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Lewis Acid-Mediated Acetal Substitution Reactions: Mechanism and Application to Asymmetric Catalysis

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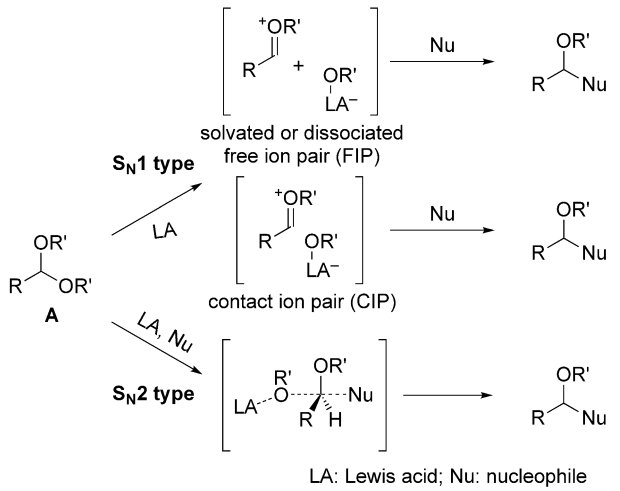
Abstract: Substitution reactions of acetals with carbon nucleophiles are fundamental and conventional organic reactions. We succeeded in the preparation of an optically active acetal, which reacted with a silyl enol ether smoothly to afford the desired adducts in racemic forms. By comparison of the *ee*s of the products with the *ee*s of the recovered acetals, we concluded that the aldol-type reactions proceeded not *via* direct displacement (S_N2) or contact ion pairs (intimate ion pair) (S_N1) but by a free oxocarbenium ion (S_N1) mechanism. Next, a study to achieve asymmetric catalysis of the acetal substitution reactions was conducted. After many trials, it was found that a chiral niobium complex prepared from pentamethoxyniobium [$Nb(OMe)_5$] and a tetradentate BINOL derivative could achieve high enantioselectivities. Asymmetric aldol-type reactions of acetals with silyl enol ethers proceeded smoothly to afford the corresponding aldol-type adducts in good yields with high enantioselectivities.

Keywords: acetals; asymmetric catalysis; contact ion pair; Lewis acids; niobium; oxocarbenium ions

Substitution reactions of acetals with carbon nucleophiles are powerful methods for carbon-carbon bond formation, providing functionalized ether compounds. In general, acetals are protecting groups of carbonyls under neutral and basic conditions, whereas they are decomposed (deprotected) to provide the parent carbonyl compounds under acidic conditions. However, under appropriate acidic conditions, substitution reactions of acetals occur. For example, aldol-type reactions of acetals with silyl enol ethers in the presence of titanium(IV) chloride ($TiCl_4$),[1] boron trifluoride (BF_3)[2] or trimethylsilyl triflate (Me_3SiOTf)[3] take place to afford the corresponding aldol-type adducts in high yields. These reactions are recognized as being among the most useful carbon-carbon bond-forming reactions, and have been applied to medicinal chemistry and natural product synthesis. Other substitution reactions of acetals have also been developed.[4,5]

In the acetal substitution reactions, there are two possible mechanisms; direct displacement (S_N2) and oxocarbenium ion (S_N1) mechanisms. The S_N1 mechanism involves a contact ion pair (CIP) (intimate ion pair) mechanism and a solvated or dissociated free ion pair (FIP) mechanism (Scheme 1).[6] Denmark,[7] Bartlett and Heathcock,[8] and Sammakia[9] studied the mechanism of acetal substitution reactions independently. While their model systems to investigate the mechanism were different, another aspect is that they often used *cyclic acetals* to investigate the mech-



Scheme 1. Two possible mechanisms of acetal substitution reactions.

