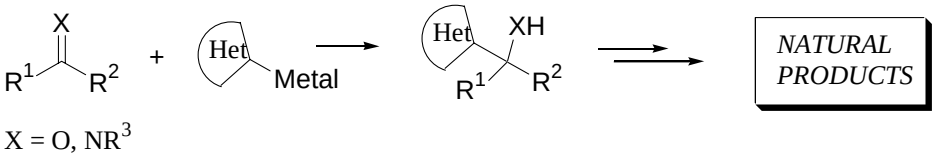
9. Recent Advances in the Reaction of Metalated Aromatic Heterocycles with Carbonyl Compounds and Their Imino Derivatives

9.1 Introduction

A vast number of organic natural products with important biological activities contain in their structure a heterocycle. In order to develop new synthetic strategies for preparing such compounds, a diverse armament of synthetic methods is required to introduce the heterocyclic moiety into the carbon framework.

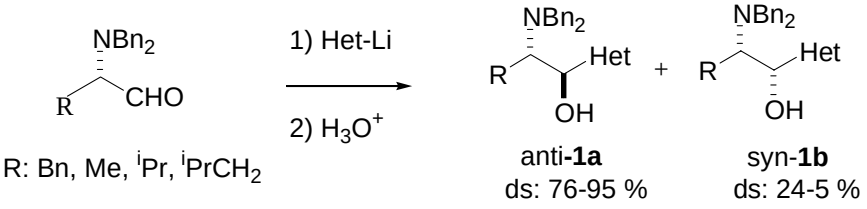


X = O, NR^3

9.2 General studies

It has been reported that lithiated heterocycles added mainly anti to N,N-dibenzyl-α-amino aldehydes affording the corresponding amino alcohols **1**. The observed selectivity could be increased by adding $MgCl_2$ and $ZnCl_2$ as additives in order to trans-metalate the organometallic heterocyclic derivarives. [*Hetereocycles*, **1989**, 707]

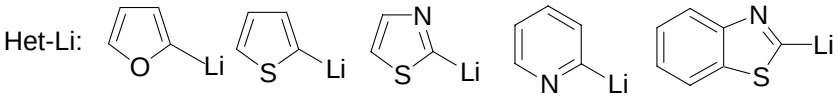
[The stereochemistry of addition refers the Lowry's "Mechanism and theory in organic chemistry" p. 690.]



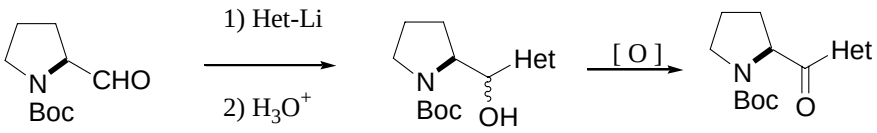
R: Bn, Me, ^{i}Pr, ^{i}PrCH$_2$

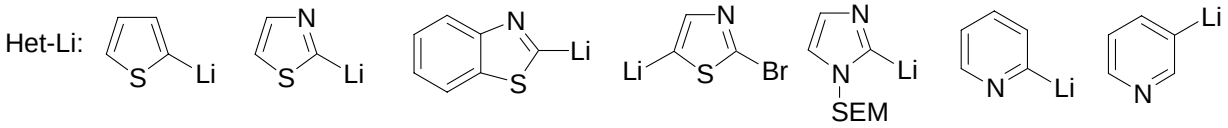
anti-**1a** ds: 76-95 %

syn-**1b** ds: 24-5 %

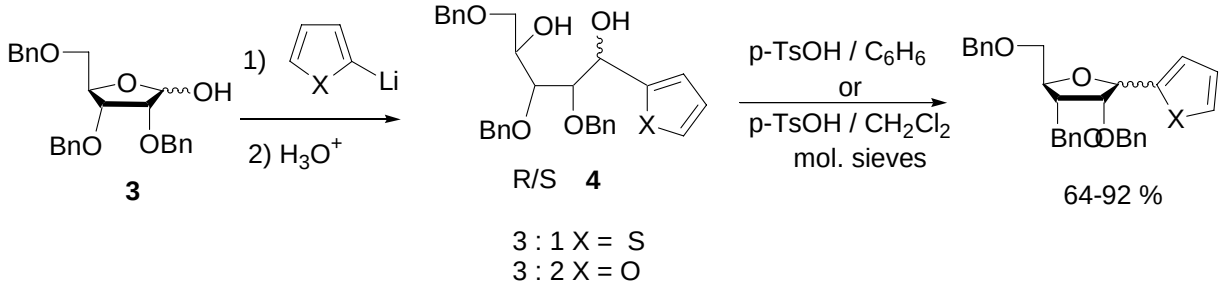


Tsutsumi et al. reported the addition of various lithiated heterocycles to N-Boc-L-prolinal **2**. [*JMC*, **1994**, 3492]

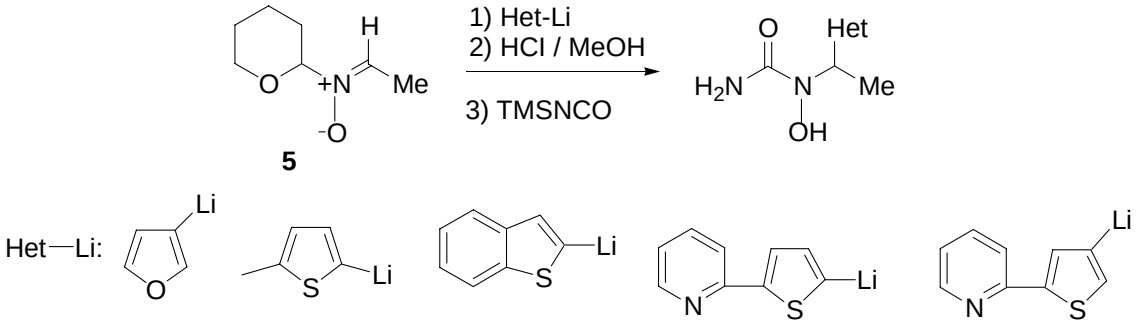




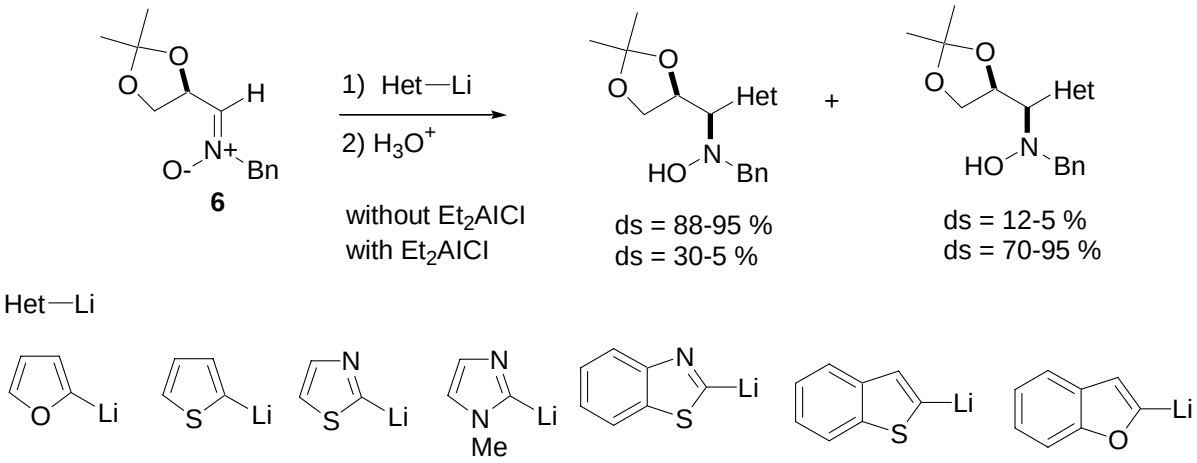
Lithium salts of thiophene or furan reacted with 2,3,5-tri-O-benzyl-D-ribose **3** to give alcohols **4**. [*Synthesis*, **1993**, 517]



The addition of various lithiated heterocycles to nitrone **5** was studied in order to obtain α-branched primary hydroxylamines. [*TL*, **1991**, 3783]

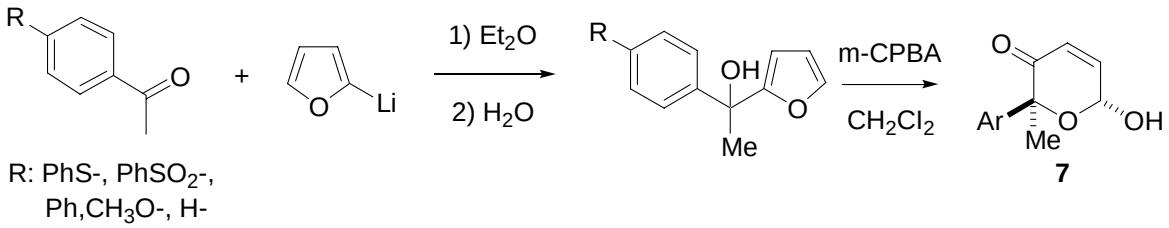


A general study on the addition of several metalated heterocycles to the nitrone **6**, derived from D-glyceraldehyde has been reported. In all cases the addition of metalated heterocycles afforded the syn adduct as the major isomer with high levels of diastereoselectivity. On the other hand when the addition was carried out in the presence of diethylaluminum chloride, a reversal of the diastereofacial selectivity was observed and the anti adduct was obtained preferentially.



