form part of an ongoing programme of research and these results will be reported in due course. As such, this method represents a shorter and easier method than currently exists in the literature and has the added flexibility of permitting the incorporation of many differing substituents.

Acknowledgements

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6. Typical experimental procedure for indium trichloride mediated reaction: the aldehyde (3 mmol) and alcohol (3 mmol) were dissolved in dry dichloromethane (25 ml) under an inert argon atmosphere at room temperature and indium trichloride (3 mmol) added in one portion. The reaction was stirred at room temperature for between 5 and 12 h. Water (50 ml) was added to the reaction mixture and the organic phase was separated. This was subsequently washed with water and brine, dried ($MgSO_4$) and concentrated to an oil that was purified by flash chromatography (typically hexane:ethyl acetate, 4:1) to give the desired product. All compounds were in good agreement with previously reported data or gave satisfactory analytical data.
7. Representative data, including NOE, for *syn*-2-(2-phenylmethyl)-6-methyloxacyclohex-3-ene (Table 2, entry 1): δ_H (400 MHz, $CDCl_3$) 7.24–7.33 (5H, m, **Ar**), 5.80 (1H, m, C(4)**H**), 5.63 (1H, m, C(3)**H**), 4.36 (1H, m, C(2)**H**; 5.95% NOE enhancement on irradiation of C(6)H), 3.72 (1H, m, C(6)**H**; 6.02% NOE enhancement on irradiation of C(2)H), 3.03 (1H, dd, $J=13.8$ and 6.3, one of benzylic C$\mathbf{H_2}$), 2.70 (1H, dd, $J=13.8$ and 6.3, one of benzylic C$\mathbf{H_2}$), 1.98 (2H, m, C(5)$\mathbf{H_2}$), 1.26 (3H, d, $J=7.7$, C$\mathbf{H_3}$); δ_C (100 MHz; $CDCl_3$) 138.3 (*ipso*-**C**), 129.7 (Ar), 129.0 (**C**(3)H), 128.4 (Ar), 126.2 (Ar), 124.9 (**C**(4)H), 75.8 (**C**(2)H), 70.1 (**C**(6)H), 42.1 (benzylic **C**H_2), 32.9 (**C**(5)H_2), 21.7 (Me).