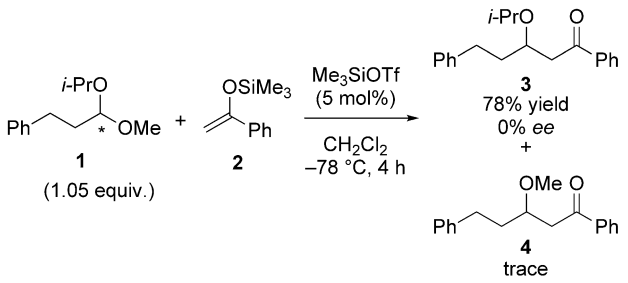
anism, and it might be difficult to exclude the neighboring effect of the tethered oxygen atoms with Lewis acids in an intramolecular fashion. More recently, Davies investigated the mechanism of the nucleophilic substitution of benzaldehyde *acyclic simple alkyl acetals* with Me_2CuLi in the presence of $BF_3{\cdot}OEt_2$, concluding that the mechanism involved both S_N1 solvated or dissociated FIP and CIP or S_N2 pathways.[10] While the results are critical, acetal substrates are limited to benzaldehyde acetals, where nucleophilic substitution occurs at benzylic positions.[11]

On the other hand, desymmetrization of acetal **A** could provide optically active ethers. While the use of a catalytic amount of a chiral Lewis acid is the most efficient, to the best of our knowledge no successful examples of chiral Lewis acid-catalyzed substitution reactions of acyclic acetals have been reported. We thought that this was related to the mechanism. If the mechanism is S_N2 or involves the S_N1 CIP, a standard method of desymmetrization using a chiral Lewis acid may be possible. On the other hand, if the mechanism involves the S_N1 solvated or dissociated FIP, control of the newly created stereogenic centers might be difficult because solvated or dissociated free chiral oxocarbenium ion/counter anion pairs must be controlled, and successful examples of such a process are rare.[12]

We focused on substituion reactions of *acyclic simple alkyl acetals*. We thought that *simple alkyl acetal*s were more appropriate for investigating the mechanism of acetal substitution reactions, because effects of alkyl groups (sometimes with chiral moieties) could be minimized. We assumed that the Lewis acid-mediated reaction of *enantiomerically pure chiral acyclic acetals* with nucleophiles could provide us with valuable information on the reaction mechanism.[10] The obtained information would be very simple; if the reaction proceeds *via* the S_N1 solvated or dissociated FIP mechanism, the product should be a racemate, and if the reaction proceeds *via* the S_N2 mechanism or the S_N1 CIP mechanism, the product should retain an enantiomeric excess (*ee*).

We synthesized chiral acetal **1** derived from 3-phenylpropionaldehyde, which was purified by preparative HPLC with a chiral column (DAICEL CHIRALCEL OD-H) to afford an optically pure form (>99% *ee*). The aldol-type reaction of **1** with silicon enolate **2** prepared from acetophenone was conducted in the presence of 5 mol% of Me_3SiOTf in dichloromethane (Scheme 2).[3] The reaction proceeded at −78 °C for 4 h to afford only β-isopropyloxy ketone **3** selectively, and the ketone was found to be completely racemic. It is suggested that Me_3SiOTf coordinated to the less hindered MeO moiety rather than the *i*-PrO moiety of **1**, and that an oxocarbenium ion was formed and attacked by **2** to afford racemic **3**.

We then examined the possibility of racemization of the starting acetal **1** under the reaction conditions



Scheme 2. Aldol-type reaction of optically active acyclic acetal **1**.

(Table 1). It was confirmed that racemization of **1** occurred under the current reaction conditions even when the reaction time was very short (Table 1, entries 1–4). The *ee* of the acetal decreased to 83% after 10 min and 16% after 80 min. On the other hand, it was shown that the desired substitution reaction with **2** proceeded at the same time, and the product **3** was obtained in 16% yield after 10 min and in 83% yield after 80 min. In both cases, the product was completely racemic. These results indicate that the desired reaction proceeded faster than the racemization of **1**, and the enantioselectivity (0% *ee*) of the product suggested the S_N1 mechanism of the reaction *via* nucleophilic addition to the solvated or dissociated free oxocarbenium ion intermediate.

Next, the effect of solvents and other Lewis acids in the current reaction system was investigated (Table 2). Typical Lewis acids such as $RuCl_3$, $FeCl_3$, $TiCl_4$, $AlCl_3$, and $SnCl_4$ were evaluated in the aldol-type reaction of **1** with **2**. In all cases except for $AlCl_3$, the reactions proceeded well to afford the desired product **3** in moderate to high yields, and the products were racemic in all cases (entries 1–7). Not only in CH_2Cl_2, but also in toluene and THF, the reactions proceeded to afford the racemic products (entries 8 and 9). It was also confirmed in these cases that the aldol-type reactions were faster than racemization of **1**, and these results indicate that the aldol-type reaction of **1** with **2** also proceeded *via* the S_N1 solvated or dissociated FIP mechanism.

