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Diastereoselective reactions of enolates

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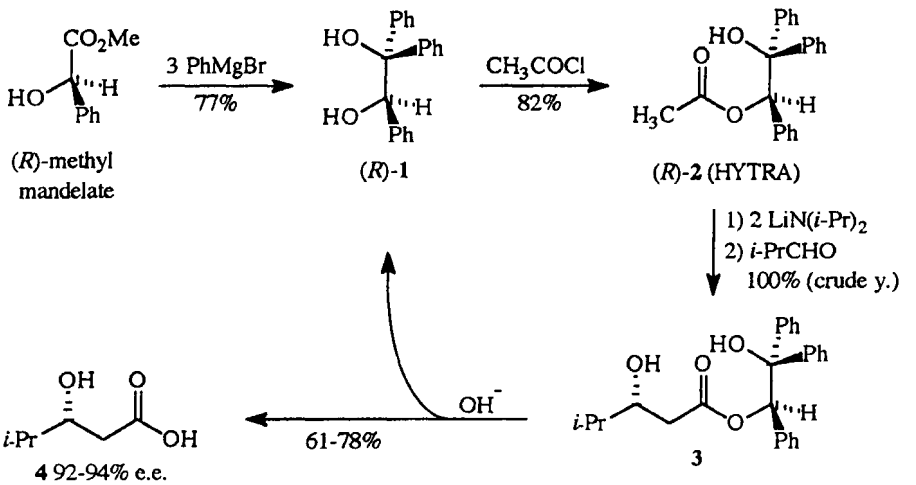
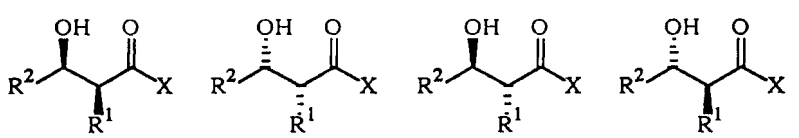
Abstract: Triphenylglycol-derived esters **2** and **8a** have been applied in asymmetric aldol reactions. The homochiral propionates **7** and **8a,b** react with imines in a stereodivergent manner: Doubly deprotonated **7** delivers *anti*-β-lactams **14** whereas the lithium enolates of **8a/b** afford *cis*-β-lactams **15** in 87-97% e.e. Diastereoselective carbon silylation occurs when deprotonated **8a** is treated with chlorotrimethylsilane. Approaches towards the construction of quaternary carbon centers are based on diastereoselective carboxalkylations of enolates with menthylchloroformate **17** and on a novel tandem reaction (**16** → **20**).

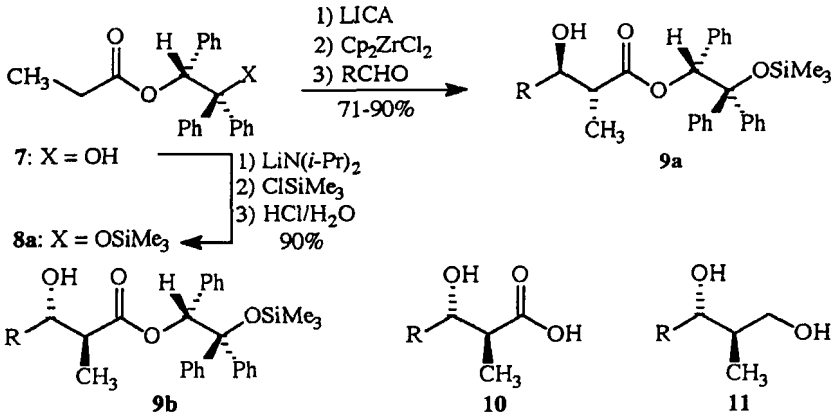
The generation of preformed enolates discovered three decades ago turned out to be extremely fruitful with respect to the formation of carbon-carbon bonds in a diastereoselective and/or enantioselective manner (1). Thus, the versatility of the aldol reaction has been enhanced substantially due to preformed enolates (2).
A couple of years ago, we reported on (*R*)- and (*S*)-2-hydroxy-1,2,2-triphenylethyl acetate **2** ("HYTRA"), a chiral reagent which offers a solution for the long-standing problem of the stereoselective aldol addition of α-unsubstituted enolates (3). HYTRA **2** is readily available from mandelic acid via triphenylglycol **1**. As shown in the illustrative procedure given below the crude mixture of adducts (**3**: predominant diastereomer) delivers β-hydroxycarboxylic acid **4** upon alkaline hydrolysis. Thereby, the chiral auxiliary reagent **1** is recovered and can be reused (4). The HYTRA-aldol method has been widely applied in syntheses of natural products and drugs (5).