9.3 Furan

9.3.1 Aldehydes and ketones

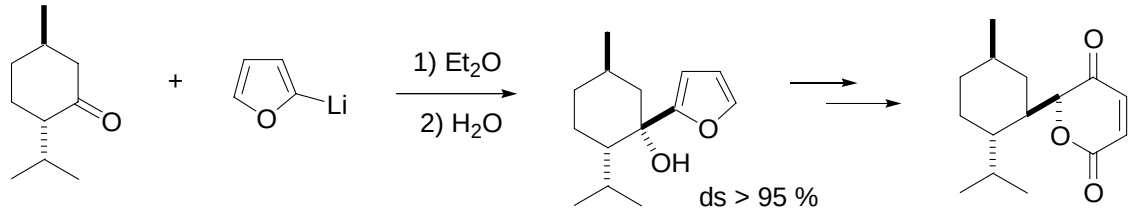


R: PhS-, $PhSO_2$-, Ph,CH_3O-, H-

7

[*JOC*, **1982**, 3054]

The key step of the synthesis was the stereoselective addition of 2-lithiofuran to (-)-mentone. [*Tetrahedron Asymmetry*, **1995**, 2961]



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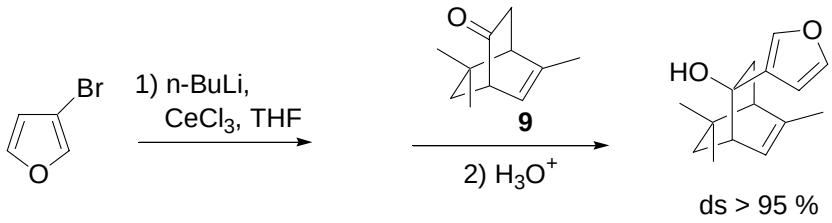
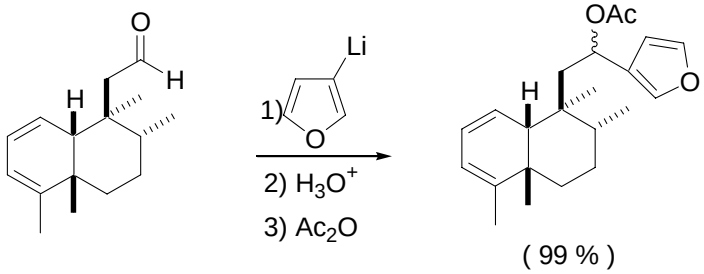
Addition of the organocerium reagent derived from 3-lithiofuran to enantiomerically pure ketone 9 afforded the corresponding alcohol with an excellent diastereoselectivity. [*JOC*, **1992**, 7118]

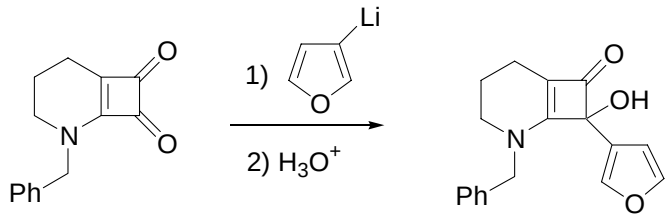


ds > 95 %

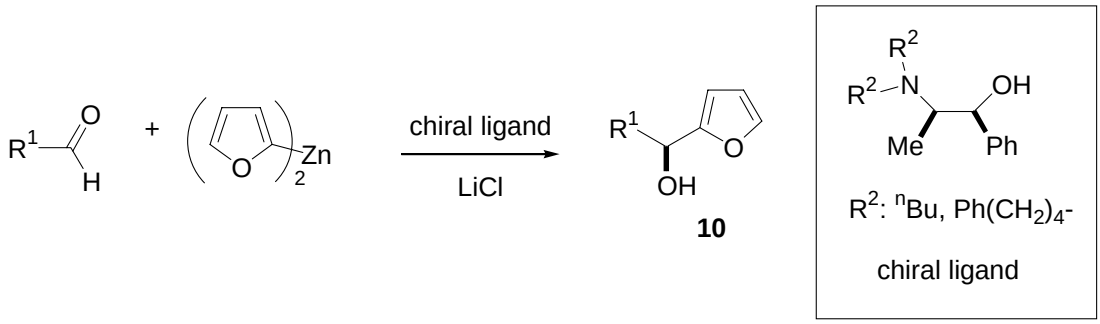
3-Lithiofuran added directly to aldehyde and ketone to afford corresponding carbinols. [*JOC*, **1991**, 6379]



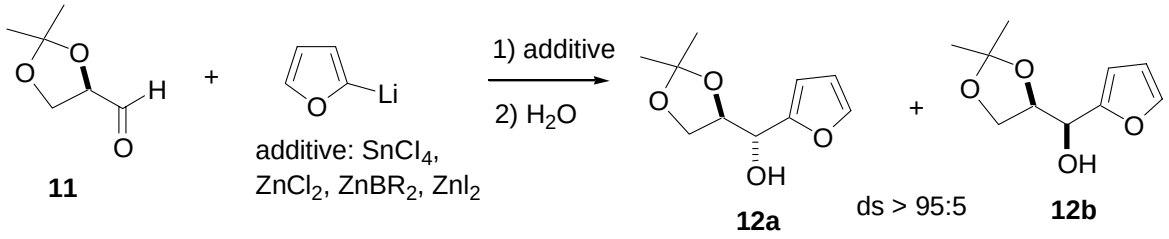
(99 %)



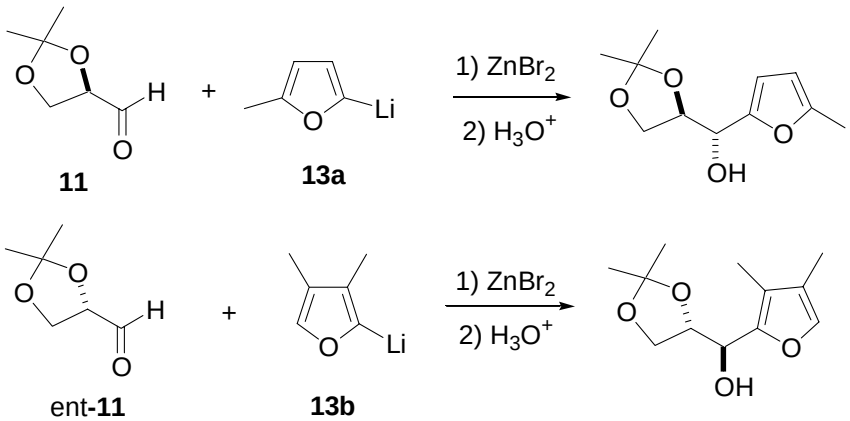
Difurylzinc added to aldehydes in the presence of a chiral ligand to give 2-furylmethanols 10 in good enantiomreic excess (30-72%). [*JCS, Perkin 1*, **1990**, 3214]



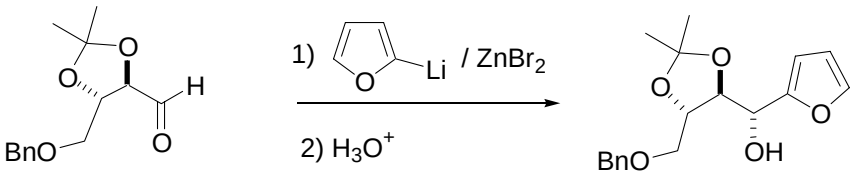
Nucleophilic additions of 2-lithiofuran to chiral α-alkoxy aldehydes have also carried out. In particular, excellent levels of asymmetric induction were obtained in the addition to 2,3-O-isopropyllidene-D-glyceraldehyde **11** using several Lewis acids as additives. In all cases the anti adduct was obtained as the major isomer. [*Chem. Lett*, **1981**, 1529]



Extend to substituted furans. [*JOC*, **1993**, 4274]