Table 1. Racemization of optically active acetal **1**.[a]

Entry	Time [min]	Yield of **3** [%]	*ee* of **3** [%]	Recovery of **1** [%]	*ee* of **1** [%]
1	10	16	0	84	83
2	20	34	0	77	62
3	40	56	0	55	50
4	80	83	0	28	16

[a] The reaction of **1** with **2** was conducted at −78 °C in CH_2Cl_2 for the indicated time in the presence of Me_3SiOTf (1 mol%).

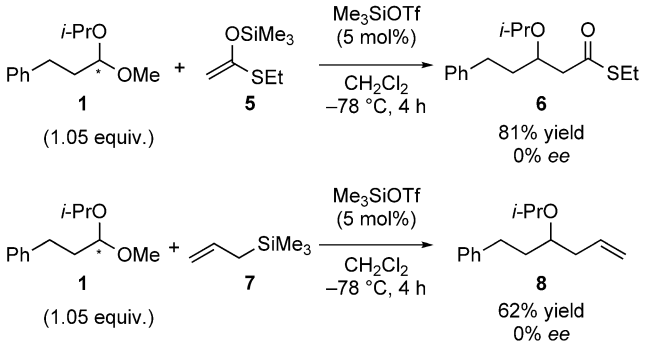
Table 2. Effect of solvents and Lewis acids.[a]

Entry	Solvent	Lewis acid	Yield [%]	*ee* [%]
1	CH_2Cl_2	Me_3SiOTf	78	0
2	CH_2Cl_2	$RuCl_3$	73	0
3	CH_2Cl_2	$FeCl_3$	84	0
4	CH_2Cl_2	$TiCl_4$	46	0
5[b]	CH_2Cl_2	$TiCl_4$	78	0
6	CH_2Cl_2	$AlCl_3$	0	–
7	CH_2Cl_2	$SnCl_4$	43	0
8	toluene	Me_3SiOTf	40	0
9	THF	Me_3SiOTf	55	0

[a] The reaction of **1** with **2** was conducted at −78 °C for 4 h using a Lewis acid (5 mol%), unless otherwise noted.
[b] 50 mol% of Lewis acid was used.

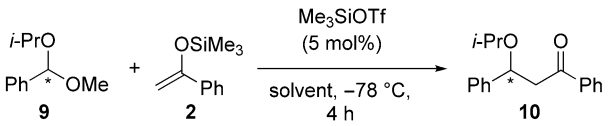
Nucleophilic additions using other substrates were also investigated (Scheme 3 and Table 3). The aldol-type reaction of **1** with silicon enolate **5** derived from a thioester proceeded in the presence of Me_3SiOTf (5 mol%) in dichloromethane at −78 °C for 4 h to afford the desired product **6** in 81% yield as a racemic form (Scheme 3). Allylation of **1** with allylsilane **5** also proceeded in the presence of Me_3SiOTf (5 mol%) to give homoallylic ether **8** in 62% yield, and this product was also proven to be a racemic form. Furthermore, the same tendency was also observed in the reaction of aromatic aldehyde-derived acyclic acetal **9** (Table 3). Chiral acyclic acetal **9** (> 99% *ee*) was treated with silicon enolate **2** in the presence of Me_3SiOTf (5 mol%) in dichloromethane at −78 °C for 4 h to afford the desired adduct **10** in 91% yield, and this compound was found to be racemic. In other solvents, completely racemic **10** was obtained in high yields. It was assumed that the aromatic moiety of **9** could stabilize the free oxocarbenium ion intermediate to accelerate the S_N1-type reaction pathways *via* solvated or dissociated free oxocarbenium ions.

These experimental results indicate that Lewis acid-mediated acetal substitution reactions with silicon nucleophiles proceed *via* solvated or dissociated free oxocarbenium ion intermediates, that is, the reaction



Scheme 3. Aldol-type and allylation reactions.

Table 3. Effect of solvents in the aldol-type reaction of **9**.