Whereas both enantiomers of *syn*-aldols **5** and *ent*-**5** are available by several excellent procedures (2) the controlled and predictable preparation of *anti*-aldols **6** and *ent*-**6** was a "problem child" of stereoselective synthesis, and solutions haven't been uncovered until very recently. Guided by the fact that triphenylglycol **1** is an extremely easily available reagent, we tried to apply triphenylglycol-derived propionates **7** in order to bring about *anti*-selective aldol additions which are diastereofacially selective as well.



Thus, triphenylglycol **1** is esterified to give the propionate **7** (96%) which is converterd into the *O*-silyl-protected ester **8** by one pot deprotonation, silylation, and subsequent acidic hydrolysis. When **8** is deprotonated with lithium isopropylcyclohexylamide (LICA) transmetalated by the addition of dichloro-cyclopentadienyl-zirconium, and finally treated with aldehydes, the predominant formation of *anti*-adducts **9a** results. The *anti*:*syn*-ratios lie between 88 : 12 and 98 : 2. High diastereofacial selectivity is reached as well: diastereomeric ratios of **9a** : **9b** range from 95 : 5 to > 98 : 2. Alkaline hydrolysis of the esters **9** provides carboxylic acids (e. g. **10**, R = Ph in 96% e.e.). On the other hand, reduction with $LiAlH_4$ affords diols **11** (R = *i*-Pr, *t*-Bu) in enantiomeric excesses of > 96% e.e. (6a).



The X-ray structure analysis of **8** (6b), shown in Fig. 1, reveals a remarkably long carbon-carbon distance (1.56 Å) of the triphenylethane moiety (C4-C5). This is explained by the accumulation of sterically demanding substituents at vicinal carbon atoms, and one may assume that the bulkiness of the diphenyl-trimethylsiloxy-methane unit plays an important role with respect to the stereoselecivity which is reached in aldol additions of the corresponding zirconium enolate.