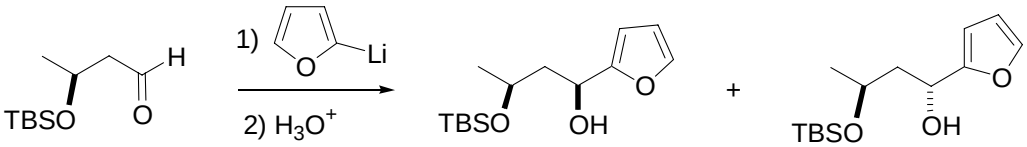
[*JOC*, **1995**, 276]



14

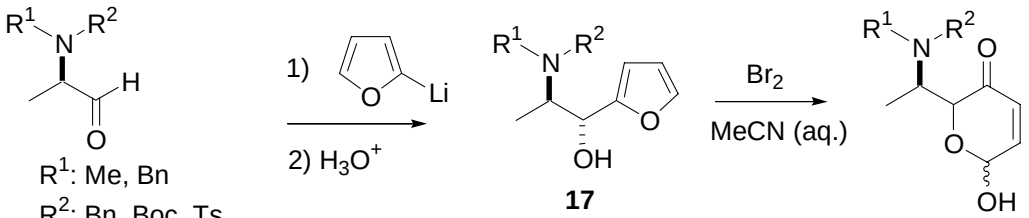
ds = 98 %

[*TL*, **1995**, 7631]



16a 1.5 : 1 **16b**

[*TL*, **1990**, 3797]



R^1: Me, Bn

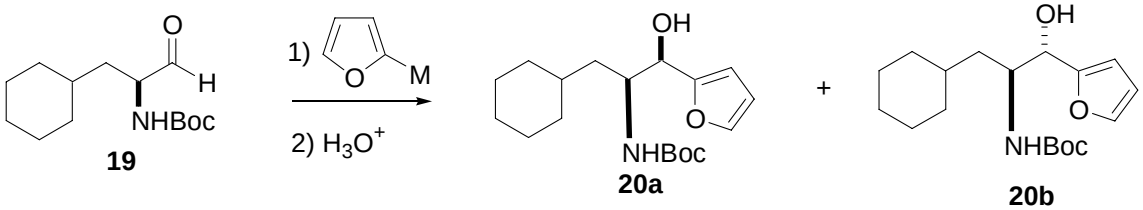
R^2: Bn, Boc, Ts

17

ds = 90-96 %

18

[*TL*, **1992**, 1441]



19

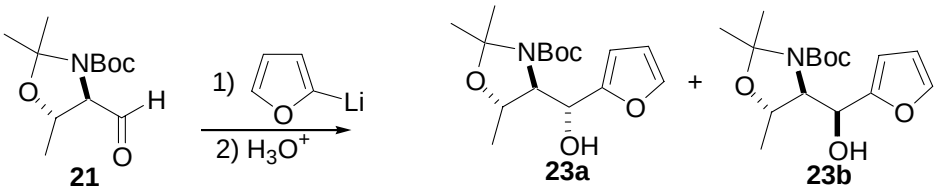
20a

20b

M: Li **20a : 20b** 1: 1

M: ZnBr **20a : 20b** > 10 : 1

[*JOC*, **1992**, 401]

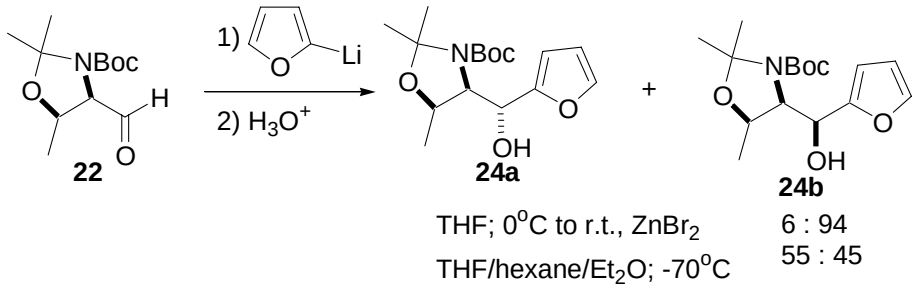


21

23a **23b**

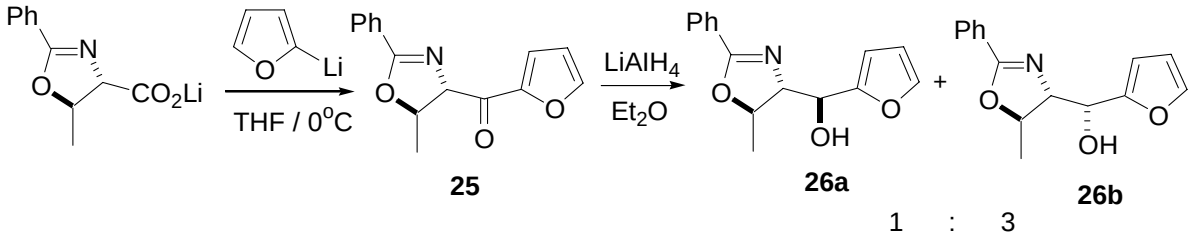
Et_2O; 0 ^oC to r.t., $ZnBr_2$ 14 : 86

Et_2O; -70^oC 81 : 19

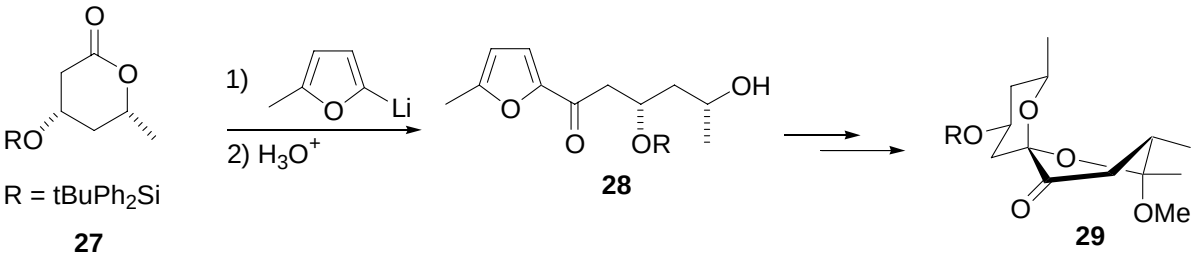


9.3.2 Carboxylic acids and derivatives

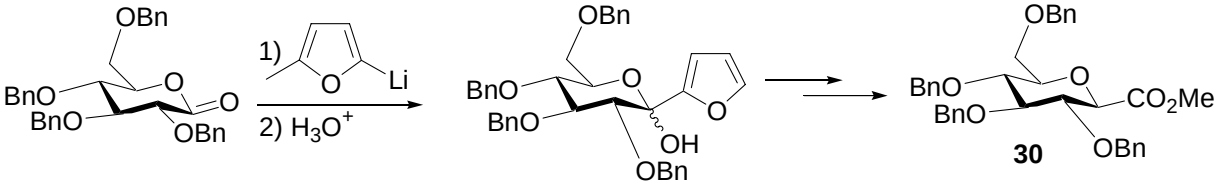
2-Furylketones can be prepared from the lithium salts of the corresponding carboxylic acids by addition of 2-furyllithium. [*Tetrahedron*, **1981**, 949]



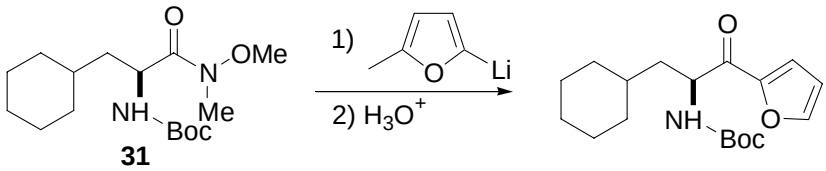
The addition of 5-methyl-2-furyllithium to the chiral lactone **27** afforded the furyl ketone **28**. [*TL*, **1991**, 4081]



Czernecki and Ville demonstrated that both 2- and 3-lithiofuran reacted with lactones, such as those derived from carbohydrates, to give the corresponding lactols. [*JOC*, **1989**, 610]



Howell and coworkers reported the addition of 2-lithiofuran to the N-methoxy-N-methyl amide **31** derived from N-t-Boc-L-3-cyclohexylalaninal to give the corresponding ketone in goodyield. [*Heterocycles*, **1993**, 737]



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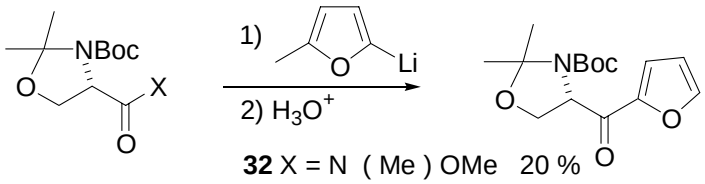
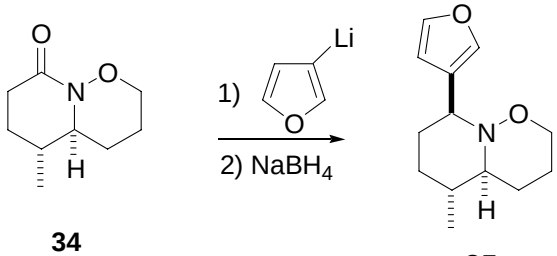


