2-Mercaptopyridine – Anchimerically-Assisted Activation of Thiols, Thioates and Ketene Thioacetals

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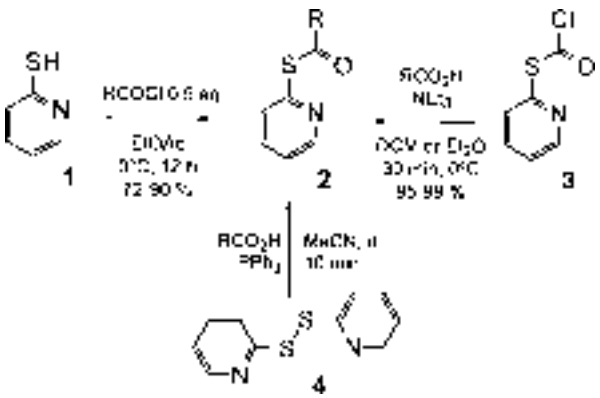
Abstract. The 2-mercaptopyridine reagent is reviewed with particular emphasis on a) recent developments, and b) comparison to alternative and sometimes superior methodologies. The useful application to macrocyclization or carboxyl activation is limited to special cases featuring additional functionalities. More recently, the reagent was utilized for the stereoselective synthesis of substituted β-lactones, β-lactames and carbohydrates.

Contents

1. Thioates and Grignard Reagents

The conversion of carboxylic acid to ketones is an attractive C–C bond forming reaction, and many syntheses based on organometallic reagents for this transformation have been reported. The inherent selectivity problem arising from the higher reactivity of the resulting ketone towards the nucleophile was overcome by several approaches. The classical reactions of Grignard reagents with acid chlorides, nitriles or anhydrides have their value, but were improved by replacement of the chlorides by *N*-acylimidazoles [1] and 8-acyloxy-quinolines. These reagents are now being replaced by the more selective Weinreb-amides [2–4]. Only two other reliable methods compete with these Weinreb amides: i) the recently reported activation of acid chlorides by trialkyl phosphines [5] combine a facile *in situ* preparation of the activated species, good selectivities and readily available starting materials, and ii) the 30 years [6, 7] old, yet up-to-date, 2-mercaptopyridine thioates **2**, which provide the ketones by simple reactions with magnesium organyls in excellent yields [8]. The original procedures by Young [7] and Mukaiyama [8], respectively, required the conversion of mixed anhydrides or acid chlorides with 2-mercaptopyridine **1** in the presence of tertiary amines. This approach often demands a laborious purification of the thioates. Whenever crystallisation or distillation is feasible, this method still has its value. Alternatively, the free acid, **1** and dicyclohexylcarbodiimide [7] or 2,2'-dipyridyl disulfide [9, 10] **4** in combination with triphenylphosphine may be used. However, the Corey reagent **3**, which is prepared from **1** and phosgene (or more conveniently from triphosgene), provides the thioester **2** almost quantitatively after removal of the ammonium chloride, and the crude product is usually sufficiently pure for immediate further conversion and easily prepared *in situ* [11]. A simple crystallisation is recommended prior to storage of the thioates.



Scheme 1

The reaction mechanism was already lined out in Mukaiyama's first report. The reaction is assumed to proceed *via* thioate coordination of the Grignard reagent to give the reactive intermediate **5**, which is further activated by the *Lewis* acid for attack by the nucleophile. The immediate delivery of the nucleophile to the carbonyl group gives the complex **6**, slowing down further attack from nucleophiles. The stability of this complex

