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Rapid access to CF_3-containing heterocycles

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Abstract

The silyl-Prins and aza-silyl-Prins reactions have been employed for the preparation of 6-CF_3-substituted dihydropyrans and 6-CF_3-substituted tetrahydropyridines. The product heterocycles have been further elaborated to a number of products, including CF_3-substituted pipecolates and hydroxylated pyrans and piperidines.

Keywords: Silyl-Prins reaction; Aza-silyl-Prins reaction; 6-CF_3-substituted dihydropyrans; 6-CF_3-substituted tetrahydropyridines; Pipecolic acid derivatives

The pyran and piperidine skeletons are found widely both in natural products and pharmaceutically active compounds and may impart a wide range of biological activities. It has been well documented that the incorporation of fluorine into these heterocycles may modify greatly the biological activity of the compound; the most common replacements being fluorine for hydrogen or a hydroxyl group and a trifluoromethyl moiety in place of a methyl group.[1,2] As such, methods for the selective incorporation of fluorine and trifluoromethyl[3] moieties into organic molecules are still highly sort after. It has recently been reported that the synthesis and the preparation of trifluoromethyl-substituted aromatic and non-aromatic heterocycles is still of great synthetic and medicinal interest.[4] However, another such area, which has only been subject to limited exploration, is the selective preparation of 6-trifluoromethyl (6-CF_3) pyrans[5] and piperidines,[6–10] with existing methods for their preparation generally being limited to iminium ion cyclisations,[6] via chiral lactam intermediates[10] and ring-closing olefin metathesis reactions.[7,9] As a part of our ongoing interest in incorporating fluorine into heterocycles,[11] we herein report a rapid route for the preparation of CF_3-substituted oxygen- and nitrogen-containing heterocycles using the recently developed silyl-Prins[12,13] and aza-silyl-Prins reactions.[13–15]

We have recently reported the silyl-Prins[12,13] and aza-silyl-Prins[13,14] reactions as novel and powerful methods for the rapid preparation of dihydropyrans **2** and tetrahydropyridines **4**. These methodologies involve the reaction either of a vinylsilane-containing homoallylic alcohol **1** or amine **3** with an aldehyde, epoxide or acetal in the presence of a Lewis acid to give the corresponding heterocycle. In the dihydropyran series, exclusive 2,6-cis-diastereoselectivity was observed across the heteroatom, whereas this becomes exclusively trans in the nitrogen series.

We imagined that these methods might represent an easy route for the preparation of 6-trifluoromethyl pyrans and piperidines simply by the incorporation of a trifluoromethyl group into the homoallylic alcohol or amine precursors. The desired α-trifluoromethyl homoallylic alcohol **7** was prepared rapidly in two steps starting from commercially available 3,3,3-trifluoropropylene oxide **5**: ring opening with trimethylsilylacetylide/diethylaluminium chloride was followed by DiBAL-H reduction of the acetylene to the *Z*-vinylsilane (50% overall yield over the 2 steps). The

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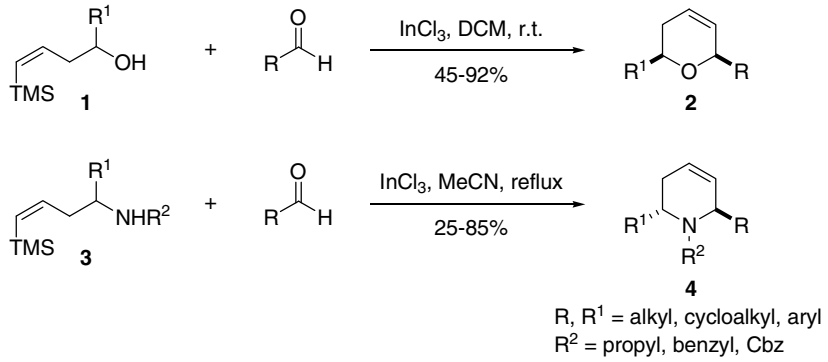


Scheme 1. The silyl-Prins and aza-silyl-Prins reactions.

pre-requisite alcohol **7** was then subjected to standard silyl-Prins reaction conditions of an aldehyde and Lewis acid in dry dichloromethane for 5 h, with indium trichloride being utilised as a continuation of our previous work, where this has been found to be the most efficient Lewis acid for the promotion of these reactions.[13] While reaction of all the aldehydes at room temperature failed to give any of the desired dihydropyran products, simple elevation of the reaction temperature to reflux temperature and providing longer reaction times gave dihydropyran products **8** and/or **9** in moderate yields. The results are presented in Table 1.

