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Asymmetric Routes Towards Polyfunctionalized Pyrrolidines: Synthesis and Reactivity of a Chiral Silyloxypyrrole.

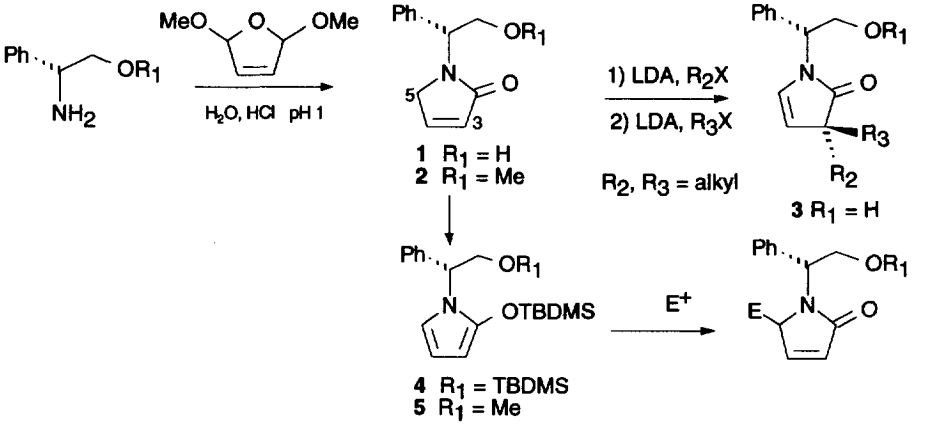
Isabelle Baussanne and Jacques Royer*

Institut de Chimie des Substances Naturelles, CNRS,
1 avenue de la Terrasse, F-91198 Gif-sur-Yvette, France

Abstract : Starting from *O*-protected (*R*)-(-)-phenylglycinol, chiral silyloxypyrrole **5** was prepared in two steps and its reaction with achiral aldehydes under Mukaiyama' s reaction conditions was investigated. Addition occurred at the C-5 position of the pyrrolidine ring with complete *lk* selectivity (except in the case of acetaldehyde) and a modarate to good diastereofacial (*RR vs SS*) selectivity.

We recently reported[1] a simple one-step preparation of chiral lactam **1** (75% yield from (*R*)-(-)-phenylglycinol) and its highly diastereoselective bis-alkylation at C-3 to give **3** (Scheme 1). Lactam **1** and its derivatives are potentially useful for the development of new asymmetric routes to substituted pyrrolidinones and pyrrolidines. Such compounds are found as substructures in many products of biological interest (*e.g.*: polyhydroxylated indolizidines[2] and pyrrolidines[3], kainates[4] or necine bases[5]) and new methodologies for their asymmetric synthesis are still needed.

For this purpose, we have now investigated the reactivity of silyl ketene N,O-acetals **4** and **5** prepared from **1** or its derivative **2**. These silyloxypyrroles **4** or **5** undergo electrophilic substitution at C-5 in contrast to the corresponding lithium enolates which were previously shown[1] to be alkylated at C-3 when quenched with primary halides (Scheme 1). Ricci was the first to report[6] that N-methyl-silyloxypyrroles react with aldehydes

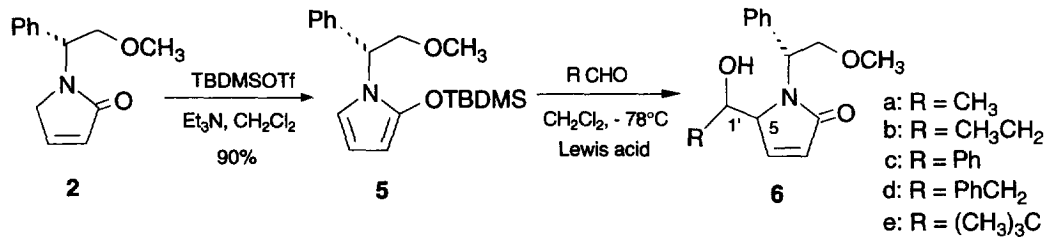


Scheme 1

at the C-5 position, while Rassu and Casiraghi[7] investigated the highly diastereoselective reaction between N-Boc-2-(dimethyl-*tert*-butylsilyloxy)pyrrole and chiral aldehydes. We thus chose to study the reaction of a chiral silyloxypyrrole with achiral aldehydes.[8,9]

Although simpler groups could be suitable, we decided to use (*R*)-(-)-phenylglycinol derivatives as chiral auxiliaries, since we have already shown that they lead to specific diastereoselectivities.[1] For this purpose, the preparation of **4** was first attempted (Scheme 1) but this compound proved to be unstable under a variety of experimental conditions. We thus turned to the O-methyl derivative **5** to initiate our study.

