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Metal Versus Silyl Triflate Catalysis in The Mukaiyama Aldol Addition Reaction

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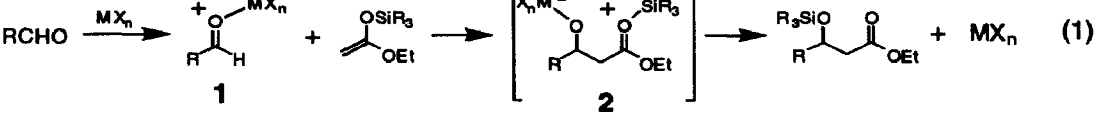
Abstract: A mechanistic study of the Mukaiyama aldol addition reaction employing benzaldehyde and hydrocinnamaldehyde along with a selection of Lewis acids including BF_3•OEt_2, $LiClO_4$, Yb(OTf)$_3$, Sn(OTf)$_2$, and Zn(OTf)$_2$ is presented. The results of experiments conducted with doubly-labeled silyl ketene acetals implicate a Lewis acidic silicon species and not the metals as the catalyst in the Mukaiyama aldol addition reaction.

Since the initial studies by Mukaiyama on the $TiCl_4$–mediated addition of silyl ketene acetals to aldehydes, many Lewis acidic metals have been reported to mediate this powerful C–C bond–forming process.[1] Some of the Lewis acids include BF_3•OEt_2, $SnCl_4$, $MgBr_2$, $ZnCl_2$, $LiClO_4$, $BiCl_3$, $InCl_3$, Ln(OTf)$_3$, Sn(OTf)$_2$ as well as derivatives of Ti(IV), Zr(IV), Ru, Rh, B, and Al.[2] The metal-mediated reaction proceeds by addition of a silyl ketene acetal to an activated aldehyde **1** to give **2** (Eq 1). The generation of **2** or R_3SiX during the course of the reaction may allow a silyl–catalyzed process to compete with the metal–mediated process. For the reported metal–catalyzed reactions, the mechanistic details of the steps that follow addition and regenerate the metal catalyst have not been extensively investigated.[3] We have been engaged in a study of metal-mediated additions of silyl ketene acetals to aldehydes with the aim of understanding the nature of the catalyst in this powerful synthetic transformation.[4]

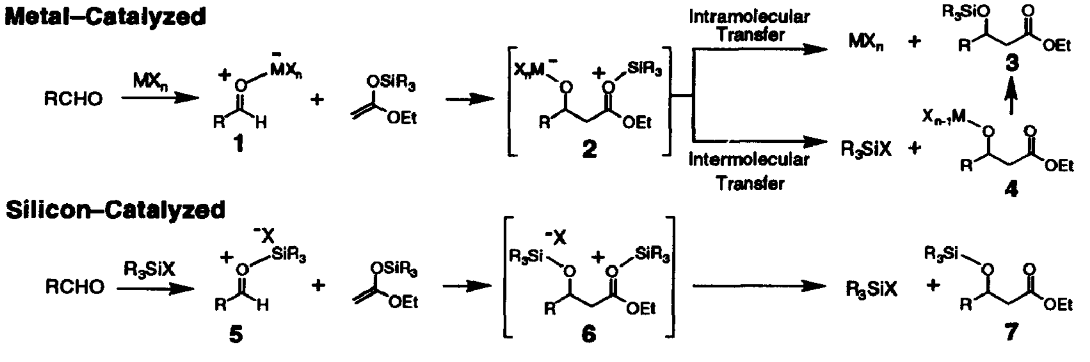


(1)

In our investigations of the aldol addition reaction of silyl ketene acetals, we have utilized benzaldehyde and hydrocinnamaldehyde as representative aromatic and aliphatic substrates, respectively, along with a selection of Lewis acids including BF_3•OEt_2, $LiClO_4$, Yb(OTf)$_3$, Zn(OTf)$_2$, and Sn(OTf)$_2$. This letter describes experimental results which implicate an active trialkylsilyl species and not the Lewis acidic metals as the catalyst in the Mukaiyama aldol addition reaction.