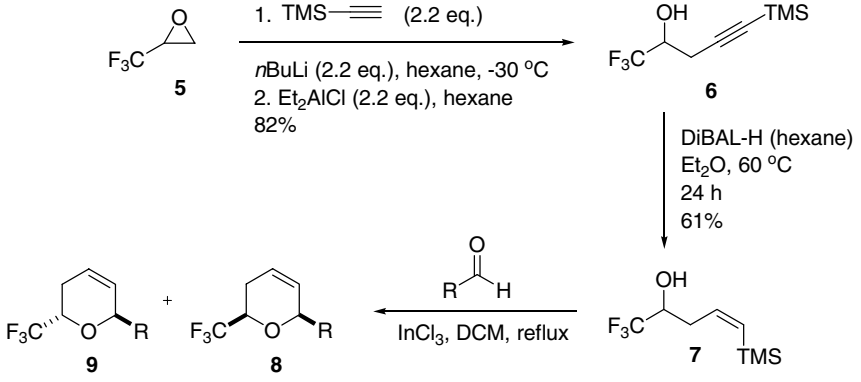
The use of aliphatic aldehydes is clearly the most successful in these reactions (Table 1, entry 2), more so than the use of cycloalkyl aldehydes, which is slightly surprising as these have been equally successful in previous studies. However, in keeping with previous work, both of these gave exclusive cis-selectivity across the oxygen atom.[12] Also in a similar fashion to our previous work, aromatic aldehydes (Table 1 entry 3) were only poorly successful in these reactions, giving an inseparable mixture of cis and trans adducts, which has not been observed before. Chain homologation to phenylacetaldehyde reverted to the usual pattern of improved yield and only the single cis diastereomer. Although this product was pure after chromatography, it was, surprisingly, unstable and decomposed on analysis by GC–MS and also rapidly with time. This instability was thought to contribute towards the lower yield when compared with the previous examples.

Table 1
Silyl-Prins reactions of 6-CF_3-silylated homoallylic alcohols

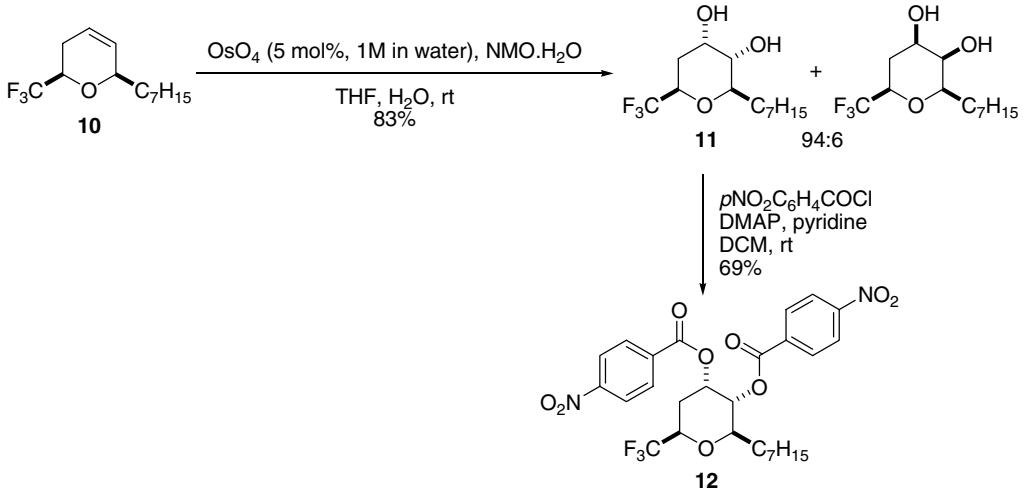
Entry	Aldehyde	Reaction time (h)	% Yield	Cis (**8**):trans (**9**)
1	*c*HexCHO	43	32	100:0
2	$nC_7H_{15}CHO$	66	55	100:0
3	PhCHO	42	25	60:40
4	$PhCH_2CHO$	44	42	100:0
5	(COOEt)CHO	24 (rt)	Traces	—

