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Highly Diastereoselective Aldol Reaction of Benzaldehyde Derivatives Having a Chiral Ortho Substituent with Silylated Carbon Nucleophiles

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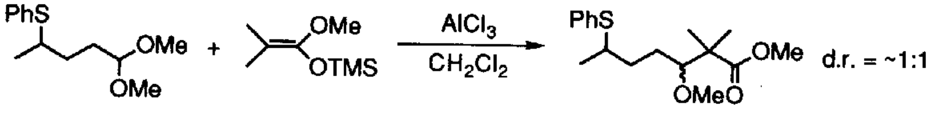
Abstract: 2-[1-(Mesitylthio)alkyl]benzaldehyde dimethyl acetals react with silylated carbon nucleophiles under Lewis acidic conditions to give the corresponding aldol adducts with high diastereoselectivity. This is the first example of such a highly diastereoselective reaction by 1,4-remote asymmetric induction through the ortho positions of a benzene ring.

A sulfenyl group is well known to participate and stabilize the carbocation at the β-position to form an episulfonium ion.[1] We have already reported a regioselective pinacol rearrangement and a reaction of allylic acetate with silylated carbon nucleophiles based upon this phenomenon.[2,3] A sulfenyl group can also participate the carbocation at the δ-position to give a five-membered cyclic sulfonium ion.[4] In this paper we report on the highly diastereoselective aldol reaction of benzaldehyde derivatives having a chiral ortho substituent by means of 1,4-remote asymmetric induction through the ortho positions of a benzene ring, which is caused by the neighboring participation of an arylthio group.

There are a number of reports concerning the stereoselective aldol reactions of acetals, especially focusing attention on *syn/anti* selectivity.[5] However, only a few groups have reported on the 1,2-asymmetric induction in aldol reactions.[6,7] For example, we have presented the highly *anti*-Cram selective aldol reaction of α-sulfenyl acetals with silylated carbon nucleophiles under Lewis acidic conditions.[7] In this reaction, the sulfenyl group plays a major role for determining diastereoselectivity. Then, we next tried the reaction of γ-sulfenyl acetal **1** with a ketene silyl acetal in the presence of a Lewis acid in expectation of 1,4-asymmetric induction through a five-membered cyclic sulfonium ion. But, contrary to our expectation, the aldol product obtained was a nearly 1:1 mixture of the diastereomers (Scheme 1).[8] This result would be attributed to 1) the five-membered cyclic sulfonium ion intermediate is difficult to be formed, or 2) if it can be formed, its conformational flexibility causes the non-stereoselective manner of the reaction. On the basis of these considerations, in order to generate a cyclic sulfonium ion easily and to make its conformation rigid, we chose benzo-substituted derivatives of **1**, namely



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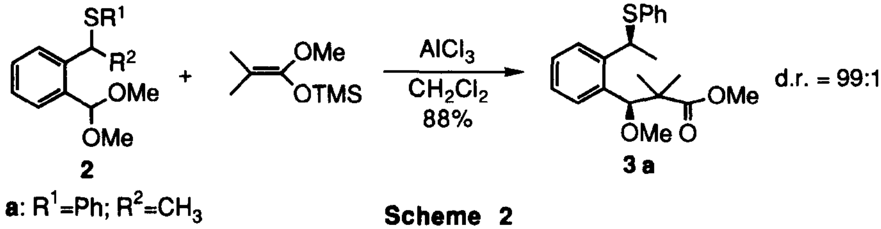
Scheme 1

2-(1-sulfenylalkyl)benzaldehyde dimethyl acetals **2** as substrates for the aldol reaction.

First of all, the reaction of 2-[1-(phenylthio)ethyl]benzaldehyde dimethyl acetal **2a** with ketene silyl acetal of methyl isobutylate was attempted in the presence of aluminium chloride. The reaction gave the corresponding aldol adduct **3a** in 88% yield with a satisfactory diastereomer ratio of 99:1 (Scheme 2).[9]



Scheme 2

A similar reaction of **2a** with silyl enol ether of pinacolone was tried, but the diastereomer ratio of the product obtained was not so good (72:28). Then, the reaction conditions, such as solvent, Lewis acid, and temperature were optimized using this combination of reactants. As a result, the best result was realized, when the reaction was carried out in dichloromethane using an equimolar amount of aluminium chloride or titanium(IV) chloride at -78 ℃-room temperature (gradually raised up). In addition to the external reaction conditions, the diastereoselectivity largely depended on the sulfenyl group in substrate **2**. Among several alkylthio and arylthio groups tested, arylthio groups highly participated in the 1,4-induction to give satisfactory results. Moreover, the diastereoselectivity was improved with the increase of electron donative character of the sulfenyl group (Table 1, Entries 1-3), and the mesitylthio derivative **2c**[10] turned out to give the best result. By using mesitylthio as a sulfenyl group and under the optimized reaction conditions, the aldol reaction with various silylated carbon nucleophiles was carried out. The results are summarized in Table 1.

