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Mechanistic investigations of the Mukaiyama aldol reaction as a two part enantioselective reaction

Sachin G. Patel, Sheryl L. Wiskur *

Department of Chemistry and Biochemistry, University of South Carolina, 631 Sumter St., Columbia, SC 29208, USA

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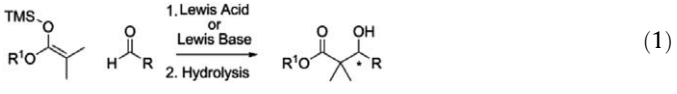
ABSTRACT

Herein, we report a mechanistic investigation of an enantioselective tandem Mukaiyama aldol reaction, consisting of a carbon–carbon bond-forming reaction and a silylation protection step in which the enantioselectivity results exclusively from the silylation step. The reaction is carried out in the presence of a Lewis base paired with a chiral quarternary ammonium salt. Mechanistic studies indicate that the enantioselectivity of the silylation step is a kinetic resolution of the aldolate intermediate. The effects of sterics and electronics on the aldehyde starting material are also presented.

The Mukaiyama aldol reaction (Eq. 1) is a useful and powerful reaction for the synthesis of complex products.[1] Its utility arises from the ability of the reaction to form a carbon–carbon bond and generate up to two stereocenters under mild conditions.[2] While this reaction has been intensely examined, most researchers have overlooked the fact that this transformation is actually a combination of two reactions: a carbon–carbon bond-forming reaction and a protection step (silylation of the newly formed alkoxide) (Eq. 2). While in some reactions this happens simultaneously,[3] there are other examples where this is a stepwise process[4] allowing for an asymmetric silylation to occur. Most researchers have focused on the enantioselectivity of the carbon–carbon bond-forming step, while never realizing that the silylation step can also be enantioselective. We have identified reaction conditions where the enantioselectivity of our Mukaiyama aldol reaction arises exclusively from the silylation step. In this process, the first step is not enantioselective, yielding racemic aldolate, which is then enantioselectively silylated in the second step. Thus, this is an example of a kinetic resolution employing a silyl protecting group.[5] In this study, we have explored the mechanism of this tandem reaction as well as the effect of sterics and electronics with regard to the aldehyde starting material.



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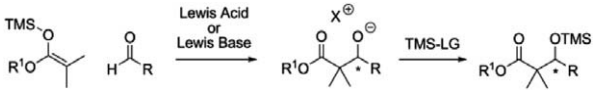
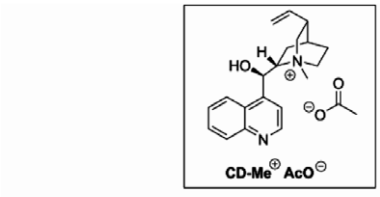


(2)

While searching for a new asymmetric Lewis base-catalyzed Mukaiyama aldol reaction,[6] it was discovered that more than just an aldol reaction was taking place. Specifically, the investigation began with the addition of a TMS silyl ketene acetal to benzaldehyde catalyzed by a Lewis base chiral ammonium salt, a methylated cinchona alkaloid paired with acetate[6e,7] (**CD-Me$^+$AcO$^-$**). The reaction produced the expected products, a combination of the alcohol and silylated product, which through a traditional TBAF workup yielded the alcohol **1** (Eq. 3). We were initially disappointed to find that the alcohol was racemic. However, upon examination of the two products (**1** and **2**) prior to the TBAF deprotection (Eq. 4), it was discovered that the alcohol product (**1**) was enantioenriched and the silylated product (**2**) was enantioenriched in the opposite enantiomer. What we believe to be hap-



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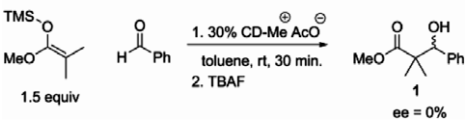

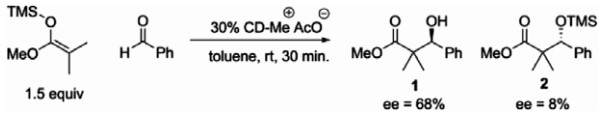

(4)

* Corresponding author. Tel.: +1 803 777 8143; fax: +1 803 777 9521.
E-mail address: wiskur@mail.chem.sc.edu (S.L. Wiskur).