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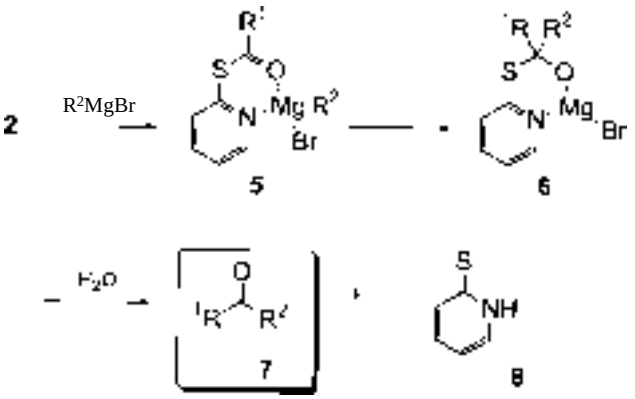
in THF is low, therefore an absorption at 1710 cm^{-1} is observed in IR spectra of the reaction mixture [12]. The crude product is usually contaminated by less than 1% of the tertiary alcohol in reactions with stoichiometric amounts of the Grignard reagent. Excess of the organometallic reagent, such as RMgX, organolithium species or cuprates has to be avoided, since the yield of tertiary alcohols increases proportionally. On the other hand, methylenephosphoranes may be used in 2-fold excess to give crystalline keto ylides for Wittig reactions [13]. The Weinreb amides will be the better choice, if excess of the organometallic species is unavoidable [14] as for the reversed addition of the electrophile to the organometallic reagent. The chelate is finally hydrolysed in the work-up to give the desired ketone **7** and the tautomeric form of auxiliary **8**, readily removed by extraction of the organic solution with aqueous base. The equilibrium of the tautomeric species **1** and **8** is strongly solvent- and concentration-dependent, with the dimer of the NH-form dominating at higher concentration in neutral solution [15].



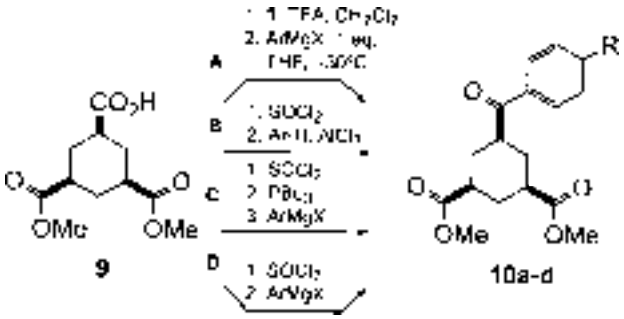
Scheme 2

Table 1 Reaction of **2** with 1 eq of RMgBr to give **7**

Entry	R^1	R^2	Yield (%) **2**–>**7**	Weinreb–>**7**
1	Ph-	Ph	99 [12]	93 [3] [b])
2	$PhCH_2CH_2$-	*n*-C_4H_9	97 [8]	
3	$PhCH_2CH_2$-	*c*-C_6H_{11}	95 [8]	
4	$PhCH_2CH_2$-	*sec*-C_4H_9	83 [8]	
5	CH_3-	Ph	91 [8]	93 [3] [b])
6	*n*-C_5H_{11}-	Ph	86 [8]	
7	-$(CH_2)_4$-	Ph	92 [8]	
8	R^1CO = *N*–Phth–Phe-	allyl	53 [16] [a])	
9	$Bn(CH_2CO_2Bu^t)CH$-	Et	98 [17]	
10	R^1CO = *N*–Boc–Pro-	Et	63 [17]	
11	EtO_2C–$(CH_2)_4$-	Ph	85 [12]	
12	MeCO–$(CH_2)_4$-	Ph	73 [12]	

THF, 0 °C, argon atmosphere, addition of 1 eq R^2MgBr to 0.2–0.5M solutions of **2**. [a]) 2.5 eq of R^2MgBr, [b]) 3 eq of R^1MgBr or R^1MgCl

The use of stoichiometric Grignard reagent is compatible at 0 °C with a number of functional groups, such as phthalimides (table 1, entry 8), esters (entries 9, 10, 11) and even ketones (entry 12), not tolerated by the Weinreb technique. Thus, the thioates allow the chemoselective arylation of cyclohexane-1,3,5-tricarboxylates **9** to ketodiesters **10** (Table 2, entries 1, 3, 8). In this study, Corey's thioate method proved to be superior to acid chlorides or phosphine activation. In all cases studied, the activation was followed by addition of Grignard reagent, and compared to the alternative Friedel-Crafts acylation [18]. Typical reaction conditions for Weinreb amides utilize an excess of organometallic reagent which would have a deleterious effect on yield and isomeric purity of **10a**–**d**.