32 X = N (Me) OMe 20 %
33 X = OMe 82 %

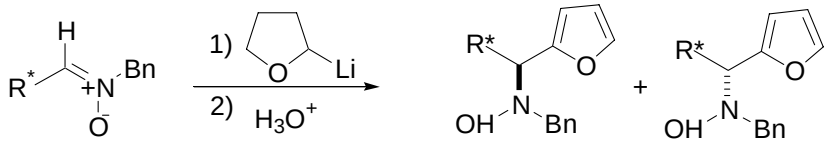
The addirion of 3-furyllithium to bicyclic hydroxamates like **34** gives hydroxylamines via the reduction of an intermediate enamine with sodium borohydride. [J*OC*, **1985**, 3885]



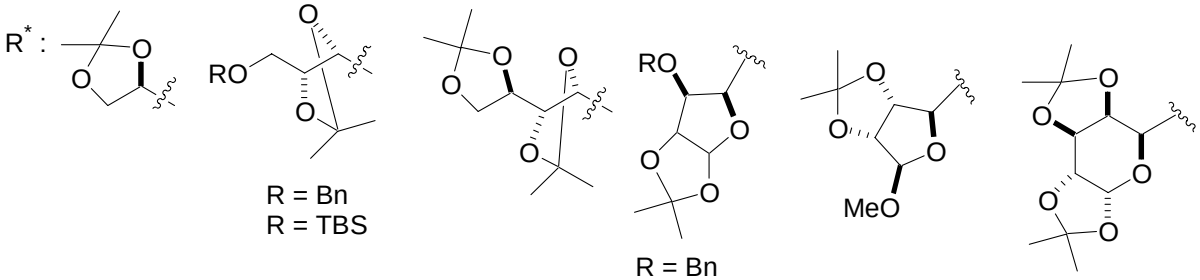
34 **35**

9.3.3 Imino derivatives

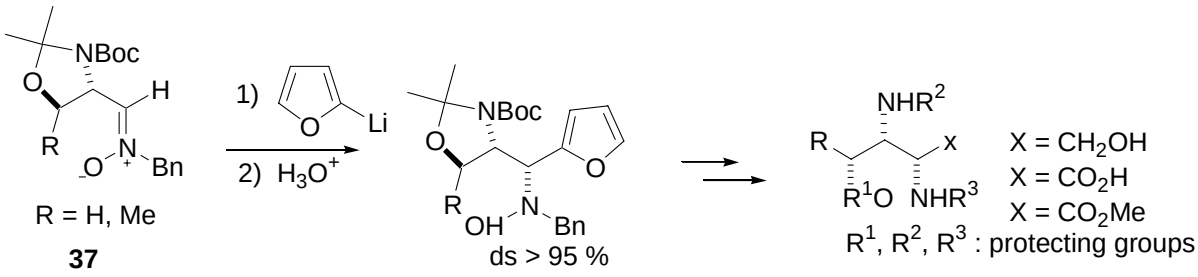
2-Lithiofuran added to α-alkoxy nitrones derived from both aldoses [*Synthesis*, **1994**, 1450] and dialdoses [*JOC*, **1997**, 5484] to give diastereomeric mixtures of the corresponding furfuryl hydroxylamines.



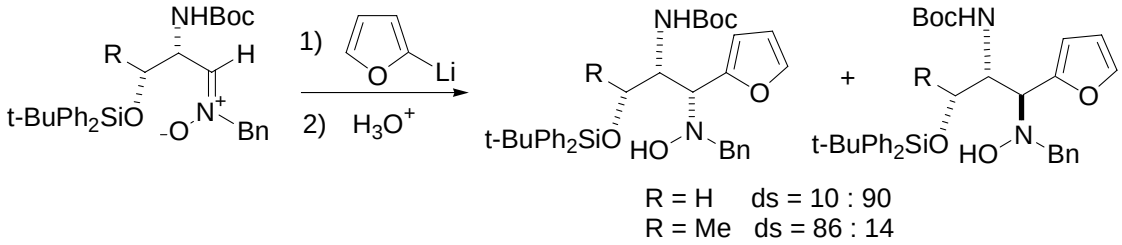
36a **36b**



Compounds bearing two nitrogenated functionalities in 1,2-position were obtained when 2-lithiofuran was added to a-amino nitrones derived from optically active a-amino acids. [*Acta. Cryst. Sect*. *C* **1996**, 2536]



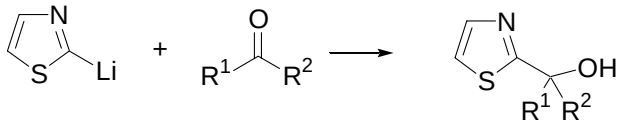
A stereochemical control of the reaction was exerted, when the protecting groups were changed.



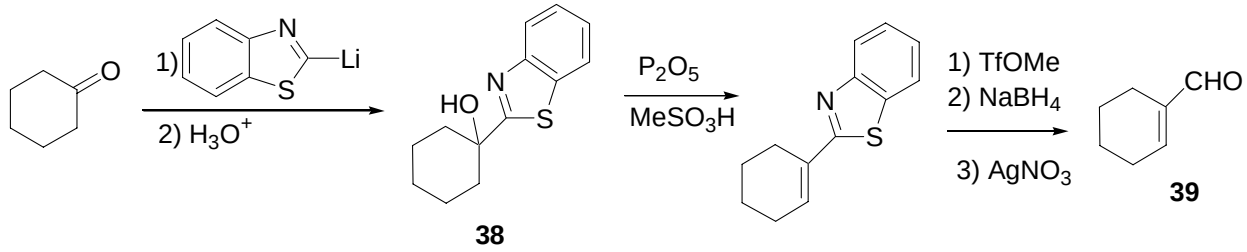
9.4 Thiazole

9.4.1 Aldehydes and ketones

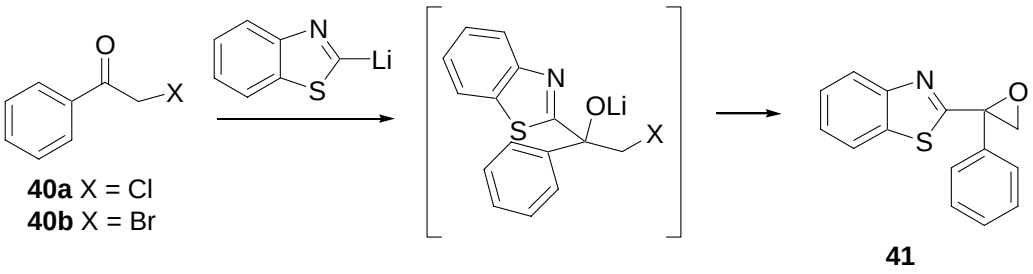
2-Lithiothiazole, generated either by direct metalation or by halogen-metal exchange, underwent nucleophilic addition reactions with both aldehydes [*JOC*, **197**3, 3318] and ketones [*JCS*, **1965**, 4265] to give the corresponding alcohols.



Pioneering Corey's work on this topic demonstrated the synthetic utility of the benzothiazole ring as a carbonyl equivalent. [*TL*, **1978**, 5; 9; 13]



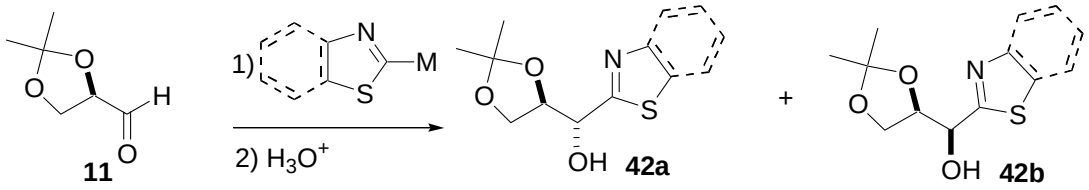
The reaction of 2-lithiobenzothiazole with a-haloacetophenones **40** gave intermediates which cyclized spontaneously to oxirane **41**. [*Bull. Chem. Soc. Jpn*. **1990**, 497]