Using the method we have described for the preparation of **1** from (*R*)-(-)-phenylglycinol,[1] lactam **2** was synthesized in 75% yield[10] from (*R*)-(-)-2-methoxy-1-phenyl-ethylamine.[11] Treatment of **2** with *tert*-butyldimethylsilyl triflate (TBDMSOTf) in the presence of Et3N then gave silyloxypyrrole **5** in 90% yield.



2 **5** **6**

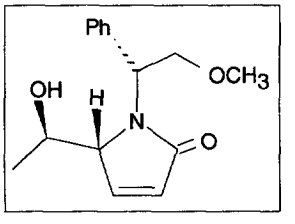
Scheme 2

We first examined the reaction of **5** with acetaldehyde (Scheme 2, R=CH3) and various Lewis acids to give **6a**. All reactions were carried out in methylene chloride at -78°C. As shown in Table 1 the diastereomeric ratios were only slightly changed by the use of different Lewis acids in contrast to results reported for *N*-Boc-silyloxypyrrole.[7c] The two major diastereomers both possess an *l* configuration[12] based on their ^{1}H NMR coupling constant ($^3J_{5-1'}$) of 5-6 Hz.[13] Furthermore, the absolute configuration of the major isomer[14] of **6a** was determined by X-ray crystallography[15] to be *R, R, R* (Figure).

Table 1: Ratio of diastereomers **6a** produced in the Lewis acid mediated reaction between silyloxypyrrole **5** and acetaldehyde

Lewis acid	overall yield (%)	diastereomeric ratio[(a)] *RR / SS / RS / SR*	*l / u* [(b)]
$TiCl_4$	50	74 : 18 : 4 : 4	92 : 8
$SnCl_4$	45	66 : 27 : 3.5 : 3.5	93 : 7
$AlCl_3$	33	50 : 35 : 7.5 : 7.5	85 : 15
$ZnBr_2$	35	45 : 35 : 10 : 10	80 : 20
$BF_3.OEt_2$	75	53 : 31 : 8 : 8	84 : 16

Figure:
The major diastereomer for **6a**



(a) determined by GC and 1H NMR analyses. (b) see ref. 12

The highest diastereofacial selectivities were obtained with titanium tetrachloride and stannic chloride but the yields were modest and not easily reproducible. For studies with other aldehydes (and ketones) boron trifluoride etherate was utilized since it gave good diastereoselectivities with high and reproducible yields.

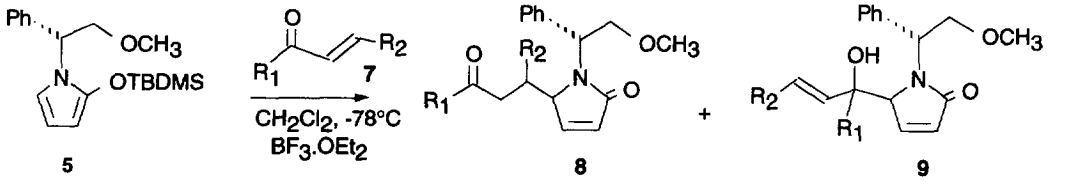
Table 2: Boron trifluoride etherate mediated reaction between silyloxypyrrole **5** and different aldehydes

adduct	R	overall yield (%)	diastereomeric ratio [a] *RR / SS / RS / SR*
6a	CH_3	75	52 : 31 : 8 : 8
6b	CH_3CH_2	63	64 : 36 : 0 : 0
6c	Ph	25[b]	90 : 10 : 0 : 0
6d	$PhCH_2$	59	75 : 25 : 0 : 0 [c]
6e	$(CH_3)_3C$	56	93 : 7 : 0 : 0

(a) determined by GC and ^1H NMR analyses (b) about 15% of dehydration product and 25% of **2** were recovered (c) a very small amount of a third unidentified compound was detected.