Scheme 3

Table 2 Conversion of **9** to Arylketones (**10**)

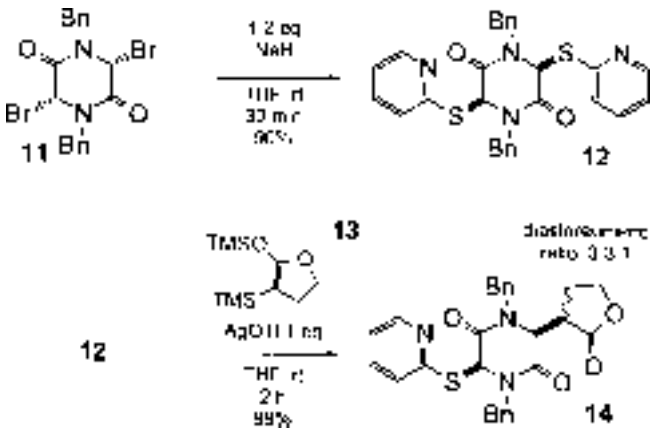
Entry	Product	R	Method	Yield %[18]
1	**10a**	OBn	A	65
2	**10a**	OBn	B [a])	0
3	**10b**	O^{t}Bu	A	65
4	**10b**	O^{t}Bu	B [a])	0
5	**10c**	OMe	B	69
6	**10c**	OMe	C	52
7	**10c**	OMe	D [b])	35
8	**10d**	H	A	67
9	**10d**	H	D	67

[a]) $SnCl_4$ instead of $AlCl_3$ [b]) Zn instead of Mg

2. Anchimerically-Assisted Peptide Coupling Reactions

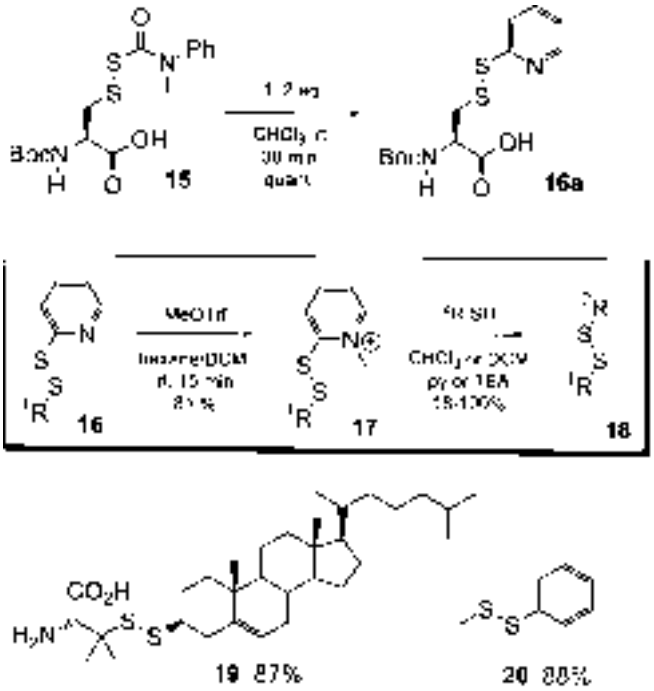
The intramolecular general base-catalysed hydrolysis (anchimeric assistance) of 2-pyridyl thioates and 2-pyridyl esters was first applied to peptide synthesis by Young [7] and Morley [19] and provided Boc- or Z-protected dipeptides free of racemisation. Although the