40a X = Cl
40b X = Br

41

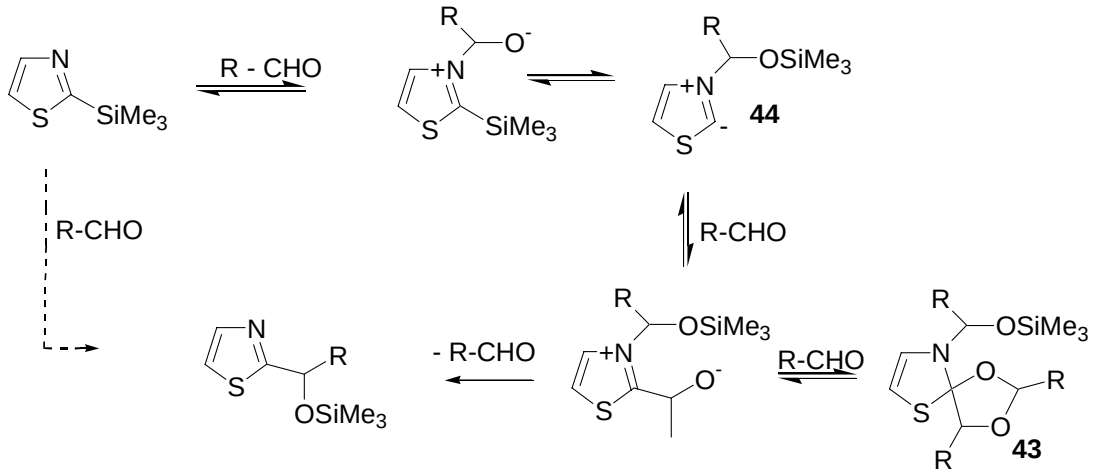
The addition of both 2-lithiothiazole and its derivatives to chiral aldehydes **11** gave a lack of selectivity products, but the TMS derivatives gave the anti isomer preferentially. [JOC, **1989**, 693]



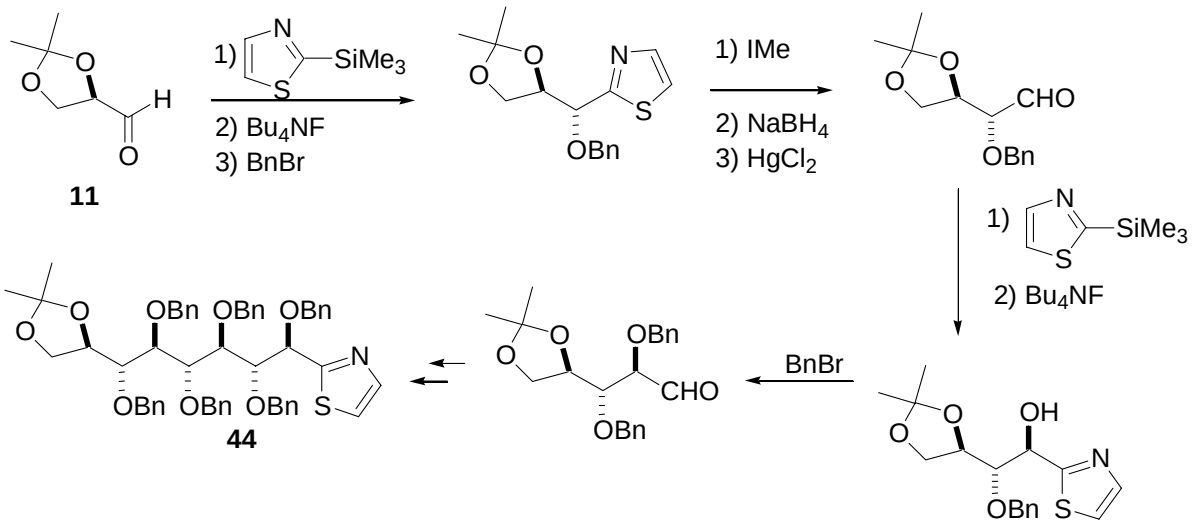
11 **42a** **42b**

	42a	**42b**
M = Li	50 (50) :	50 (50)
M = $SiMe_3$	95 (80) :	5 (20)

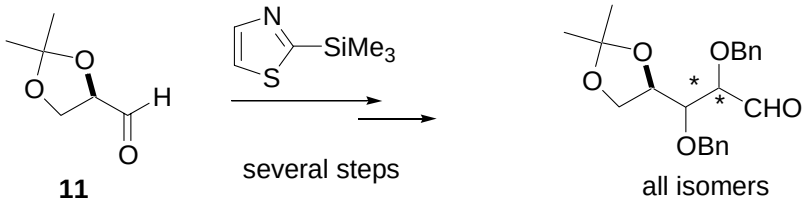
A detailed experimental study of the reaction indicated the presence of spirodioxalane intermediate **43**, thus supporting a mechanism based on the formation of a thiazoly-2-ylide. Further theoretical calculations were consistent with the proposed ylide-intermediate **44**. [JOC, **1993**, 3916; **1996**, 1922]



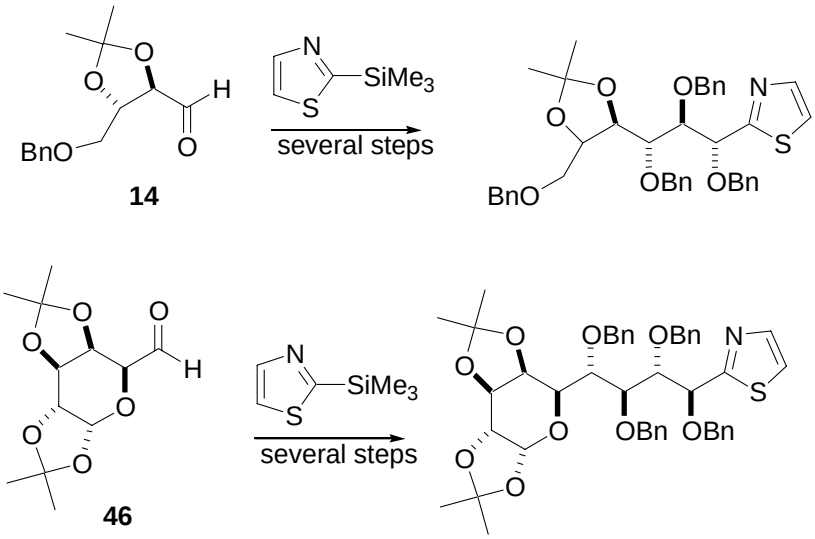
The long chain sugars **44** synthesized via an iterative homologation of compound **11**. [JOC, **1989**, 693]



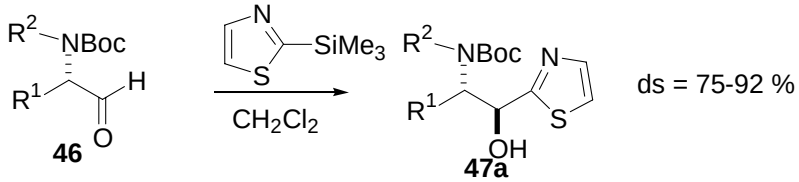
The use of 2-(trimethylsilyl)thiazole was further used in the synthesis of all D-tetrose and D-pentose stereoisomers. [Synthesis, **1992**, 196; 201]

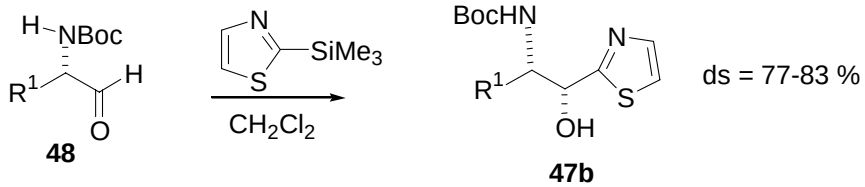


[JOC, **1989**, 693] --- **14**, [Tetrahedron, **1987**, 3533] ---**46**



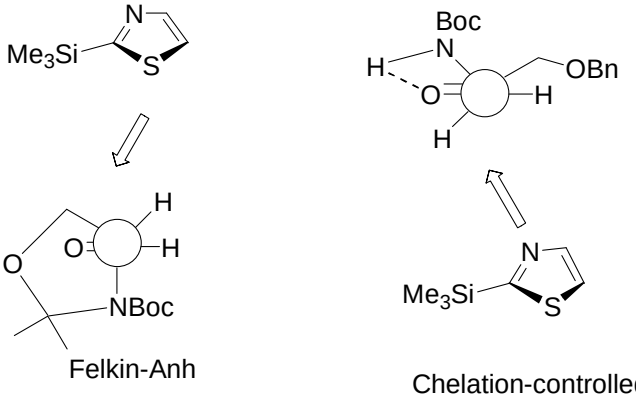
N,N-Diprotected α-aminoaldehydes **46** afforded the anti isomer **47a** predominantly, and N-monoprotected compounds **48** gave the syn adduct **47b** as the major product of the reaction. [JOC, **1995**, 8074]