Three mechanistic pathways which account for the formation of silylated products in this aldol addition reaction are illustrated in Scheme 1. In a metal–catalyzed process, the Lewis acidic metal is regenerated upon silylation of the metal aldolate. Silylation of this alkoxide may occur through either of two mechanisms: direct intramolecular silyl transfer (**2** → **3**) or intermolecular silylation (**2** → **4** → **3**). In the event that aldolate silylation is slow, a silyl–catalyzed process (**5** → **6** → **7**) may effectively compete with metal catalysis. We have conducted double labeling experiments that allow these mechanistic issues to be addressed.

Scheme 1

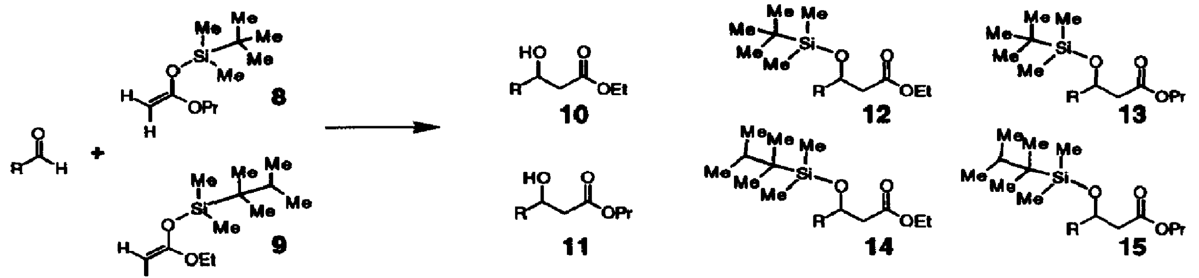


Two silyl ketene acetals of similar steric and electronic demands **8** and **9** were prepared (Scheme 2).[5] Intramolecular silyl transfer in **2** should afford aldol adducts **13** and **14** (Scheme 2); in contrast, intermolecular silyl transfer should give a mixture of **12**, **13**, **14**, and **15**. A 1:1 mixture of **8** and **9** (0.50 equiv of each) and benzaldehyde were allowed to react in dichloromethane at -78 °C in the presence of 20 mol % Lewis acid ($Yb(OTf)_3$, $Sn(OTf)_2$, $Zn(OTf)_2$, $LiClO_4$, and $BF_3{\bullet}OEt_2$). In all cases examined, the reaction mixtures were maintained at -78 °C and were complete in less than 30 min. Upon work-up, the product composition was subsequently determined by capillary GC chromatography.[6] As shown in Scheme 2 (R = Ph), the aldol addition reactions employing $Yb(OTf)_3$, $Sn(OTf)_2$, $Zn(OTf)_2$, and $LiClO_4$ reproducibly gave 1–3 % alcohol product along with a mixture of silyl ethers **12**, **13**, **14**, and **15**. The $BF_3{\bullet}OEt_2$ the aldol addition reaction gave 20% alcohol product (equivalent to the amount of Lewis acid employed) along with a mixture of the four silyl-scrambled products.

The analogous reactions were conducted with hydrocinnamaldehyde, (R = CH_2CH_2Ph, Scheme 2). With the exception of $BF_3{\bullet}OEt_2$, the aldol addition reactions were markedly slower, proceeding in 6-8 h at 23 °C.[7] In the $Sn(OTf)_2$–mediated reaction, alcohol product was observed initially and was consumed during the course of the reaction giving only a mixture of **12**, **13**, **14**, and **15**. In the $Yb(OTf)_3$, $Zn(OTf)_2$, and $LiClO_4$ mediated reactions, all four products resulting from trialkylsilyl group scrambling are observed along with 1-6% alcohol product. With $BF_3{\bullet}OEt_2$, the aldol addition reaction of hydrocinnamaldehyde exclusively afforded alcohol product in proportion to the amount of Lewis acid present in the reaction mixture; no silylated aldolates **12**, **13**, **14**, **15** were observed. In order to rule out catalysis by adventitious Bronsted acid, the aldol addition reactions with both aldehydes were repeated in the presence of 20 mol% 2,6-di-*tert*-butyl-4-methylpyridine; in all cases, identical results were obtained. Additional control experiments indicated that the silylated aldol adducts (**12**, **13**, **14**, **15**) were stable at 23 °C in the presence of 20 mol% Lewis acid, showing no evidence of scrambling over 8 h. Moreover, 1:1 mixtures of the silyl ketene acetals in CH_2Cl_2 did not show evidence of silyl scrambling at 23 °C in the presence of any of the Lewis acids investigated. These results along with the observation of silyl–scrambled products for both aldehydes tested exclude a reaction mechanism in which the metal catalyst is regenerated via intramolecular silylation (**2** → **3**, Scheme 1).