reaction rates (< 1h) and yields (79–92%) for notoriously complicated dipeptides (*e.g.* Z–Ile–Val–OMe, Phth–Aib–Aib–OMe) were quite remarkable, the more recent condensation reagents [20] (*e.g.* EDC, PyBop, BOP–Cl and PyBroP [21]) give better and more reliable yields even for the most difficult cases. For instance, DCC couplings of *N*–methylated amino acids are more effective in the absence of HOB*t* and other additives than in their presence. BOP–Cl was recommended for condensation of dipeptides such as Aib–Aib–OMe [20]. Thus, the synthetic value of 2-mercaptopyridine for peptide synthesis rests in other applications, such as α-substitution of α-amino acids by nucleophiles, which allow selective conversion of the dibrominated piperazindione **11** into the butyrolactone **14** [22]. The *meso*-dibromide was transferred into the *bis*-*N*,*S*-acetal **12** with complete diastereoselectivity by 2 equivalents of **1** and sodium hydride. The activation of the *syn*-configurated *bis*-pyridine **12** by silver triflate results in a stable chelate, which reacts upon addition of ketene trimethylsilyl acetals to form the *mono*-coupled and *syn*-configurated product **14** only. The outcome of the reaction is extremely sensitive towards the order of addition of Ag^+ and the ketene acetal. The stereochemistry of the *syn*-product was explained by the preference of 2,5-piperazindiones to adopt the boat conformation with the mercaptopyridine and the incoming nucleophile **13** in axial positions. The insufficient differentiation of the ketene acetal side chains gave rise to mixtures with diastereomeric excesses ranging from 16–58%, which may be worsened by epimerisation.



Scheme 4

Another application for **2** was reported [23] for the *N*-protection of amino acids by *Z*-technique. The 2-benzyloxycarbonylthiopyridine displayed improved properties in comparison to *Z*–Cl. However, the introduction of other protecting groups and their inexpensive, commercial reagents (*e.g.* BOC_2ON, Fmoc-succinimide) reduced the practicability of this approach.

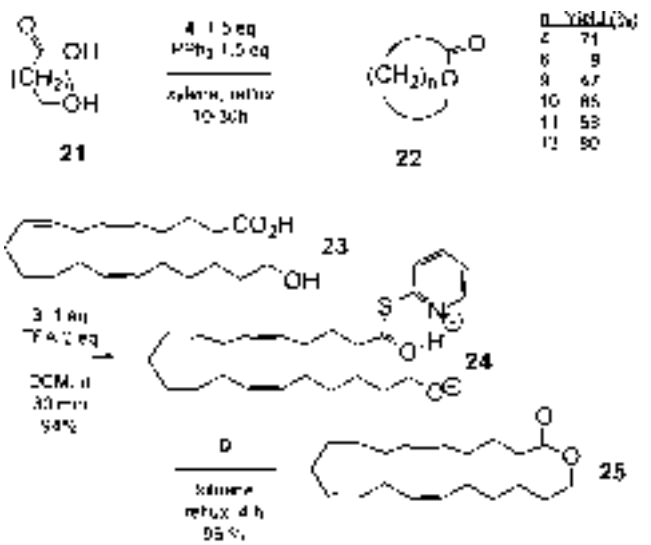


Scheme 5

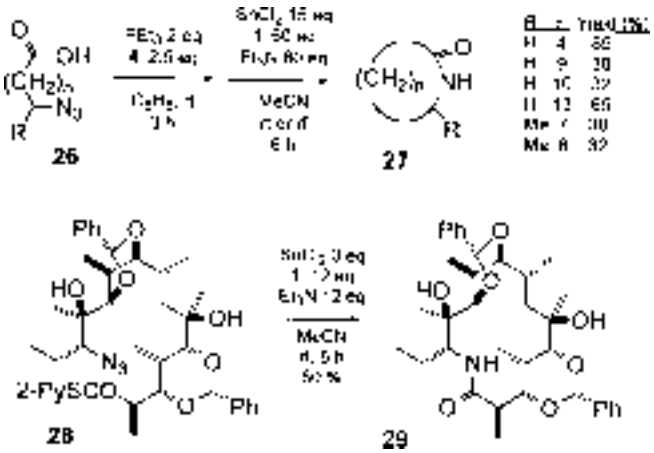
A fare more versatile application was found in the thiolysis [24] of disulfides (*e.g.* **15**), because the resulting 2-pyridyldisulfides **16** can be *N*-alkylated to *N*-alkylpyridinium disulfides **17**, shown by the late D. H. R. Barton [25] to be potent sulfenyl transferring reagents. The proreagent **16** can by generated either by thiolysis of **4** or by thiolysis of symmetrical disulfides by **1**. Alkylation was achieved with a number of electrophiles (*e.g.* Et_3OBF_4, MeOTrf), and the pyridinium salts can be used *in situ* or isolated by crystallisation. Treatment of **17** by thiols results in rapid release of the *N*-alkylated pyridine thiones and the desired asymmetrical disulfides (*e.g.* **19**, **20**), but most reactions require a base in order to be driven to completion. Pyridine was often used for the isolation of the soluble products, yet care has to be taken in case of heterocyclic thiols, as pyridine shifts the initial tautomeric equilibrium of the starting material (**1**–>**8**) and thus causes the formation of considerable amounts of side products. Therefore, a hindered base like ethyldiisopropylamine was recommended for most applications. The flexibility of the reaction allows even introduction of bulky multifunctional groups such as D-(–)-penicillamine (–>**19**) in very good yields.

