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A Valine-Derived Lithiated 3-Methylthiomethyl-1,3-oxazolidin-2-one for Enantioselective Nucleophilic Hydroxymethylation, Formylation, and Alkoxycarbonylation of Aldehydes

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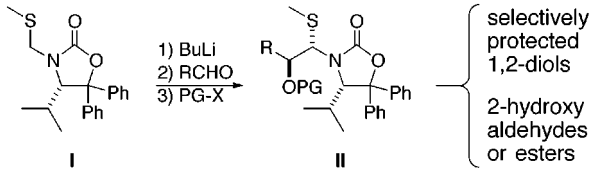
ABSTRACT



The 3-methylthiomethyl-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one (I, prepared in three steps from Boc-valine ester) is lithiated and added to aldehydes, with protecting in situ trapping of the primary adducts, to give the *N,S*-acetal derivatives II of 2-hydroxy aldehydes in high yields and diastereoselectivities. Cleavage (with ready recovery of the oxazolidinone auxiliary) is possible, to afford, for instance, enantiopure 1,2-diols, selectively protected (OBn, OMOM, OTBS) in the 2-position.

Retrosynthetic analysis of molecules as simple as 1,2-diols or 2-hydroxy aldehydes and esters reveals that organic synthesis already provides an enormous number of possible routes. If we focus on C,C bond-forming processes, of the type indicated in the formulas **A**, **B**, and **C** (Figure 1), we realize that an umpolung of reactivity[2] is required, and we still find numerous methods in the literature. Even if we narrow down our query further, to enantioselective versions with C,C bond-formation, there are more solutions than we can possibly refer to in a preliminary communication such as this.[3] If we finally request that the process involves the stoichiometric application with recycling of a chiral auxiliary, there are only a few methods left, such as the use of formaldehyde hydrazones[4] and of lithiated heterocycles (cf. the oxathianes[5] or a 2-metalated *N*-Boc-oxazolidine in the presence of sparteine[6]).

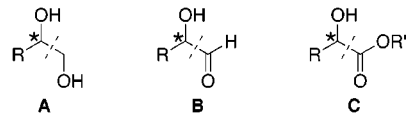


Figure 1. C,C bond-forming preparation of 1,2-difunctionalized hydroxy compounds.

(1) Part of the projected Ph.D. Thesis of C.G., ETH Zürich.

(2) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

(3) Some synthetic equivalents of chiral formyl anions used for simple carbonyl additions are deprotonated dithiane and dithiolane oxides (Scolastico, Aggarwal) or certain lithiated α-heterosubstituted vinyllithium compounds (Braun). (a) Colombo, L.; Gennari, C.; Scolastico, G.; Guanti, G.; Narisano, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1278. (b) Aggarwal, V. K.; Thomas, A.; Schade, S. *Tetrahedron* **1997**, *53*, 16213. (c) Aggarwal, V. K.; Franklin, R.; Maddock, J.; Evans, G. R.; Thomas, A.; Mahon, M. F.; Molloy, K. C.; Rice, M. J. *J. Org. Chem.* **1995**, *60*, 2174. (d) Aggarwal, V. K.; Schade, S.; Adams, H. *J. Org. Chem.* **1997**, *62*, 1139. (e) Braun, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 430. (f) Mahler, H.; Braun, M. *Chem. Ber.* **1991**, *124*, 1379.

(4) (a) Enders, D.; Bolkenius, M.; Vazquez, J.; Lassaletta, J. M.; Fernandez, R. *J. Prakt. Chem.* **1998**, *340*, 281. (b) Pareja, C.; Martin-Zamora, E.; Fernandez, R.; Lassaletta, J. M. *J. Org. Chem.* **1999**, *64*, 8846.

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We present here a preliminary account of our work on the application of an Evans auxiliary to the enantioselective preparation of products of type **A**, **B**, and **C** with formation of the central C,C bond.

When we first noticed[7] the steric hindrance to nucleophilic carbonyl addition caused by the geminal phenyl groups in oxazolidinone **1**,[7−11] it occurred to us that we might be able to directly lithiate a suitable derivative, such as methylthiomethyl-substituted compound **2**, by treatment with BuLi (Figure 2).