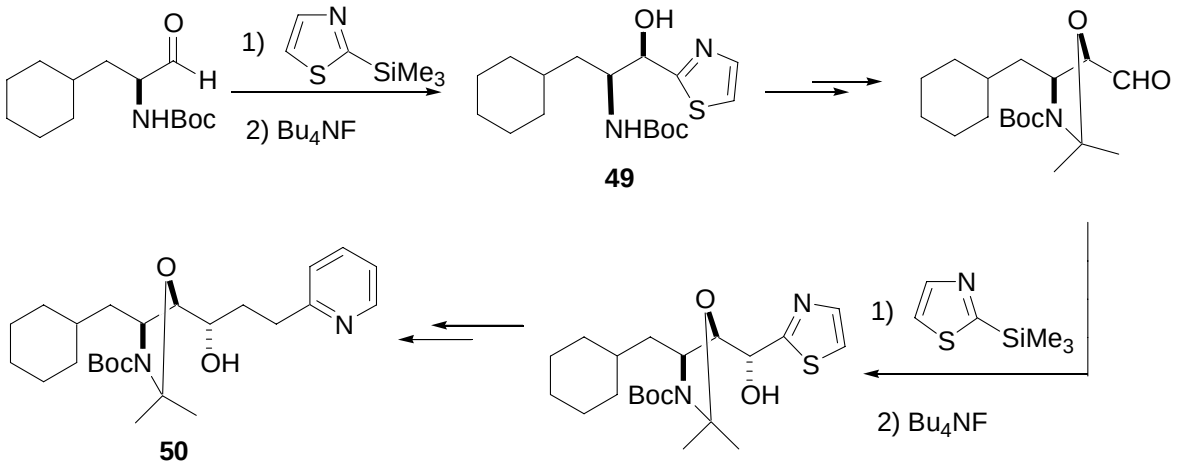


R^1 : $ROCH_2$(R=CMe_2, TBS, Bn), Ph, Bn,^{t}Bu R^2 : Bn, PMB, CMe_2

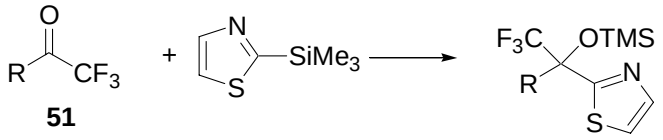
These behaviors could be explained by considering a Felkin-Anh model of addition for boubly protected derivatives or a chelation controlled model in the case of singly protected α-aminoaldehydes. [JOC, **1990**, 1439]



The iterative homologation using 2-(trimethylsilyl)thiazole has also been used by Wagner and Mollath in the synthesis of a dipeptide mimic. [TL, **1993**, 619]



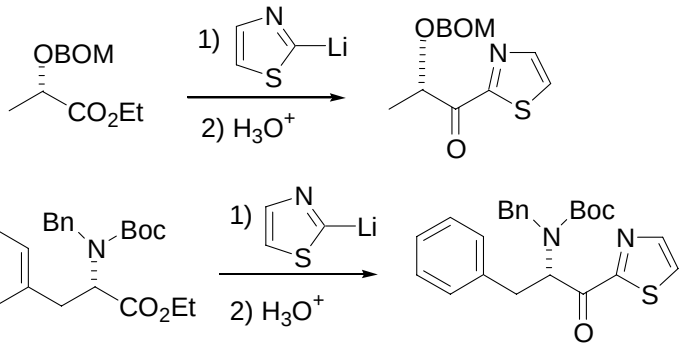
The organometallic derivative of 2-(trimethylsilyl)thiazole was unreactive with most ketones. Exception: **51**. [Synthesis, **1995**, 654]



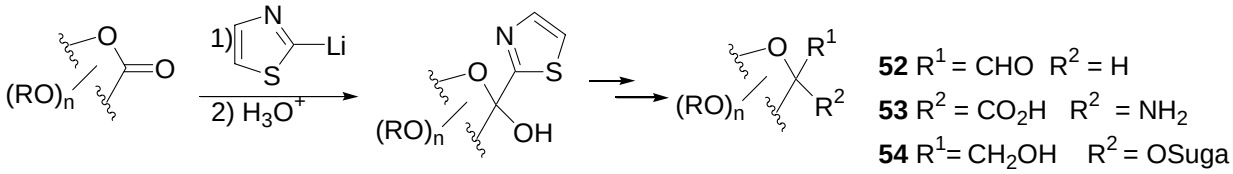
51

9.4.2 Carboxylic acids and derivatives

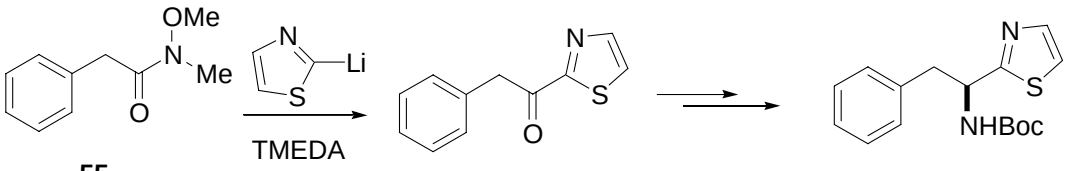
2-Lithiothiazole was added to both α-alkoxy eaters [Tetrahedron, **1993**, 2939] and α-amino esters [Synthesis, **1993**, 1162] and obtained ketones were converted into biologically important compounds such as aza sugars [JOC, **1995**, 4749], deoxysugars [Tetrahedron, **1989**, 141], dipeptide isosteres [TL, **1992**, 7259] and unusual α-amino acids. [Synthesis, **1993**, 1162]



Also, 2-lithiothiazole reacted with carbohydrate-derived lactones affording lactols which were transformed into C-glycosyl aldehydes **52** [JOC, **1994**, 6404], anomeric α-amino acids **53** [JOC, **1994**, 7517] and α-linked ketodisaccharides **54** [Tetrahedron, **1996**, 3057].



52 R^1 = CHO R^2 = H
53 R^2 = CO_2H R^2 = NH_2
54 R^1= CH_2OH R^2 = OSuga

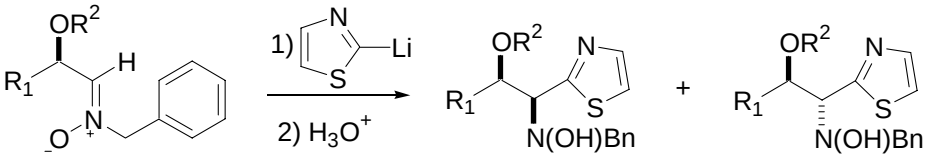


55 **56** **57**

9.4.3 Imino derivatives

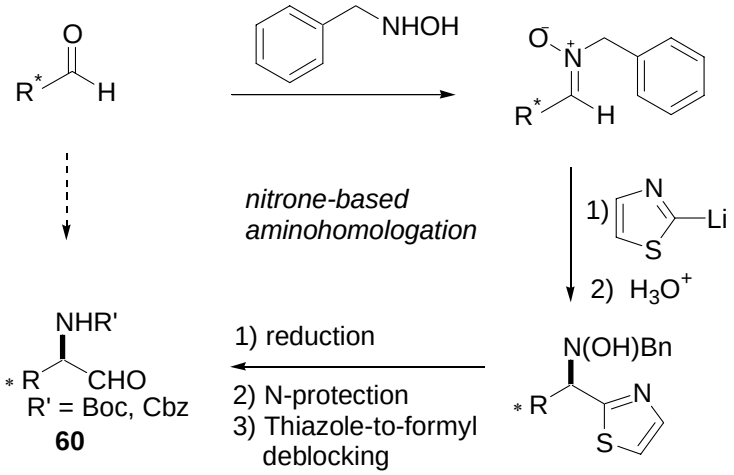
The addition of 2-lithiothiazole to α-alkoxyl nitrones **58** led to syn hydroxyamines with good levels of diastereoselectivity [Chem. Eur. J. **1995,** 505]. The optically active (hydroxyaminomethyl)thiazoles 59 were used as starting materials in the synthesis of a variety of natural products and derivatives, including aminosugars [Synlett, **1993**, 78],

azasugars [Chem. Eur. J. **1995,** 505] and C-glycosyl-α-amino acids [JOC, 1997, 5484].

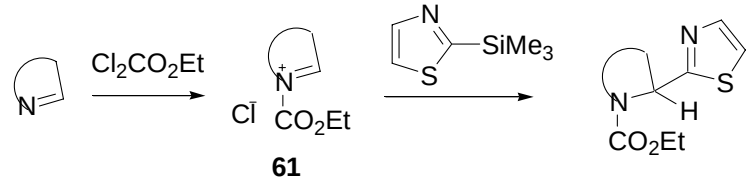


58 **59a** **59b**

A stereoselective aminohomologation.