3. Macrolactonization/Macrolactamization

Corey's continued interest in thioates[10] for macrolactonisations (*e.g.* **21**–> **22**) stimulated the development of the chloroformate [11] **3** and its application [26] to **23** in order to validate conformational studies on 20-hydroxy arachidonic acid. The anchimeric assistance of the pyridine activates, both the carboxyl and hydroxyl groups by proton transfer as in **24**. The combined, excellent yields for activation, cyclization and the high reaction rate (96%, < 4 h) in formation of the 21-membered lactone **25** were assigned to the predicted, antiparallel alignment as depicted for **23**, which brings the reactive ends into close proximity. However, the potential of thioates for macrolactonization is no longer unrivalled. The extremely powerful Yamaguchi cyclization gives access to most difficult lactones in excellent yields [27–29].



Scheme 6



Scheme 7

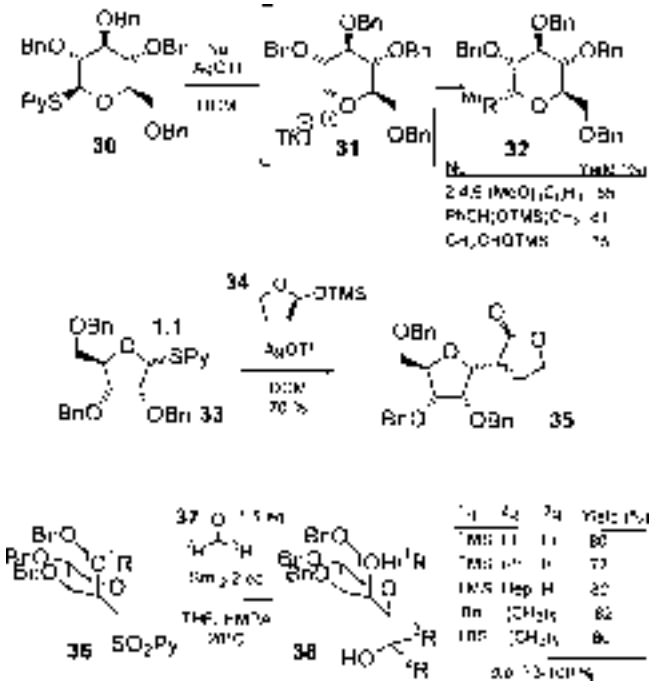
The similarly challenging 10–13 membered lactams are accessible by a tandem reduction/cyclization [30] from azido acids **26**, which furnishes even the difficult ring sizes (**27**) in 30–40% yield. This method was applied to the lactamization of an erythronolide analogue (**28** –> **29**) in 60% yield [28].