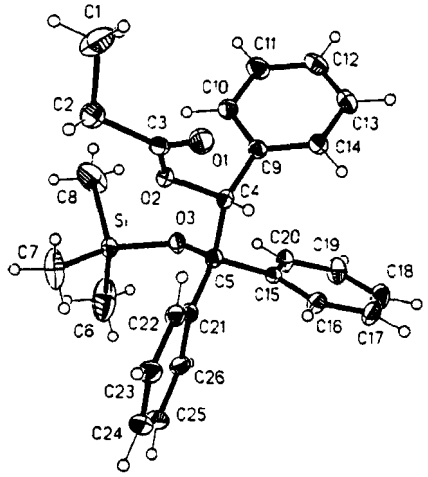


Fig. 1: X-Ray Structure of **8a**

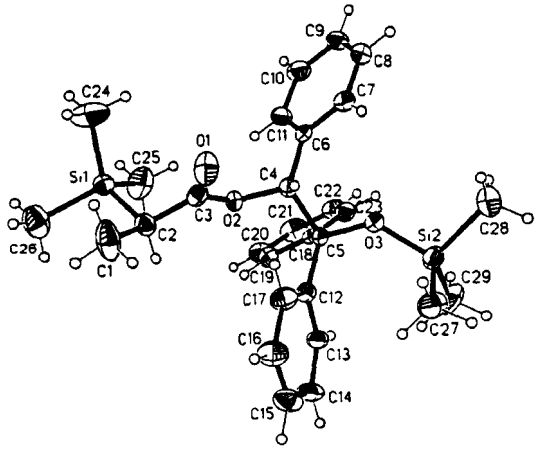
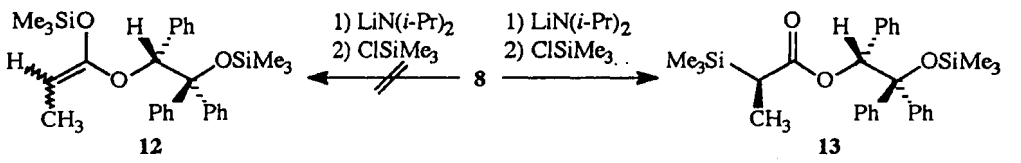


Fig. 2: X-Ray Structure of **13**

The following unexpected reaction might be caused by the sterical demand of the alcoholic moiety of the ester **8a**: When the propionate **8a** is deprotonated and the enolate formed thereby is treated with chlorotrimethylsilane, the formation of the silylketene acetal **12** has been anticipated. However, the α-carbon atom, obviously the most accessible nucleophilic center of the enolate, is silylated rather than the oxygen atom so that the α-silyl ester **13** is obtained. This carbon silylation reaction occurs with remarkable diastereoselectivity (diastereomeric ratio: 94.5 : 5.5). The configuration of the major diasteromer **13** is proven by the X-ray structure analysis shown in Fig. 2 (6b).



The esters **7** and **8a,b**, although homochiral, give rise to a different stereochemical outcome in the reaction with N-protected imines which leads to the formation of β-lactams. Thus, *trans*-β-lactams **14** are obtained in the condensation of imines with doubly deprotonated ester **7** whereas *cis*-azetidinones **15** are formed predominantly when the enolates of propionates **8a/b** are allowed to react with imines. The chiral auxiliary group is cleaved in situ. Remarkable enantioselectivities of both *trans* and *cis*-β-lactams are reached (Table 1).

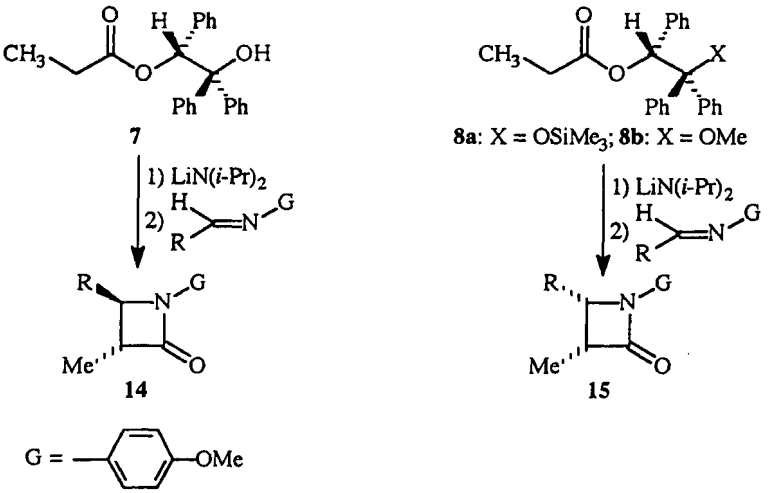
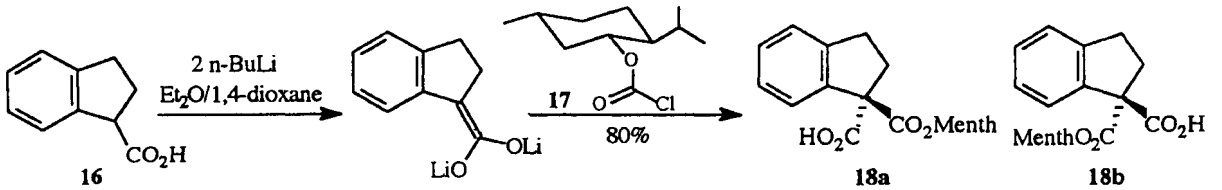