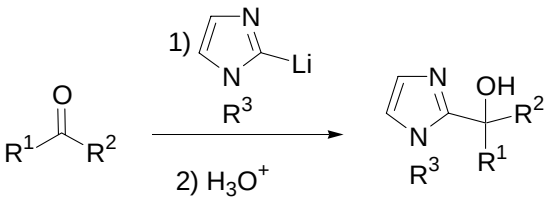
2-(Trimethylsilyl)thiazole did not react with imino compounds such as imines, oximes or nitrones. Only the reaction of 2-(trimethylsilyl)thiazole with several heterocyclic cations such as **61** was reported. [TL, **1984**, 3637]



: pyridine, quinoline, isoquinoline, benzothiazole, thiazole

9.5 Imidazole

The reaction of N-substituted 2-thioimidazole with aldehydes and ketones gave the corresponding alcohols. [Heterocycles, **1994**, 2487]

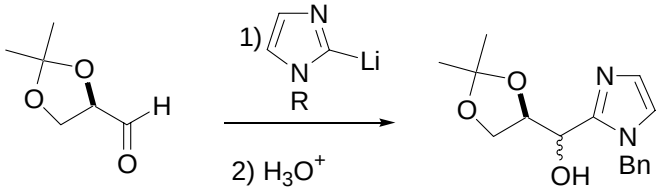


62

R^1, R^2: H, alkyl, aryl

R^3: Me, Bn, Boc, Ts,Tr

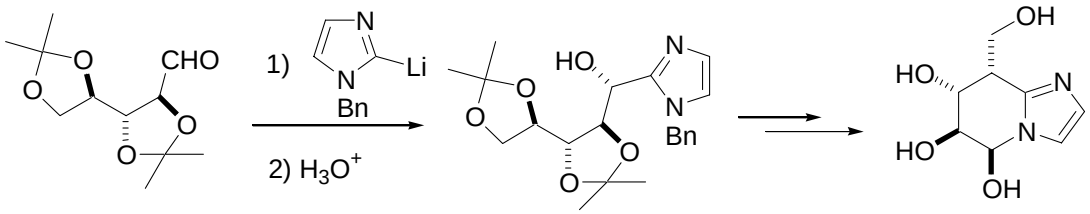
The addition of N-substituted 2-lithioimidazoles to chiral aldehydes. [Heterocycles, **1994**, 673]



11

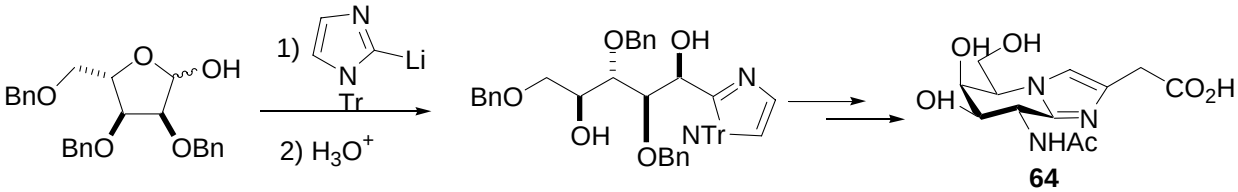
R = Bn, SO_2NMe_2

Application of this reactivity to an aldehyde derived from arabinose led to the anti alcohol **63**, and further used in the synthesis of a deoxnojirimycin analog containing an imidazole ring.



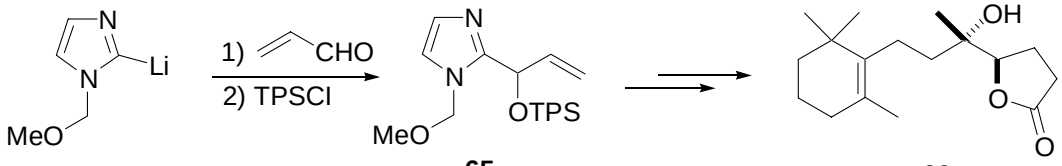
63 ds = 66 %

The synthesis of nagstatin **64**: a potent glucosaminidase inhibitor. [TL, **1995**, 1085, 6721]



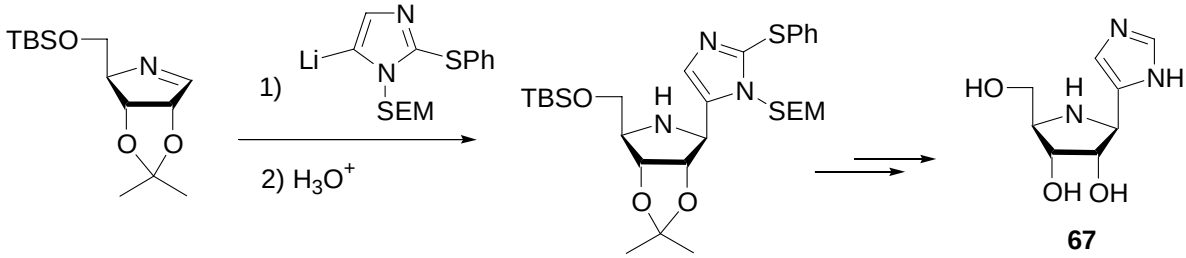
64

Total synthesis of racemic cavernosine **66**. [Tetrhedron, **1992**, 7839]



65 **66**

The synthesis of compound **67**: an inhibitor of nucleoside hydrolase. [TL, 1993, 7213]

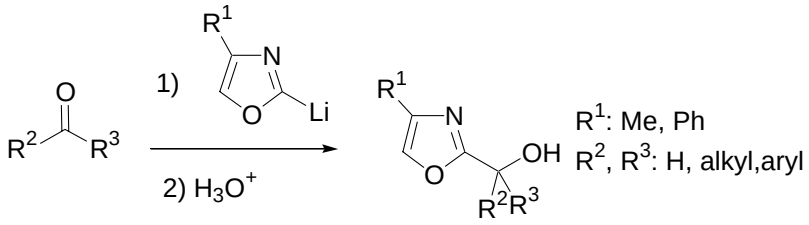


67

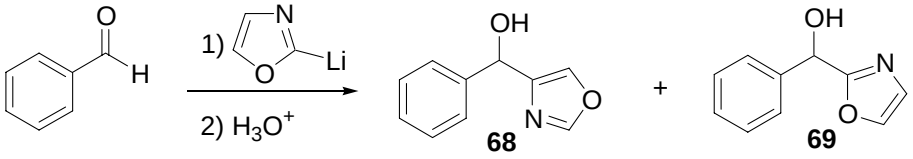
9.6 Oxazole

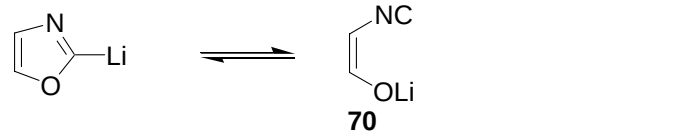
The equilibrium between 2-lithiooxazole and the ring-opened lithioisocyanoenolate. [Chem. Ber. **1997**, 1213]

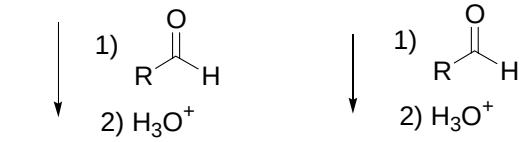
When the 4-position is substituted a normal reactivity of 2-lithiooxazole towards both aldehydes and ketones was observed. [JOC, **1991**, 3058]

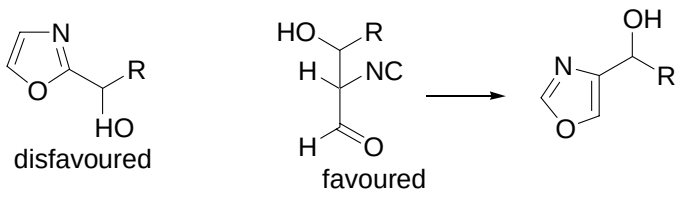


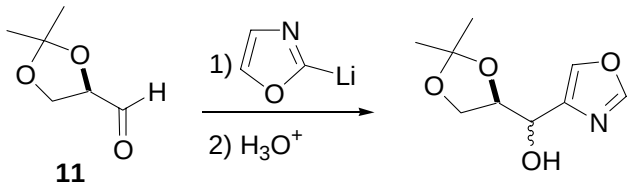
When the 4-position was unoccupied, aldehydes reacted with 2-lithiooxazole to give predominantly products of 4-substitution. It is possible to rationalize this behaviors on the basis of the equilibrium of 2-lithiobenzoxazole with the open form. [JOC, **1991**, 449]