Entry	Solvent	Yield [%]	*ee* [%]
1	CH_2Cl_2	91	0
2	toluene	95	0
3	THF	94	0
4	hexane	91	0

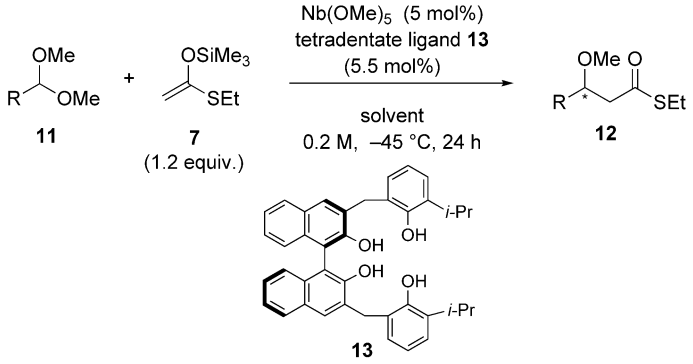
mechanism is the S_N1 solvated or dissociated free ion mechanism shown in Scheme 1.

Asymmetric Catalysis: We next undertook the task of developing asymmetric catalysts for acetal substitution reactions. Because the mechanism of these reactions has been proven to be the S_N1 FIP mechanism, we faced a difficulty, namely, that selection of one face of a chiral ionic intermediate by an incoming attacking nucleophile is needed to obtain an enantiopure adduct. Although several methods for chiral induction have already been developed, examples using chiral ionic pairs are rare, presumably because such electronic or π-π electron interactions are weak in most cases.[12–16]

We have previously developed a highly functionalized chiral niobium catalyst and have demonstrated its synthetic utility as a catalyst for Mannich reactions,[17] aza-Diels–Alder reactions,[18] and in the desymmetrization of *meso*-epoxides and *meso*-aziridines with aniline nucleophiles.[19] A characteristic feature of this catalyst system is its ability to discriminate between groups with closely matched steric and electronic demand, e.g., facial selectivity when prochiral substituents include ethyl and methyl groups.[19] This property was demonstrated by the ability of the catalyst to perform kinetic resolution of non-terminal unsymmetrical epoxides bearing a methyl group.[19] We reasoned that given this highly controlled asymmetric environment in which discrimination between small steric differences is achievable, it might be possible to apply this system to the desymmetrization of simple prochiral compounds such as acetals.

The chiral Nb catalyst was first used in the aldol-type reaction of the dimethyl acetal **11a** prepared from *p*-anisaldehyde with the silicon enolate derived from *S*-ethyl thioacetate in a toluene-CH_2Cl_2 (1:1) mixed solvent system (Table 4, entry 1). To our delight, the desired reaction proceeded smoothly with moderate enantioselectivity (59% *ee*). During optimization of the reaction conditions, it was found that a coordinating additive, THF, could improve the enantioselectivity to 77% *ee* (entry 2).[20] In the presence of THF, the reaction gave the desired product in good yield with high enantioselectivity even when toluene,

Table 4. Catalytic asymmetric aldol reactions of acetals.



Entry	R	Solvent	Yield [%]	*ee* [%]
1[a]	4-$MeOC_6H_4$ (**11a**)	toluene-CH_2Cl_2 (1:1)	94	59
2[a,b]	**11a**	toluene-CH_2Cl_2 (1:1)	90	77
3[a,b]	**11a**	toluene	87	87
4[a,c]	**11a**	toluene	83	90
5[a]	**11a**	toluene-Et_2O (1:1)	91	90
6	**11a**	toluene-Et_2O (1:1)	88	91
7[d]	**11a**	toluene-Et_2O (1:1)	88	91
8[e]	**11a**	toluene-Et_2O (1:1)	81	83
9	4-MeC_6H_4 (**11b**)	toluene-Et_2O (1:1)	81	82
10	4-$MeSC_6H_4$ (**11c**)	toluene-Et_2O (1:1)	86	85
11	3,4-$(MeO)_2C_6H_3$ (**11d**)	toluene-Et_2O (1:1)	78	89
12	2-thienyl (**11e**)	toluene-Et_2O (1:1)	78	89
13	3,4-$(OCH_2O)C_6H_3$ (**11f**)	toluene-Et_2O (1:3)	92	83
14	(*E*)-PhCH=CH (**11g**)	toluene-Et_2O (1:1)	83	92
15[a,f]	C_6H_5 (**11h**)	Et_2O	55	62
16[a,f]	$PhCH_2CH_2$ (**11i**)	Et_2O	N.R.	-