Except for the reaction with trimethylsilyl cyanide (Entry 6), only one of the diastereomers was detectable by NMR and GC analyses. The reaction with silyl enol ether of cyclohexanone was best performed by using aluminium chloride (Entry 8); when titanium(IV) chloride was used, the elimination reaction of methanol from the adduct proceeded and lowered the yield of the aldol product. The stereochemistry of the selected major diastereomers was determined by X-ray crystallography.[9]

The representative reaction procedure is as follows: To a mixture of **2c** (21.2 mg, 0.0532 mmol) and 3,3-dimethyl-2-trimethylsilyloxy-1-butene (11.3 mg, 0.0657 mmol) in 5 ml of dry dichloromethane was added a dichloromethane solution of titanium(IV) chloride (1.13 mol·l^{-1}, 0.06 ml) at -78 ℃ under an argon atmosphere, and the reaction mixture was stirred for one hour at that temperature. Then, the mixture was allowed to warm to room temperature and stirred for one hour. After an aqueous work up, the organic materials were extracted with dichloromethane (2 × 10 ml). The combined organic layers were dried, concentrated under reduced pressure, and purified by silica-gel thin layer chromatography (eluent: ethyl acetate/hexane = 1/6) to give 1-[2-[1-(mesitylthio)ethyl]phenyl]-1-methoxy-4,4-dimethylpentan-3-one (24.5 mg, 96%). The 270 MHz ^{1}H NMR spectral and capillary gas chromatographic analyses showed a diastereomer ratio of >99:1 (the minor diastereomer was not detected).

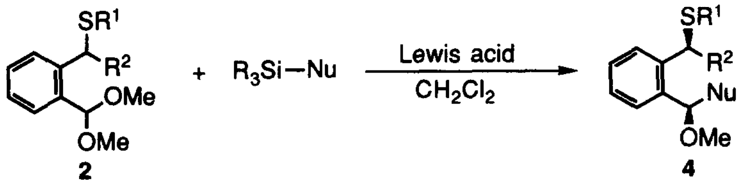
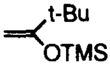
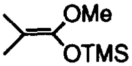
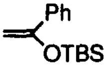
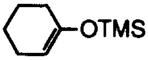
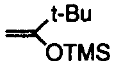
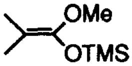
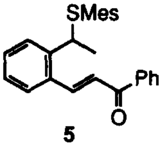


Table 1. Reactions of **2** with silylated carbon nucleophiles

Entry	R^1	R^2		Nu	Lewis acid	reaction time / h	yield / %	diastereomer ratio
1	Ph	CH$_3$	**2a**		TiCl$_4$	2	85	72 : 28
2	4-MeC$_6$H$_4$		**2b**			2	50	85 : 15
3	2,4,6-Me$_3$C$_6$H$_2$		**2c**			2	96	>99 : 1
4						1	79	>99 : 1
5					AlCl$_3$	1	92	>99 : 1
6				TMSCN	TiCl$_4$	2	91	89 : 11
7						3	57 [a)]	>99 : 1
8					AlCl$_3$	2	81	>99 [b)] : 1
9		C$_2$H$_5$	**2d**		TiCl$_4$	2	90	>99 : 1
10						1	86	>99 : 1

a) Chalcone derivative **5** was obtained in 29% yield.
b) *Syn* : *anti* = 83 : 17.



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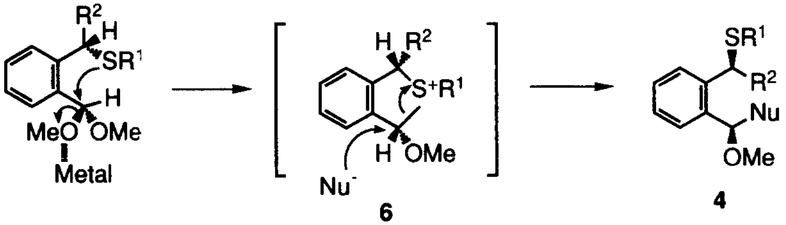
Two experimental results suggest the intermediacy of a cyclic sulfonium ion, although it was not detected by any analytical methods: 1) When substrates having a phenyl or benzyloxy group instead of an arylthio group were submitted for the reaction under the same conditions, almost completely 1:1 mixtures of diastereomers were obtained. This striking difference indicates indispensability of the sulfenyl group for the diastereoselection, of which the origin is apparently not only a simple steric reason. 2) As mentioned above, the diastereomer ratio drastically changed, depending on the substituent on the sulfur atom. The successful results for the substrates with an electron donative sulfenyl group would imply nucleophilic participation of the sulfur atom toward the cationic center. A possible reaction mechanism is illustrated in Scheme 3. The lone pair of the sulfenyl group assists the elimination of an alkoxy group to form 1,3-*cis*-cyclic sulfonium ion **6** by an intramolecular S_N2 mechanism. A nucleophile attacks this sulfonium ion from the back side of the sulfur atom to occur S_N2 inversion again, and consequently diastereomer **4** is obtained selectively.

Detailed mechanism and extension of this type of 1,4-induction are now under investigation in our laboratory.



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Scheme 3

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8. It is known that γ-Alkoxy acetals having bulky acetal groups react with nucleophiles under Lewis acidic conditions to give the corresponding aldol adducts with high diastereoselectivity. Molander, G. A.; Haar, Jr., J. P. *J. Am. Chem. Soc.* **1993**, *115*, 40.
9. The stereochemistries of **3a** and the product of Entry 3 in Table 1 were unambiguously determined by the single crystal X-ray structural analyses of the corresponding sulfone and sulfoxide, respectively.
10. This compound was synthesized from 1-(2-chlorophenyl)ethanol as follows: Mesylation and subsequent nucleophilic displacement by mesitylene thiol gave the corresponding 1-(2-chlorophenyl)ethyl sulfide. Formylation *via* the Grignard compound, followed by acetalization, gave **2c** in 52% yield.

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