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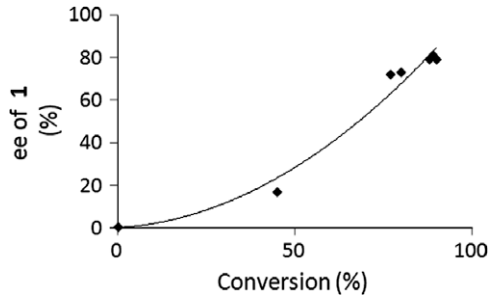
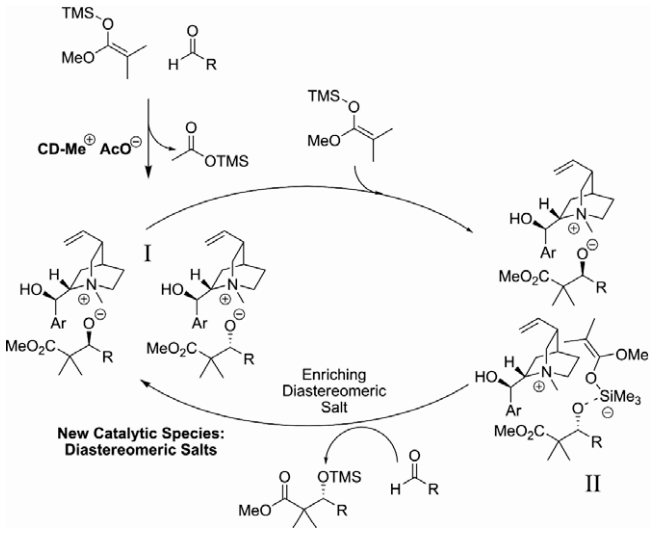


Figure 1. A plot of conversion versus enantiomeric excess showing that the ee of **1** changes over the course of the reaction.

pening is a kinetic resolution via an enantioselective silylation of the racemic alkoxide intermediate generated, in other words an enantioselective separation of the two alkoxide enantiomers through derivatization of one of the enantiomers. This process was further studied to verify that the enantioselectivity was arising from the second step and not from the first bond-forming step.

A kinetic resolution is a separation of enantiomers through selectively reacting one enantiomer over the other in an asymmetric reaction. When the reaction involves a simple enantioselective derivatization, without altering the stereocenter, the starting material and product should be enriched in the opposite enantiomers. The degree of enrichment depends on the conversion.[8] The products from our system were enriched in the opposite enantiomers, the alcohol product 68% (S)[9] and the deprotected silylated product 8% (R) (Eq. 4). Thus, the low ee of the deprotected product and a high ee of the remaining alkoxide 'starting material' indicated that the reaction proceeded to a high conversion, which is consistent with the observed ratio of silylated to unsilylated product (6:1). To further confirm that this process is a kinetic resolution, the ee of the reaction was examined at different degrees of conversion. Figure 1 shows that enantioselectivity of the alcohol varies over the course of the reaction and increases with increasing conversion which is consistent with a kinetic resolution process.

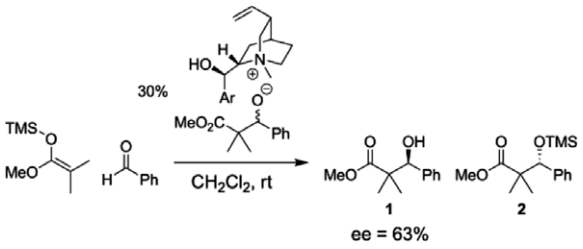
Scheme 1 shows the proposed mechanism. The acetate Lewis base[10] activates the silyl ketene acetal for nucleophilic attack on the aldehyde yielding the racemic alkoxide which is paired with the chiral cinchonidine cation forming diastereomeric salts (I).



Scheme 1. Proposed mechanism for the enantioselective silylation of the alkoxide intermediate.