[a] 10 mol% Nb catalyst.
[b] THF (5 mol%) was added.
[c] THF (20 mol%) was added.
[d] 2.5 mol% Nb catalyst, at 0.4 M.
[e] 1 mol% Nb catalyst, at 0.7 M.
[f] The reaction time was 48 h.

a less polar solvent, was used as the sole solvent (entry 3). The amount of THF was also crucial; the enantioselectivity was further improved to 90% *ee* when 20 mol% of THF was employed (entry 4). We then searched for solvent systems again, and finally found that Et_2O was very effective as a cosolvent, and the highest *ee* (91%) was obtained without THF additive (entry 5). Under these reaction conditions, the catalyst loading was successfully reduced, and 5 mol% of the Nb catalyst was found to work well and the highest *ee* was obtained (91%) (entry 6). A further decrease in the amount of the catalyst was also possible in more concentrated reaction conditions (entries 7 and 8). The substrate scope was then investigated, and dimethyl acetals derived from electron-rich aromatic aldehydes bearing methyl, methoxy, and methylthio groups reacted smoothly under the optimum reaction conditions with good to high enantioselectivities (entries 9–14). The reaction of the dimethyl acetal derived from benzaldehyde also proceeded; however, the yield and the selectivity were moderate (entry 15). The reaction of the dimethyl acetal derived from 3-phenylpropanal did not proceed under these conditions (entry 16).[21]

In summary, we have conducted a mechanistic study of aldol-type reactions of acyclic acetals. The reactions of an optically active acetal proceeded smoothly to afford the desired adducts in racemic forms. By comparison of the *ee*s of the products with the *ee*s of the recovered acetals, we concluded that the aldol-type reactions proceeded not *via* direct displacement (S_N2) or CIP (S_N1) but by a solvated or dissociated free oxocarbenium ion (S_N1) mechanism. Further study to achieve asymmetric catalysis of the acetal substitution reactions was then carried out, and it was found that a chiral Nb complex prepared from $Nb(OMe)_5$ and a tetradentate BINOL derivative could achieve high enantioselectivities. Asymmetric

aldol-type reactions of acetals with silyl enol ethers proceeded smoothly to afford the corresponding aldol-type adducts in good yields with high enantioselectivities in a toluene-Et_2O solvent system. Further studies to improve the substrate scope and to develop other asymmetric reactions of acetals are now in progress.

Experimental Section

General Procedure for Me_3SiOTf-Catalyzed Reaction of Optically Active Non-Symmetrical Acetals with Nucleophiles

A dichloromethane solution (1.5 mL) of an acetal (0.525 mmol), a nucleophile (0.500 mmol) in a two-neck 10-mL flask was cooled at −78 °C, and 25 μL of a Me_3SiOTf solution (1.0 M in dichloromethane) were then added, and the whole was stirred for 4 h at the same temperature. The reaction mixture was quenched by saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the obtained crude mixture was purified on preparative TLC to give the desired product. The *ee* was determined by HPLC analysis using a chiral column.

Typical Procedure for Asymmetric Aldol-Type Reactions of *meso*-Acetals

A solution of $Nb(OMe)_5$ (0.02 mmol) and ligand **13** (0.022 mmol) in toluene (1.0 mL) was heated at 60 °C. The mixture was stirred at the same temperature for 3 h, and then it was allowed to cool down to room temperature. The catalyst solution was concentrated and dried under reduced pressure for 30 min, and toluene (1.0 mL) was then added, and it was stirred for 10 min. After cooling down the solution at −45 °C, an acetal (0.40 mmol) in Et_2O (0.5 mL) and a silicon enolate (0.48 mmol) in Et_2O (0.5 mL) were successively added. The reaction mixture was stirred for 24 h at the same temperature. After the reaction was stopped by adding saturated aqueous $NaHCO_3$, and the mixture was extracted twice with CH_2Cl_2, and the organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure the residue obtained was purified by preparative TLC (hexane: ethyl acetate = 4: 1) to afford the desired product. The enantioselectivity of the reaction was determined with chiral column HPLC analysis.

Acknowledgements

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