In all these examples, it is assumed that the strong electron-withdrawing effect of the trifluoromethyl group has a strong bearing on the nucleophilicity of the alcohol moiety in the starting material, thus leading to a reduction in reactivity, rate of reaction and, therefore, product yield.

One advantage of the silyl-Prins and aza-silyl-Prins reactions is the formation of an olefin in the final stage of the reaction via elimination of the silane group. This, of course, is a useful synthetic handle for further reaction. The dihydropyrans produced bear resemblance to C-linked glycosides, which are currently of considerable interest. Thus, we have initiated studies into the dihydroxylation of the 6-CF_3 dihydropyrans. Taking one of the dihydropyrans formed, **10**, reaction with catalytic osmium tetroxide and NMO gave a mixture of diastereomeric diols **11**, with the cis-dihydroxylation occurring primarily from the opposite, less hindered face of the olefin relative to the substituents at C-2 and C-6 (94:6 ratio in favour of this diaste-



Scheme 2. Preparation of 6-CF_3-containing precursors and their subsequent silyl-Prins reaction.

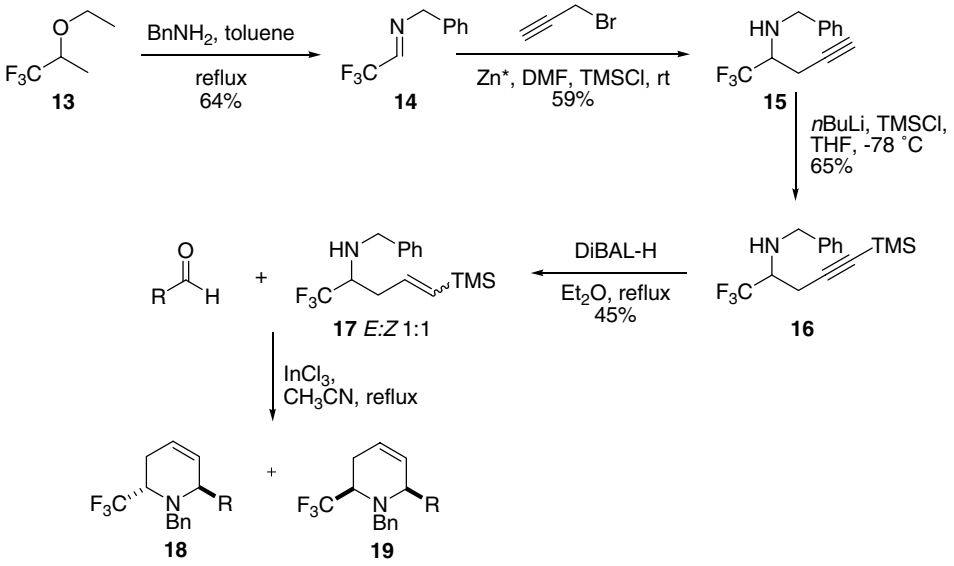


Scheme 3. Further elaboration of 6-CF_3-dihydropyrans.

reomer). These products were more easily purified and stored as the *p*-nitrobenzoate esters **12** (Scheme 3).