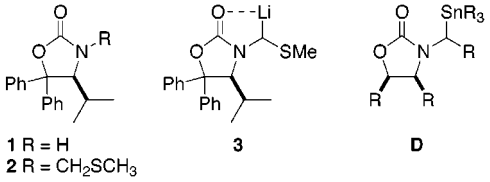
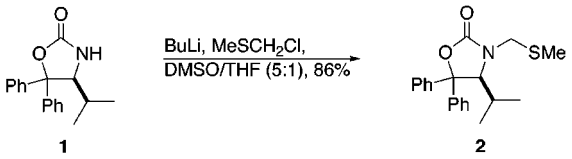


Figure 2. Oxazolidinones with nucleophilic reactivity in the 1′-position.

Li reagent **3** is indeed generated in this way,[12] and it can be trapped by electrophiles. Chiral reagents of this general type (with limited preparative usefulness) have been previously formed from tin compounds **D** by Sn/Li exchange in work by Pearson and Nakai.[13]

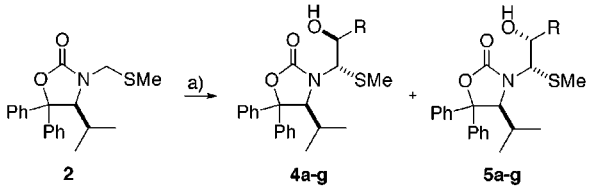
N,*S*-Acetal **2** was prepared in high yield from oxazolidinone **1** by *N*-alkylation with chloromethyl methyl sulfide (MTMCl) (Scheme 1).

Scheme 1



Treatment of **2** with BuLi in THF at −78 °C and subsequent addition of an aldehyde at −100 °C afforded adducts **4** in high yields and with good to excellent stereoselectivities (Table 1).

Table 1. Addition of *N*,*S*-Acetal **2** to Aldehydes



a) BuLi, RCHO, THF, −78 to −100 °C

			products **4**, **5**	
entry	RCHO		yield [%][a]	dr (**4**/**5**)[b]
1	C_6H_5CHO	**a**	90	93:7
2	(*p*MeO)C_6H_4CHO	**b**	92	91:9
3	furfural	**c**	90	90.5:9.5
4	3-pyridinecarboxaldehyde	**d**	72[c]	96:4[c] (84:16)[b]
5	phenylpropargyl aldehyde	**e**	80[d]	93:7
6	CH_2=CMeCHO	**f**	88	85:15
7	iC_3H_7CHO	**g**	84 (61)[d]	71:29

[a] Combined yield of both isomers after FC. [b] Determined by ^{1}H NMR (300 MHz) of the crude product. [c] Yield/dr obtained after recrystallization from MeOH. [d] Yield of the major isomer after FC.

Only two of the four possible diastereoisomers are formed. Major isomers **4** and minor isomers **5** have the same configuration at C(1′)-SMe and are epimeric at C(2′)-OH (Table 1). Lithium compound **3** adds smoothly to aromatic, heteroaromatic, and propargylic aldehydes (cf. entries 1−5) with diastereoselectivities greater than 90%, while the adducts with α,β-unsaturated aldehydes are usually formed somewhat less selectively (cf. entry 6) (products resulting from 1,4-addition are not observed). The addition of aliphatic aldehydes (cf. entry 7) is also high yielding, but the selectivities are lower. The diastereoisomeric products from aliphatic, α,β-unsaturated, and propargylic aldehydes can usually be separated by flash chromatography, with the major isomer eluting first. In the case of aromatic aldehydes, diastereoisomeric impurities are separated by recrystallization from MeOH.[14] Furthermore, simple trituration of the crude addition products in hexane affords cleanly mixtures of **4** and **5** with enhanced diastereomer ratios.

We were able to obtain suitable single crystals of several products of type **4**/**5** for the determination of the structure

(5) (a) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937. (b) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943. (c) Ko, K. Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333. (d) Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc.* **1990**, *112*, 8189.