From the results reported in Table 2 it can be seen that in all cases - except acetaldehyde - only two diastereomers were formed. These two diastereomers possess the same *l* configuration as proved by NMR and by chemical transformation.[13] Furthermore, the diastereofacial selectivity (*RR / SS*) increases with the size of the aldehyde.

Finally, we have investigated the reaction of **5** with α,β-unsaturated carbonyl compounds **7** (Scheme 3), using boron trifluoride etherate as a Lewis acid.



Scheme 3

The results given in Table 3 show that the reactions proceeded with high overall yields and that the regiochemistry depended upon the presence of substituents on the olefinic bond. Methyl vinyl ketone gave only the 1,4-addition product **8**, whereas exclusive 1,2 addition (to give **9**) was obtained with crotonaldehyde. The ratios of the different diastereomers have been determined, but their configurations could not be assigned with certainty.

Table 3: Reaction between silyloxypyrrole **5** and α,β-unsaturated aldehydes and ketone.

α,β -unsaturated carbonyl compound **7**	**8 / 9** ratio	overall yield (%)	diastereomeric ratio [a]
R_1=H, R_2=H	5.25 : 1	73	– [b]
R_1=H, R_2=CH_3	0 : 1	84	61 : 18 : 15 : 6
R_1=CH_3, R_2=H	1 : 0	80	75 : 25 : 0 : 0

(a) determined on the crude reaction mixture by GC-MS and 1H NMR analyses. (b) not determined

In the course of this work, we have shown that the easily prepared chiral silyloxypyrrole **5** reacts with aldehydes at the C-5 position of the pyrrolidine ring to give **6** in good yield and with high diastereoselectivity.

We are currently studying the use of adducts of type **6** for the synthesis of chiral polyhydroxylated pyrrolidones, pyrrolidines and indolizidines,.

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References and notes:

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8- a) One example of a reaction between a chiral silyloxypyrrole and an achiral aldehyde has been reported in the literature: Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139-2140.

b) During the preparation of this manuscript, the synthesis (using our methodology) and reaction of a chiral silyloxypyrrole has been described: Poli, G.; Ciofi, S.; Maccagni, E.; Sardone, N. *Tetrahedron Lett.* **1995**, *36*, 8669-8672.

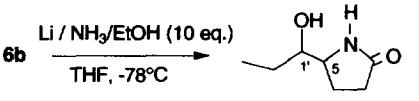
9- Aldol addition of acyclic chiral silyl ketene acetals has been extensively studied; see, for example, Gennari, C. in *Comprehensive Organic Synthesis*, Trost, B. M. Ed., Pergamon Press, 1991, vol 2, p 629-660

10- About 5% of the β, γ-unsaturated isomer was also formed in this reaction.

11- Prepared from (*R*)-(-)-phenylglycinol according to Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892-898.

12- According to the *l* (like), *u* (unlike) nomenclature proposed by Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed. English* **1982**, *21*, 654-660.

13- The 64:36 mixture of diastereomers **6b**, upon treatment with Li/NH_3 at -78°C, gave a single observable compound (enantiomeric mixture):



14- Major isomer of **6a**: $[\alpha]_D$ +156 ($CHCl_3$, c 1); ^1H NMR (C_6D_6, 300MHz) δ (ppm): 0.73 (d, J=6.3Hz, 3H, CH_3), 3.12 (s, 3H, OCH_3), 3.60 (dd, J=9.6, 5.7Hz, 1H, CH_2O), 3.95 (dq, J=6.3, 5.2Hz, 1H, H-1'), 4.18 (dt, J=5.2, 1.5Hz, 1H, H-5), 4.38 (dd [apparent triplet], J=9.5, 8.9Hz, 1H, CH_2O), 5.12 (dd, J=5.7, 8.7Hz, 1H, NCHPh), 6.15 (dd, J=6.0, 1.4Hz, 1H, H-3), 6.81 (dd, J=6.0, 1.6Hz, 1H, H-4), 7-7.4 (2m, 5H, ar.).

15- The X-ray crystallographic study was performed by A. Chiaroni and C. Riche at the Institut de Chimie des Substances Naturelles and will be reported separately.

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