Access to the prerequisite secondary amines was slightly more lengthy and problematic, since it was not possible to utilise alcohol **7** and convert it to the amine via tosylation and subsequent amination. Although both tosylation and triflate formation were possible, displacement by an amine never succeeded. Instead, an alternative route was devised using literature precedent starting from 1,1,1-trifluoro-2-ethoxypropane **13**.[7] Imine formation, **14**, and the addition of propargyl bromide under Barbier type conditions gave the α-trifluoromethyl homopropargylic secondary amine **15**, which could be TMS-protected and then reduced using DiBAL-H as in Scheme 2 to give the desired silylhomoallylic amines **17** (Scheme 4; 11% overall yield from 4 steps). Intriguingly, with these homopropargylic secondary amines, DiBAL-H reduction gave a 1:1 mixture of the *E*:*Z* vinylsilanes instead of the exclusive *Z*-selectivity observed previously in our other work[12,13] and also as seen in Scheme 2. Since it proved impossible to separate the two isomers, the 1:1 *E*:*Z* mixture was employed in the aza-silyl-Prins reactions. Recently, we have managed to utilise a hydrotitanation procedure to obtain exclusively the *Z*-vinylsilane.[16] A method for obtaining the *E*-vinylsilane exclusively is under investigation.

The results in Table 2 must be interpreted in the context that a mixture of alkenes was employed in the starting mixture, although this has provided us with new evidence on the importance of ensuring a *Z*-vinylsilane functionality utilised in these reactions. Again, lower yields, on comparison to previous examples, are thought to arise from the strong electron-withdrawing effect of the trifluoromethyl group. The use of slightly harsher reaction conditions—reflux temperature in acetonitrile—was necessary for the



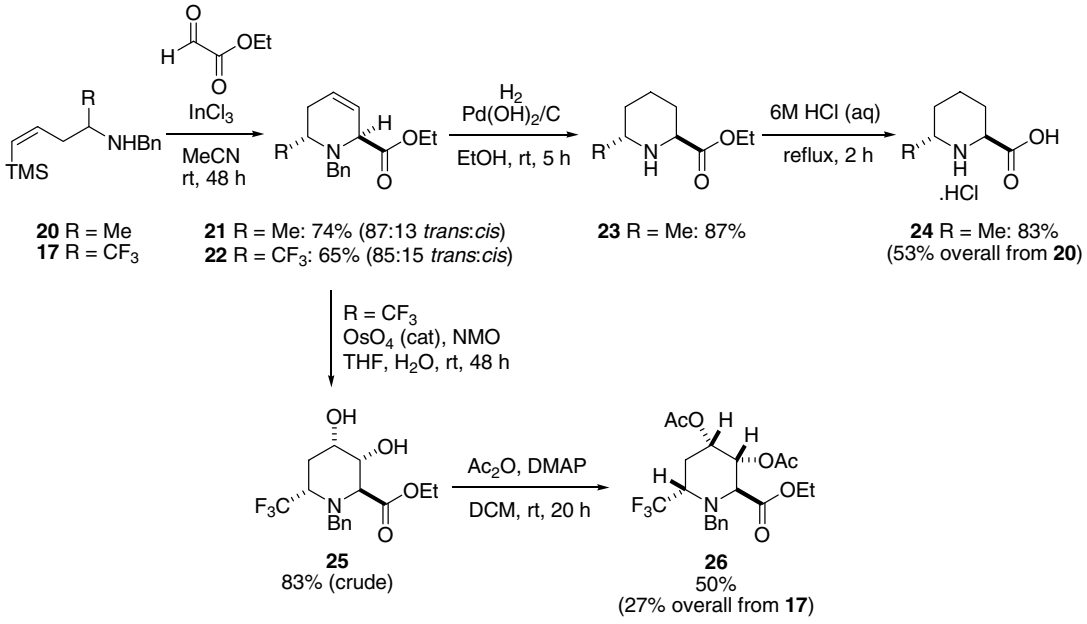
Scheme 4. Preparation of 6-CF_3-containing amine precursors and their subsequent aza-silyl-Prins reaction.