4. Anchimerically-Assisted Carbohydrate Coupling Reactions

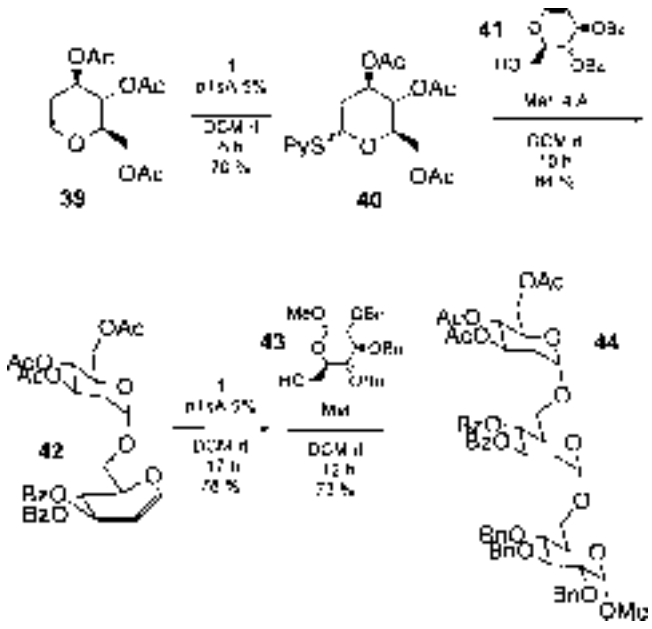
Pharmacologically active *C*-glycosides and new *C*-glycosidation reactions attract steadily increasing attention. Two developments in this area applied 2-mercaptopyridine for the activation of glycosides. The treatment of 2,3,4,6-tetrabenzyl-α–D-glucose with **4** and PPh_3 provided the β-anomer **30** [31] as a single diastereomer. Activation by silver triflate results in the formation of electrophile **31** which can be trapped by nucleophiles such as trimethoxybenzene, enol ethers and ketene acetals to give α-configurated products (**32**) in non-coordinating solvents. The β-configuration of the solvent-separated triflate ion pair is explained by the reversed anomeric effect of intermediate triflates or β-stacking of the contact ion pair and relates to the α-product upon coupling of the nucleophile. Solvent coordination (*e.g.* Et_2O) leads to the domination of β-products. Similar results were obtained for the ribofuranoside **33**, which, in spite of the initial anomeric mixture, reacted with **34** to the anomerically pure butyrolactone **35** [31]. The diastereomeric α-alkylated lactones were epimerized to a single diastereomer at a later stage of the synthesis.

2-Pyridylsulfones are substrates for the reductive samariation and subsequent coupling to carbonyl groups [32]. This was utilized in a very mild and stereospecific synthesis of 1,2-*trans*-*C*-glycosides by treatment of mannosyl, glucosyl and galactosyl 2-pyridylsulfones **36**, which are accessible from the 2-mercaptopyridines by oxidation with *m*-CPBA. Very often the metallation of the anomeric position is accompanied by β-elimination to glycals. This restricts glycoside lithiation to 2-desoxy sugars, except from deprotonated 2-hydroxy glucose [33]. On the contrary, the corresponding samarium species are rather stable towards β-elimination in spite of an 1,2-*trans*-diaxial relationship and allow the desired *Umpolung*. Some 2-hydroxy protected species are sufficiently long-lived in the presence of HMPA and can be trapped with carbonyls **37** to provide α-*C*-mannosides in high yields. However, MEM, THP or acyl protection is not tolerated. Sulfopyridyl-β-glucosides were converted into the analogous β-*C*-glucosides, but in lower yields and *exo*-anomeric diastereoselectivities. The observed anomeric selectivities for gluco (β) and mannopyranoside (α) are irrespective of the configuration of the starting material, which is advantage and limitation at the same time. This observation was assigned

to the stepwise 2 electron transfer and stabilizing p_{C1}-n_{O5} orbital interactions.