The presence of alcohol product after the reaction has reached completion indicates that the metal aldolates were not silylated at a rate comparable to that observed for silyl product formation. In such a case, the Lewis acidic silicon species generated (**2** or R_3SiX) may subsequently catalyze the Mukaiyama aldol. In this regard, TBSOTf (0.05 equiv) catalyzed the aldol addition reactions of benzaldehyde (-78 °C, 30 min) and hydrocinnamaldehyde (23 °C, 2 h) with **8** and **9** to afford **12**, **13**, **14**, and **15**. We have conducted experiments to determine the relative rate of silylation of the metal aldolate for Lewis acids which yielded >1% alcohol product.

Scheme 2



R = Ph	%(10 + 11)	12 : 13 : 14 : 15
$Yb(OTf)_3$	3	1 : 1.0 : 1.0 : 0.98
$Sn(OTf)_2$	2	1 : 1.1 : 0.88 : 0.93
$Zn(OTf)_2$	1	1 : 1.0 : 1.2 : 1.2
$LiClO_4$	1	1 : 1.1 : 1.1 : 1.1
BF_3•OEt_2	20	1 : 1.0 : 1.9 : 2.0

R = $(CH_2)_2Ph$	%(10 + 11)	12 : 13 : 14 : 15
$Yb(OTf)_3$	6	1 : 0.82 : 0.98 : 0.98
$Sn(OTf)_2$	0	1 : 0.81 : 0.94 : 0.86
$Zn(OTf)_2$	4	1 : 0.93 : 0.95 : 0.93
$LiClO_4$	1	1 : 1.1 : 0.97 : 0.87
BF_3•OEt_2	20	–

The aldolate formed in the $Sn(OTf)_2$ mediated aldol addition to benzaldehyde was consumed in 1.5 h upon warming the reaction mixture to 23 °C. In contrast, the alcohol formed in the $Yb(OTf)_3$ and BF_3•OEt_2 mediated reactions persisted after 16 h at 23 °C. These carbinols (derived from $Yb(OTf)_3$, BF_3•OEt_2) were not observed to silylate at 23 °C with added TBSOTf (20 mol%) and 2,6-di-*tert*-butyl-4-methylpyridine (20 mol%). Thus, the metal aldolates derived from $Yb(OTf)_3$, $Sn(OTf)_2$ and BF_3•OEt_2 silylate at slower rates than that observed for silyl product formation at -78 °C. This suggests that these metal-mediated reactions with benzaldehyde are *metal initiated* and subsequently *silicon–catalyzed*.

Analogous experiments were conducted with hydrocinnamaldehyde. The alcohol products produced in the $Yb(OTf)_3$ and $Zn(OTf)_2$ mediated reactions were observed throughout the course of the reaction and were not consumed upon prolonged stirring at 23 °C. Moreover, the addition of TBSOTf (20 mol %) and 2,6-di-*tert*-butyl-4-methylpyridine (20 mol%) did not lead to alcohol silylation. Thus, silicon–catalysis is implicated in the aldol additions mediated by $Yb(OTf)_3$ and $Zn(OTf)_2$. For the $Sn(OTf)_2$ mediated reaction, the fact that alcohol formation is observed initially and is subsequently consumed during the course of the reaction (see above) does not permit the silicon– and metal– catalyzed processes to be differentiated. Since the benzaldehyde-derived Sn(II)–aldolate silylates at 23 °C in 1.5 h, the $Sn(OTf)_2$–mediated addition to hydrocinnamaldehyde may proceed through either metal– or silicon– catalysis, or both. The exclusive formation of alcohol products in the BF_3•OEt_2 mediated reaction at 0 °C may be rationalized by assuming that the silylating species (**2**, Scheme 2) is quenched at a faster rate than it can silylate hydrocinnamaldehyde.