Table 2
Aza-silyl-Prins reactions of 6-CF_3 silylated homoallylic amines

Entry	Aldehyde	Reaction time (h)	% Yield	Cis (**19**):trans (**18**)	Comments
1	*c*HexCHO	48	25	0:100	*E*-Alkene remains
2	$nC_7H_{15}CHO$	48	43	0:100	*E*-Alkene remains
3	$PhCH_2CHO$	48	55	15:85	*E*-Alkene remains
4	(COOEt)CHO	17	69	15:85	Both alkenes consumed
5	*p*-$NO_2C_6H_4CHO$	48	Traces	—	*Z*-Alkene disappeared; *E*-alkene remains

nitrogen series and in keeping with previous examples (Scheme 1). As in Table 1, both alkyl and cycloalkyl aldehydes were successful and gave exclusively the tetrahydropyridine with trans-selectivity of the substituents across the nitrogen, with the CF_3 moiety expected to be the group to adopt the axial (down) orientation (Table 2, entries 1 and 2; based on previous work and assignments). Phenylacetaldehyde gave an enhanced yield (Table 2, entry 3) but in a 15:85 ratio of two diastereomers, with the same trans diastereomer being the favoured product. In each of these cases, it was the *Z*-alkene that was consumed in the reaction and the *E*-alkene was recovered from the product mixture, in approximately quantitative yields. This highlights the importance of the *Z*-vinylsilane functionality as it is more readily consumed in these reactions. We assume this is because it gives more efficient overlap of the orbitals that contribute towards the stabilising β-effect of silicon in the cyclised carbocation intermediate[12,13]; this is, presumably the driving force in these cyclisations. The use of benzaldehyde or *p*-nitrobenzaldehyde failed to give any cyclisation product although all the *Z*-alkene disappeared from the reaction mixture and only *E*-alkene was recovered in slightly increased amounts than were initially used. We postulate that this is due to the pathway of the silyl- and aza-silyl-Prins reactions being reversible (as, in other studies,[17] even when using pure *Z*-vinylsilane starting materials, traces of the *E*-vinylsilane have been isolated as a reaction by-product, indicating that the conversion from *Z*- to *E*- is possible under the reaction conditions).

The use of highly reactive ethyl glyoxylate in the two series is particularly interesting, and also offered considerable scope for further compound elaboration. The use of ethyl glyoxylate with the trifluorinated homoallylic alcohol **7** (Table 1, entry 5) failed to give any Prins product (or any other identifiable compounds), which is in keeping with our previous observations on the use of ethyl glyoxylate with homoallylic alcohols. In the nitrogen series, however, the reaction with ethyl glyoxylate gave excellent yields of 2-ethoxycarbonyl tetrahydropyridines with either no substituent α- to the nitrogen in the starting amine, or with a methyl **20** or trifluoromethyl **17** group in this position (Table 2, entry 4 and Scheme 5). Also, in the trifluoromethylamine series (Table 2, entry 4), both the *E* and the *Z* starting alkenes were consumed during the reaction, the only time that this has been observed. We assume this is due to the increased reactivity of the aldehyde and consequently of the intermediate iminium ions formed from either the *E*- or *Z*-vinylsilanes. The use of ethyl glyoxylate offers the opportunity for the rapid elaboration of the tetrahydropyridines formed to pipecolate derivatives.



Scheme 5. Synthesis of pipecolate derivatives.

Thus, hydrogenation of the 2-ethoxycarbonyl 6-methyltetrahydropyridine **21** simultaneously reduced the double bond and removed the *N*-benzyl protecting group to give the corresponding piperidine **23** in 87% yield, which upon treatment with acid gave the *trans*-6-methyl pipecolic acid **24** in 83% yield and 53% overall yield from **20**. Alternatively, treatment of 2-carboxyethyl ester 6-trifluoromethyltetrahydropyridine **22** with a catalytic quantity of osmium tetroxide and excess NMO gave the dihydroxylated piperidine **25** in 83% yield, with the cis addition of the diol occurring exclusively from the bottom face of the molecule (the same face as the CF_3 substituent). The diol could be stored and purified more readily as the diacetate **26**.

In conclusion, we have shown that the silyl-Prins and aza-silyl-Prins reactions may be employed for the preparation of 6-CF_3-substituted dihydropyrans and 6-CF_3-substituted tetrahydropyridines, and that these products may be further elaborated to a number of saturated heterocycles, including pipecolate derivatives. The use of the trifluoromethyl group in the starting materials has also raised a number of interesting mechanistic questions, and these are the subject of ongoing investigations, the results of which will be reported in due course.

Acknowledgements

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