(6) Kise, N.; Urai, T.; Yoshida, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3125.

(7) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093.

(8) See also independent work with this oxazolidinone by two other groups: (a) Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387. (b) Gibson, C. L.; Gillon, K.; Cook, S. *Tetrahedron Lett.* **1998**, *39*, 6733.

(9) Oxazolidinone **1** and its enantiomer are commercially available as (*S*)- and (*R*)-DIOZ: Shiratori Pharmaceutical Co., Ltd., Japan. Isobe, T.; Fukuda, K. Japanese Patent JP 09143173, 1995; *Chem. Abstr.* **1997**, *127*, 50635.

(10) For a recent application in the synthesis of γ-amino acid derivatives, see: Brenner, M.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 2365.

(11) For reagents generated from carbonyl compounds with *sterically protected but electronically effective C=O groups*, see for instance: (a) Ertas, M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 961. (b) Lubosch, W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102. (c) Schlecker, R.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1459. (d) Seebach, D.; Lubosch, W.; Enders, D. *Chem. Ber.* **1976**, *109*, 1309.

(12) The structure of **3** is drawn arbitrarily; the configuration of the lithiated carbon is unknown. Cf. the X-ray crystal structure of a 1-bromomagnesio-2-pivaloyltetrahydroisoquinoline: Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1.

(13) (a) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622 and earlier references therein. (b) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Synlett* **1998**, 1147. (c) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Tetrahedron Lett.* **2000**, *41*, 345.

(14) All compounds were fully characterized by physical and chemical data.

by X-ray crystallography. Thus, the X-ray crystal structure of the major furfural adduct **4c** is shown in Figure 3.

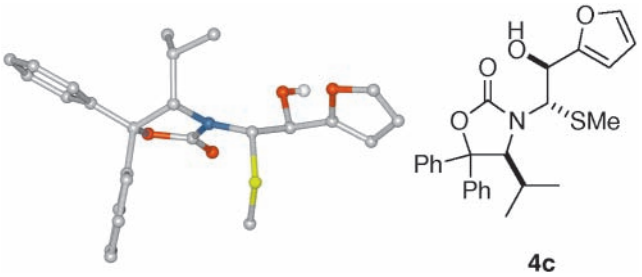


Figure 3. X-ray crystal structure of addition product **4c**. N: blue. O: red. S: yellow.

Referring to the two newly created stereocenters, **4c** has (*S*,*S*)- or *l*-configuration. Hence, the new C,C bond is formed with the relative topicity *ul*. X-ray crystal structure analysis of several other aldehyde adducts revealed the same stereochemical course for the formation of the major isomer (C(2′)H usually at higher field in the ^{1}H NMR spectra).

On the basis of the data obtained by X-ray crystallography, a model for the stereochemical outcome of the reaction may be suggested (Figure 4).[15] The intermediate organolithium

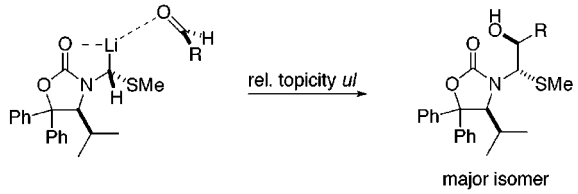
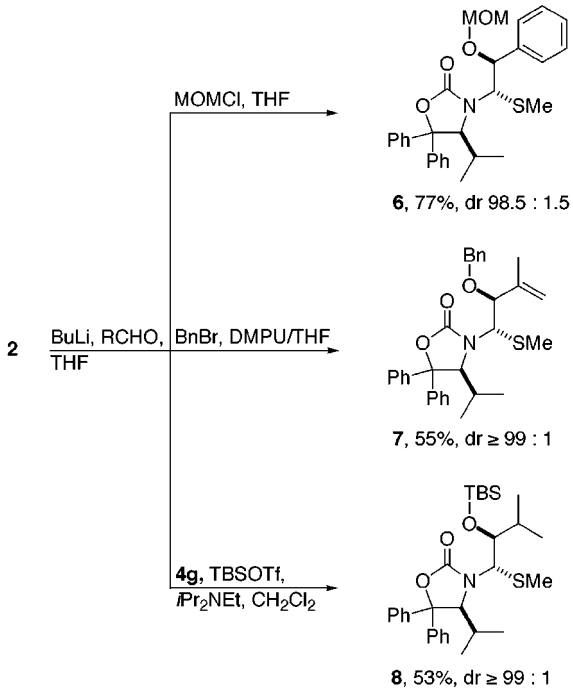