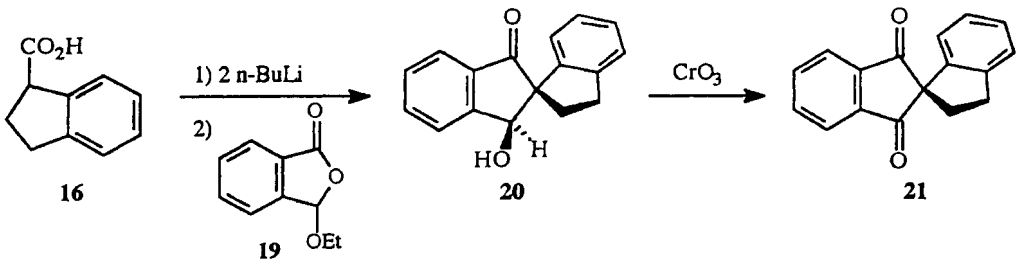
Table 1. β-Lactams **14** and **15** by condensation of esters **7** and **8a, b** with imines

R	Ester	*trans*-**14** : *cis*-**15**	e.e.	Yield
Phenyl	7	94 : 6	>97%	83
2-Furyl	7	96.5 : 3.5	>97%	85
Phenyl	**8a**	3.5 : 96.5	87%	82
2-Furyl	**8b**	9 : 91	>97%	87

Another strategy for the stereoselective formation of carbon-carbon bonds relies on the reaction of prochiral enolates with chiral electrophiles. This concept has been used by us for the generation of stereogenic quaternary carbon centers, when we became interested in studies directed towards a synthesis of Fredericamycin A (7). To give an example, doubly deprotonated indanecarboxylic acid **16** reacts in a diastereoselective carboxalkylation reaction to give predominantly the acid **18a** when treated with the commercially available chloroformate **17** derived from (-)-menthol. The diasteromeric ratio of **18a** : **18b** amounts 9 : 1. However, higher diastereoselectivities can be obtained when either ester or ketone enolates are used or when the chiral reagent **17** is substituted by the corresponding chloroformate derived from 8-phenylmenthol (8).



In another approch for the synthesis of the core skeleton **21** of Fredericamycin A, a surprizing tandem reaction has been found: When the dianion of **16** is treated with ethoxyphthalide **19** the spirocompound **20** forms diastereoselectively in one pot. Subsequent oxidation affords the diketone **21**.



16 **19** **20** **21**

A rationale for the formation of **20** is given by a tandem reaction which consists of a Claisen, decarboxylation and aldol sequence.

References

(1) C. H. Heathcock in *Modern Synthetic Methods 1992* (Ed.; R. Scheffold), Verlag Helvetica Chimica Acta, Basel; VCH, Weinheim **1992**, p. 1.

(2) D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **13**, 1 (1982); C. H. Heathcock in *Comprehensive Organic Syntheses* (Ed.: B. M. Trost), Pergamon Press, Oxford, **1993**, vol. 2, chapter 1.6; M. Braun in *Advances in Carbanion Chemistry* (Ed.: V. Snieckus), JAI Press, Greenwich, CT, USA **1992**, vol. 1, p. 177.

(3) M. Braun, *Angew. Chem. Int. Ed. Engl.* **26**, 24 (1987).

(4) M. Braun, S. Gräf, S. Herzog, *Org. Synth.* **72**, 32 (1993); M. Braun, S. Gräf, *Org. Synth.* **72**, 38 (1993).

(5) M. Braun, H. Sacha, *J. Prakt. Chem.* **335**, 653 (1993); and references given therein.

(6) (a) M. Braun, H. Sacha, *Angew. Chem. Int. Ed. Engl.* **30**, 1318 (1991). (b) H. Sacha, D. Waldmüller, M. Braun, *Chem. Ber.* **127** 1959 (1994).

(7) R. Misra, R. C. Pandey, B. D. Hilton, R. P. Roller, V. Silverton, *J. Antibiot.* **40**, 786 (1987).

(8) W. Trypke, A. Steigel, M. Braun, *Synlett* **1992**, 827.