Scheme 8

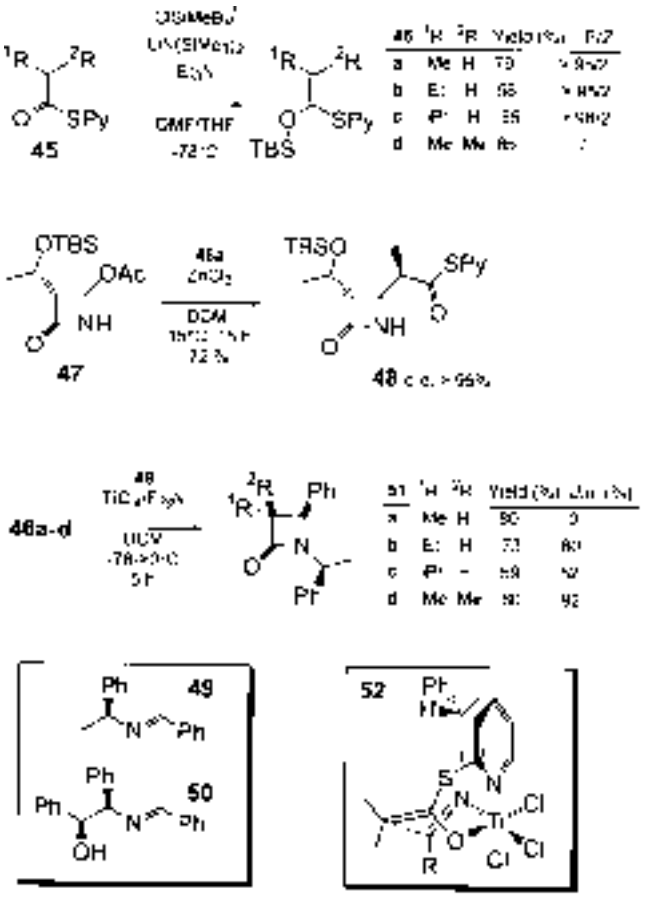


Scheme 9

Another application [34] was developed by Mereyala, who activated pyridylthioglycosides by MeI and thus obtained glycosyl donors. The thioethers were generated by acid-catalyzed addition of **1** to tri-*O*-acetyl-D-glucal (**39**) or tri-*O*-acetyl-D-galactal. Treatment with methyl iodide in the presence of the glycal acceptor **41** provided the glycal saccharide **42**, which was again treated with **1**, activated by MeI and trapped by another glycal acceptor **43**. All new connections of the α-linked trisaccharide **44** were established in high yields and good stereoselectivity.

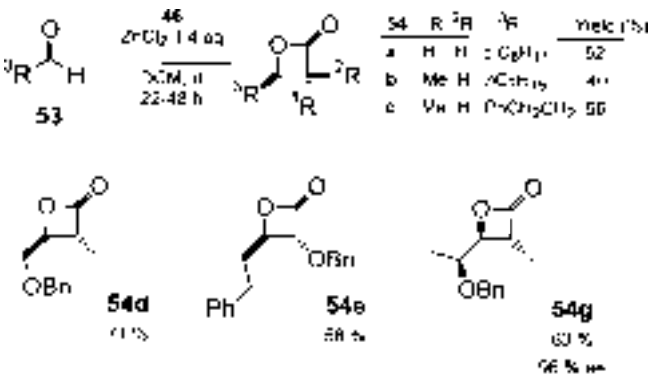
5. Tandem Processes: Mukaiyama Aldol Lactonization/Lactamisation

The enolates of 2-pyridyl thioates and their tandem Mukaiyama(aza)-aldol/condensation (TMAL) offer a one-pot synthesis of β-lactams and β-lactones. To this end, titanium [35–38], tin [38, 39] and boron [40, 41] enolates were treated with imines and ketones. Stable *E*-configurated silylketene thioacetals, prepared by reverse addition of the thioates [42] to the base, exist for R=alkyl only. α-Heterosubstituted derivatives give poorer diastereoselectivities, sometimes with predominant *Z*-configuration, yet they isomerize upon storage in chloroform to give the thermodynamically more stable products with a *d.e.* of 96% or better [37]. In all reactions, the presence of DMF (2 eq) was found to be beneficial. **46a** was coupled in an aldol reaction to the azetidinone **47** to furnish the carbapenem precursor **48** in good yield and diastereoselectivity [42]. The silylether activation and subsequent aza-aldol reaction (TMAL) is catalysed by several Lewis acids, but $TiCl_4$ and $EtAlCl_2$ provide the best yields and diastereoselectivities for a diverse set of imines [37]. After an investigation into the different diastereoselectivities of tin and titanium enolates [38], the work was extended to asymmetric induction: initially by chiral boron enolates [40, 41] and later improved by chiral imines. The necessity for selective removal limited the chiral *N*-protection to benzyl or β-hydroxy derivatives. Although the imine **50** gave the best yield and enantiomeric excess for the conversion of **46d** to the lactam **51d** (84%, *d.e.* > 96%), the cost of both enantiomers rendered **49** as the most convenient auxiliary [36]. The reaction produces up to four diastereomers, but alkyl substitution gave good *cis/trans* selectivities, and bulky substituents provided absolute stereocontrol at C-4 (the Maehr [43] convention is used to indicate relative and absolute configuration of stereocentres in **51**). Although the structure of the titanium enolate is speculative, a model for the favoured enolate was suggested: **52**, which accounts for the observed stereoselectivities and emphasises the importance of anchimeric assistance by the pyridyl nitrogen [35, 36]. A similar model was proposed for the asymmetric induction in the case of boron enolates [41].