Figure 4. Model for the stereochemical course of the addition reaction (cf. refs 12 and 13b).

species may have a defined five-membered ring chelate structure,[12] with the *i*Pr and the MeS substituents on opposite sides of the bicyclic ring system. In the formation of the major product, the aldehyde would then approach the C−Li bond on its *Re* face to avoid steric repulsion between the R and the MeS groups.

To extend the scope of the reaction, the in situ OH protection of the addition products was examined (Scheme 2). Consecutive addition of benzaldehyde and chloromethyl

Scheme 2



methyl ether (MOMCl) to a solution of compound **3** afforded MOM-protected benzaldehyde adduct **6** in 77% yield (dr 98.5:1.5).[16]

Similarly, the initially formed methacrolein adduct reacted in situ with BnBr to give **7** in 55% yield (dr ≥99:1). However, the use of *N*,*N*′-dimethylpropyleneurea (DMPU) as a cosolvent is necessary for an efficient introduction of the benzyl protecting group. In the case of isobutyraldehyde, we were unable to perform the addition reaction and the protecting step (with MOMCl, BnBr, and AcCl) in a one-pot procedure. Therefore, the major isobutyraldehyde adduct **4g** was first isolated and then treated with *tert*-butyldimethylsilyl triflate (TBSOTf) in CH_2Cl_2 to afford **8** in 53% overall yield (dr ≥99:1) from sulfur compound **2**.

With compounds **6**−**8** in hand, the hydrolysis of the *N*,*S*-acetals was envisaged. Several desulfurization reagents such

(15) This model is consistent with observations made by Pearson and Nakai (cf. ref 13).

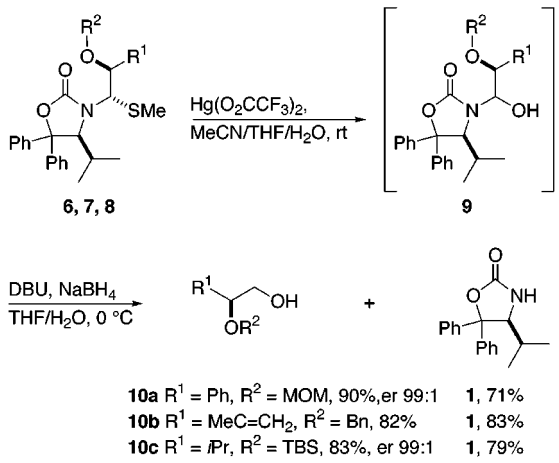
(16) **Representative experimental procedure:** To a solution of *N*,*S*-acetal **2** (500 mg, 1.46 mmol) in THF (8 mL) was added BuLi (1.20 mL, 1.76 mmol) at −78 °C. After stirring for 15 min, the reaction mixture was cooled to −100 °C and freshly distilled benzaldehyde (192 μL, 1.90 mmol) was added dropwise. The mixture was allowed to warm to −78 °C within 20 min and then MOMCl (189 μL, 2.49 mmol) was added. After stirring for 4 h at rt, the white precipitate developing in the course of the reaction was dissolved in CH_2Cl_2 and the reaction was quenched with a saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was triturated (boiling hexane, 2 × 5 mL) and recrystallized (MeOH/CH_2Cl_2) to give **6** (557 mg, 77%) as a 98.5:1.5 mixture with its C(2′)-OH epimer.

(17) For oxazolidinone-based hemiaminals, see: Bach, J.; Bull, S. D.; Davies, S. G.; Nicholson, A. D. *Tetrahedron Lett.* **1999**, *40*, 6677.