These salts become the new Lewis base catalyst, where the alkoxide activates the next silyl ketene acetal for carbon–carbon bond formation.[11] The enantioselectivity of the reaction arises from the different reactivities of the diastereomeric salts with the silyl source (II). While the silyl source could be the silyl ketene acetal or the silyl acetate,[12] it is more likely to be the silyl ketene acetal since it is present in higher concentrations (5:1). One alkoxide enantiomer becomes silylated, while the other remains as the salt resulting in the alcohol product upon protonation. With each catalytic turnover, the salt becomes more enantiomerically enriched resulting in the separation of the alkoxide enantiomers.

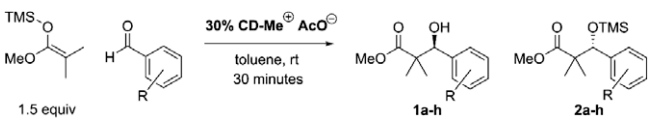
In order to investigate the mechanism, an experiment was performed to show that the diastereomeric salts could generate enantiomeric excess when introduced as the catalyst at the start of the reaction. Mukaiyama has shown that lithium alkoxide can catalyze the reaction[11], so the next step was to pair the aldolate with a chiral quarternary ammonium cation. The diastereomeric salts were preformed and subjected to a mixture of silyl ketene acetal and aldehyde. The reaction progressed as expected forming products **1** and **2**, and an ee of 63% was determined for **1** (Eq. 5). This showed that the diastereomeric salts could catalyze carbon–carbon bond formation while selectively silylating one enantiomer of the alkoxide resulting in a kinetic resolution.



(5)

Next, the effect of changing the sterics and electronics of the aromatic aldehyde was explored. It was discovered that the electronics in the para position (electron-donating and -withdrawing) did not have a significant effect on the enantioselectivity of the reaction or selectivity factor[13] (Table 1, entries f–h) compared to benzaldehyde (entry a). Since the aromatic ring is not conjugated with the nucleophilic alkoxide, the electronics are presumably too far away to have a large effect on the selectivity. It was also discovered that by placing a methyl group in the ortho position (entry e), the enantioselectivity was not altered, again showing that sterics in the ortho position were not affecting the reaction. The one factor that did have an effect on the enantioselectivity was the presence of a halogen in the ortho position. The enantioselectivity jumped

Table 1
The results of the Mukaiyama aldol kinetic resolution with different aldehydes.



Entry	R	Ratio (**1**:**2**)	Yield (**1** + **2**)[a]	ee of **1** (%)	s
a	H	1:6	85	68	2.1
b	2-F	1:3.5	78	84	3.7
c	2-Cl	1:4	81	84	3.4
d	2-Br	1:7	87	86	2.8
e	2-CH_3	1:7	88	72	2.2
f	4-F	1:6	86	72	2.3
g	4-Br	1:5	83	78	2.7
h	4-OCH_3	1:13	93	69	1.8

[a] Yields were determined by ^{1}H NMR using 2,2,6,6-tetramethylbenzo-[1,2-*d*;4,5-*d*′]bis[1,3]dioxole as an internal standard. Results are an average of multiple runs.

from the high 60's with benzaldehyde to the mid 80's with F, Cl, and Br (entries b–d), and there was an improvement in the selectivity factors as well. This selectivity could be the result of the partial negative charge of the halogens aiding in a stronger association with the cationic catalyst, slowing down the alkoxide's reactivity.

In conclusion, we have broken apart the Mukaiyama aldol reaction to show that enantioselectivity can arise from the protection step and not from the carbon–carbon bond-forming step. The enantioselectivity is a result of a kinetic resolution of the racemic alkoxide intermediates through enantioselective silylation. While this system did not produce high selectivities, it is interesting to note that there is the possibility of this phenomenon occurring in other similar systems resulting in the chance of two enantioselective competing processes. This could lead to false results if crude reaction mixtures are screened, and might warrant further investigation. We ultimately were inspired by this system to explore a more direct kinetic resolution employing asymmetric silylation reactions where further efforts will be focused.

Acknowledgments

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10. Counterions such as iodide and chloride cannot initiate the reaction, therefore starting material is recovered.
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12. If the silyl acetate delivers the silyl group, the alkoxide should still be enantioselectively silylated and the initial catalyst will be regenerated, which will start the catalytic cycle over again.
13. Selectivity factor (s) = (rate of fast acting enantiomer)/(rate of slow acting enantiomer). See Ref. 8.