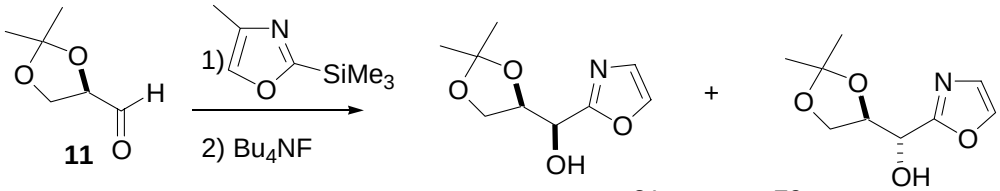


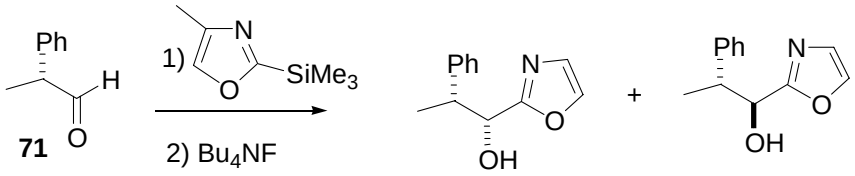






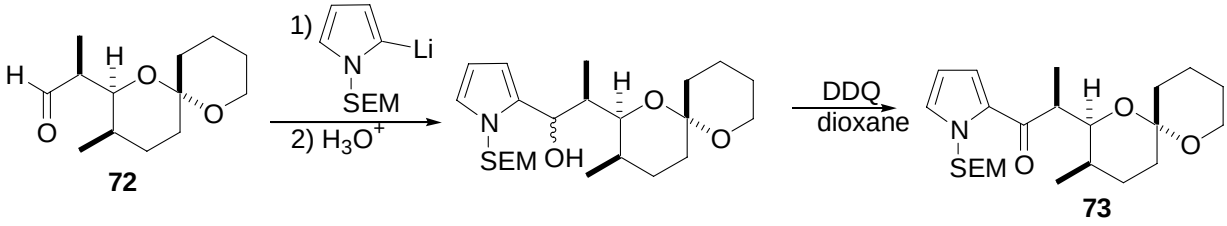
Moderate diastereoselectivity was achieved in the nucleophilic addition of 4-methyl-2-(trimethylsilyl)oxazole to chiral aldehydes. [**JOC**, 1987, 3413] Since in this case the 4-position of the oxazole ring was substituted, 2-oxazoyl derivatives were obtained.



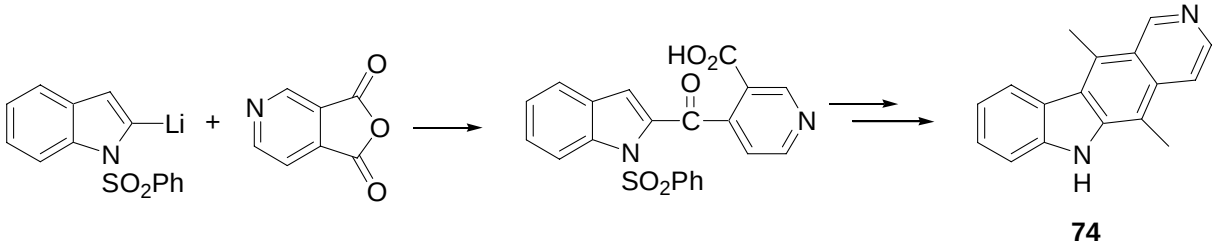


9.7 Other heterocycles

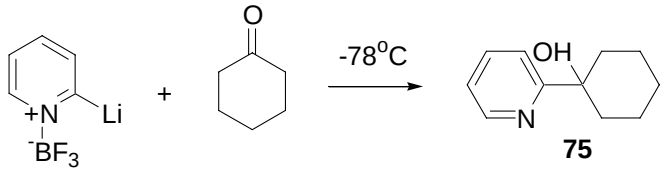
The synthesis of ketone **73** [Tetrahedron, **1992**, 7899]



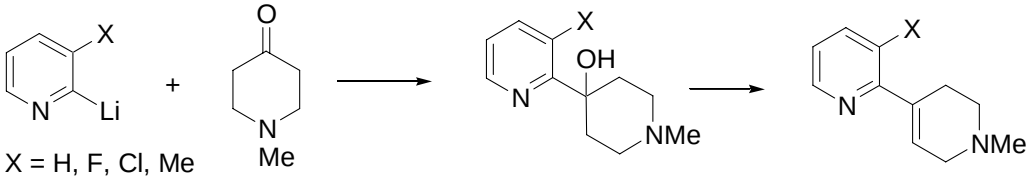
The synthesis of ellipticine **74**. [JOC, **1992**, 5891]



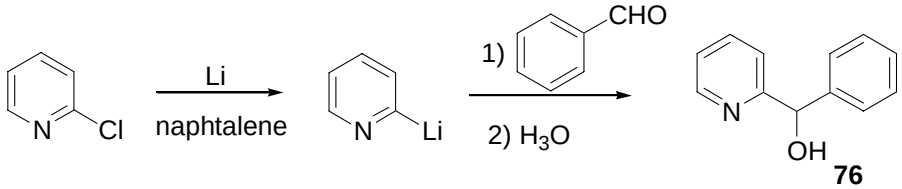
The lithium salt of the pyridine=boron trifluoride complex reacted with cyclohexanone to give a-pyridyl alcohol 75. [Chem. Commun. **1991**, 570]



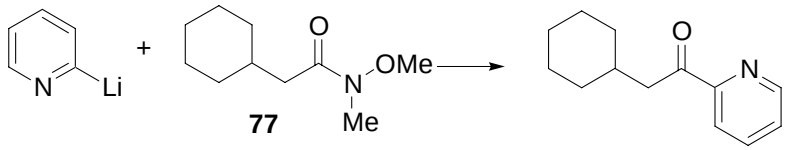
[JMC, **1984**, 1182]



[Heterocycles, **1994**, 1467]

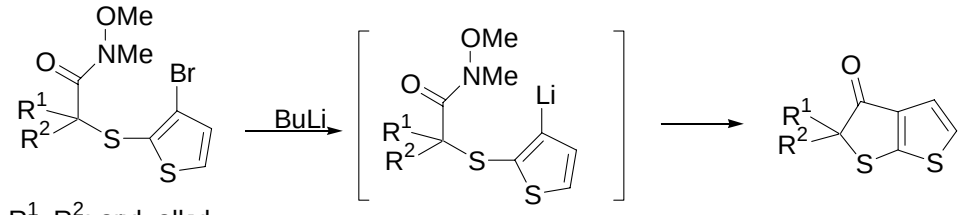


[TL, **1993**, 2259]



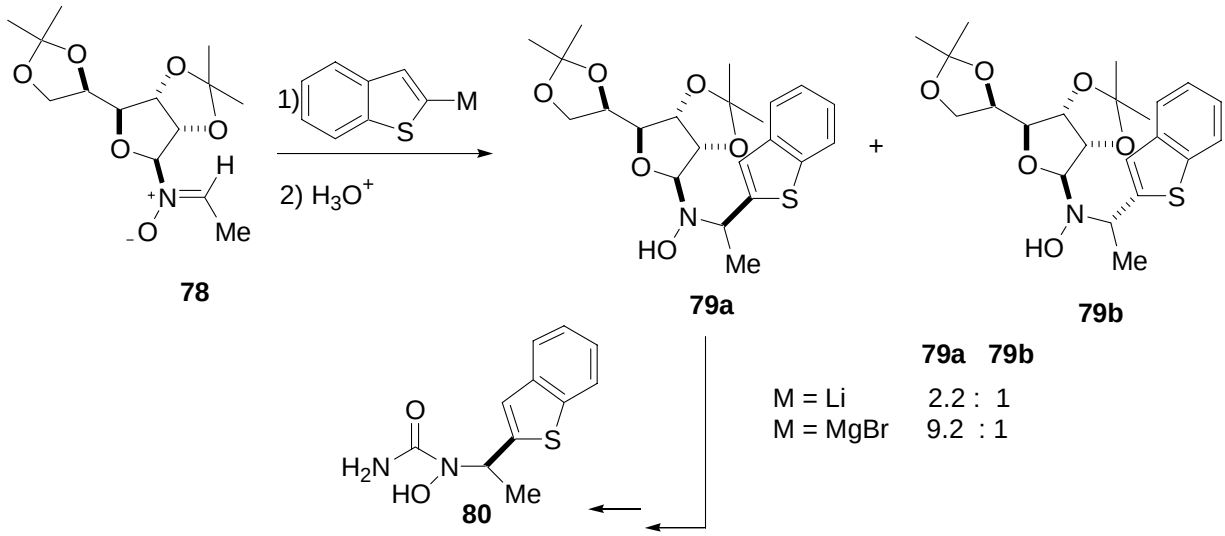
77

[TL, **1991**, 721]



R^1, R^2: aryl, alkyl

[JOC, **1994**, 6103]



78 **79a** **79b**

	79a	**79b**
M = Li	2.2 :	1
M = MgBr	9.2 :	1

80