(18) **Representative experimental procedure:** To a suspension of benzaldehyde adduct **6** (450 mg, 0.915 mmol) in MeCN (3 mL), THF (3 mL), and H_2O (1.5 mL) was added $Hg(O_2CCF_3)_2$ (430 mg, 1.01 mmol) at rt. After stirring for 5 min, the obtained clear solution was diluted with H_2O and Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (white solid) was dissolved in THF (5 mL), and H_2O (1.25 mL), $NaBH_4$ (26 mg, 0.686 mmol), and DBU (69 μL, 0.458 mmol) were added consecutively at 0 °C. Auxiliary **1** precipitated in the course of the reaction. After stirring for 15 min, a saturated aqueous NH_4Cl solution was added and the precipitate was filtered off. The precipitate was washed with saturated aqueous NH_4Cl solution and Et_2O and dried under high vacuum to yield **1** (184 mg, 71%) as a white solid. The filtrate was diluted with Et_2O, the organic layer

as $HgCl_2$, $AgNO_3$, $CuCl_2$, NBS, MeI, or bis(trifluoroacetoxy)-iodobenzene were tested, but all of them led to either complex product mixtures or to no reaction at all. To our surprise, treatment of the *N*,*S*-acetals **6**−**8** with $Hg(O_2CCF_3)_2$ in MeCN/THF/H_2O (2:2:1) at rt gave the corresponding hemiaminals **9** (Scheme 3) within 5 min. Since these

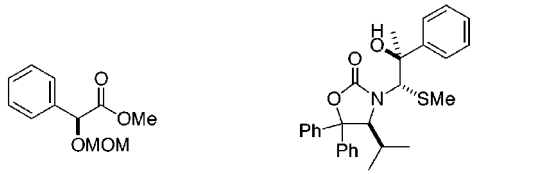
Scheme 3



hemiaminals were rather sensitive to decomposition, they were used without purification for further transformations.[17] NMR experiments in $CDCl_3$ provided evidence that hemiaminals **9** collapse instantaneously to the corresponding 2-hydroxy aldehyde and oxazolidinone **1** upon addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). As chiral 2-hydroxy aldehydes are fairly susceptible to racemization, it is desirable to convert them in situ into chemically stable target products such as 1,2-diols. Consequently, crude hemiaminals **9** were dissolved in THF/H_2O (4:1) and were treated consecutively with $NaBH_4$ and DBU at 0 °C (Scheme 3). The resulting selectively protected 1,2-diols **10** were isolated in 82−90% yield.[18] The enantiopurities of **10a** and **10c** were determined by GC (Supelco γ-Dex 120), indicating that no detectable racemization had occurred during the reduction. Oxazolidinone **1** precipitated in the course of the reaction and was recovered in 71−83% yield by simple filtration, washing, and drying.

In conclusion, we have demonstrated that lithiated *N*,*S*-acetal **3** undergoes diastereoselective addition reactions to various types of aldehydes. Hydrolysis of the addition products affords enantiomerically pure 2-hydroxy aldehydes which are reduced in situ to selectively protected 1,2-diols.

Recovery of chiral auxiliary **1** is easy and proceeds in high yields. Experiments to trap the 2-hydroxy aldehydes with C-nucleophiles, such as Grignard or Wittig reagents, or to oxidize to 2-hydroxy carboxylic acid derivatives (cf. **11**), are currently underway (Figure 5); also, preliminary results



11 (62% from **6**) **12** (56% from **2** and acetophenone)

Figure 5. An ester obtained (PCC) from a hemiaminal of type **9** and an adduct of **2** to a ketone.

indicate that addition to ketones (see **12**) is possible (Figure 5). Thus, the method described here provides access to selectively protected 1,2-diols, 2-hydroxy aldehydes (or compounds derived thereof), and 2-hydroxy esters.

Acknowledgment. We thank P. Seiler for determination of the X-ray crystal structure of compound **4c**. We are also grateful to Novartis Pharma AG for donation of 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one and for continuing financial support.

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was separated, and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography, eluting with pentane/AcOEt (4:1), afforded **10a** (151 mg, 90%) as a colorless oil.