Scheme 10

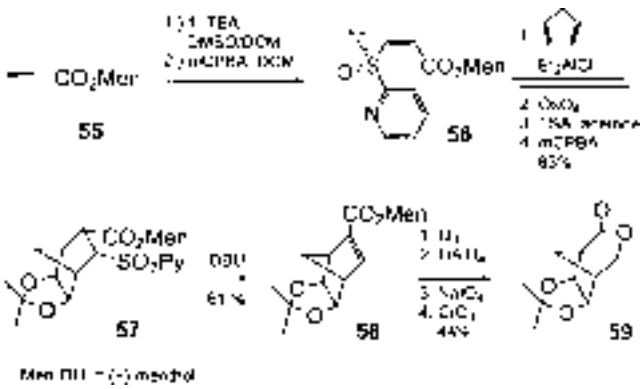
The equivalent Mukaiyama aldol-lactonization (TMAL) was reported by Romo [44, 45] recently, who condensed Hirai's ketenes to aldehydes **53**. The silylketene thioacetal **46** is activated by a Lewis acid ($ZnCl_2$) in an analogous manner. The resulting enolate reacts to form an intermediate β-hydroxy ester which gives the β-lactone **54** upon Lewis acid activation. α-Heterosubstituents lead to poorer diastereoselectivities in the lactamization, but the results are still remarkable (**54d**,**e**). A systematic evaluation [44] compared TES protection of the ketene acetals to TBS and TIPS and was found to be superior. The asymmetric induction by chiral aldehydes was utilized to prepare the enantiopure β-lactones **54g** and a large number of other chiral building blocks [45].



Scheme 11

6. Chirality Transfer

Koizumi *et al*. described [46–48] an interesting, enantioselective approach to furanosides and their carbocyclic analogues, which are key intermediates in the synthesis of nucleoside mimetics. The Michael addition of 2-mercaptopyridine to (+)-menthylpropiolate **55** and oxidation by *m*-CPBA followed by fractional crystallisation provided the diastereomerically pure sulfoxide **56** which upon activation by Et_2AlCl reacted with cyclopentadiene to give the corresponding bicyclo[2.2.1] heptane in 96% yield (*d.e.* > 96%). The additional auxiliary was required to improve the asymmetric induction in the Diels–Alder reaction. *cis*-Hydroxylation by catalytic OsO_4, acetonide formation and oxidation furnished the sulfone **57** which was treated with DBU to release the unsaturated ester **58**. Ozonolysis, reduction by $LiAlH_4$, glycol cleavage and reoxidation provided the desired lactone **59**.



Scheme 12

7. Further Applications

The application of 2-mercaptopyridine as selective reducing agent in combination with tin(II) chloride was reported for the selective, rapid conversion of nitro groups to oximes or hydroxylamines. Some other mercaptanes were reported to have higher activity [49]. The reduction of azides to amines by the same reagent was

utilized [28, 30] for macrolactamizations, but Meldal's new reduction of solid-phase bound azides by dithiols [50] avoids metal impurities and offers simpler work-up. The deprotection of sulfenamides by **1** was reported [51] for azetidinones only, therefore the general importance of this method remains to be proven.

In summary, 2-mercaptopyridine rivals and complements the Weinreb amides for C–C bond formations and competes with the Yamaguchi reagent for macrocyclizations. It is a useful reagent for carbohydrate assembly and opened a new way to β-lactams and β-lactones.

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