The observations presented in this letter exclude a metal–catalyzed aldol addition reaction in which silylation of the metal aldolate (**2**, Scheme 1) derived from $LiClO_4$, $Sn(OTf)_2$, $Zn(OTf)_2$, and BF_3•OEt_2 occurs through an intramolecular process. In addition, the results presented implicate silicon catalysis in the Mukaiyama aldol addition reactions of aromatic aldehydes mediated by $Yb(OTf)_3$, $Sn(OTf)_2$, and BF_3•OEt_2. Silicon catalysis is also implicated in the aldol addition reactions of hydrocinnamaldehyde mediated by $Yb(OTf)_3$ and $Zn(OTf)_2$. The $Sn(OTf)_2$–mediated additions to hydrocinnamaldehyde may be proceeding through metal– or silicon– catalysis or a combination of both. The observation of silylated products in the BF_3•OEt_2 mediated addition to benzaldehyde suggests that direct silyl transfer from **2** occurs with benzaldehyde.

Although the Lewis acids investigated represent a subset of "catalysts" that have been reported to date, they highlight that caution must be exercised in the design of catalysts for the Mukaiyama aldol addition reaction.

The formation of products may be dominated by silicon catalysis if the rates of aldehyde silylation exceed the corresponding rate of metal aldolate silylation. The experiments with doubly labeled silyl ketene acetals along with the study of aldolate silylation presented herein constitute a useful chemical test with which to distinguish metal from silicon catalysis.

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References and Notes

1 (a) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 989; (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

2 For an extensive recent compilation of references, see: Le Roux, C.; Iloughnane, H. G.; Dubac, J. *J. Org. Chem. Soc.* **1993**, *58*, 1835.

3 For an NMR study of the Mukaiyama Aldol mediated by $LiClO_4$ and $TiCl_4$, see: Reetz, M. T.; Raguse, B.; Marth, C. F.; Hugel, H. M.; Bach, T.; Fox, D. N. A. *Tetrahedron* **1992**, *48*, 5731.

4 For a related mechanistic study, see: Denmark. S. E.; Chen, C-T. accompanying letter in this issue.

5 Y. Kita, J. Segawa, J. Haruta, H. Yasuda, and Y. Tamura; J C S Perkin 1 **1982**, 1099.

6 General Procedure for crossover experiments: The metal salts were dried for 6 h under vacuum (2mm Hg) at 150° C. A 1.0 M solution of $BF_3{\bullet}OEt_2$ was purchased from Aldrich. To the Lewis acid (8.0 μmol, 0.20 eq) in 2 ml CH_2Cl_2, was added a solution of the aldehyde (40 μmol, 1.0 eq) in 1 ml CH_2Cl_2 via cannula. The reaction mixture was cooled to -78° C and a solution containing 4.3 mg **8** (20 μmol, 0.50 eq) and 4.6 mg **9** (20 μmol, 0.50 eq) in 1 ml CH_2Cl_2 was added dropwise. The reactions were stirred at -78° C for 2h and allowed to gradually warm toward room temperature over 1 h. They were maintained at room temperature until complete (as monitored by thin layer chromatography, products at Rf = 0.68 in 4:1 hexane/ethyl acetate) before being treated with water. The aqueous layer was was extracted with CH_2Cl_2 (3 x 10 ml); the combined organic layers were washed with brine (15 ml) and dried over anhydrous Na_2SO_4. The solution was then passed through a small plug of silica and concentrated *in vacuo*. Analytical gas-liquid chromatography was carried out on a Hewlett Packard 5890 chromatograph, equipped with a split mode capillary injection system and a flame ionization detector, using a 25 m x 0.2 mm HP-5 fused silica capillary column wall coated with phenyl methyl silicone. Helium was used as the carrier gas. Two slightly different conditions were employed for each of the aldehydes investigated. Column condition 1: initial time: 3 min, intial temp.: 225° C, rate: 10° C/min, final temp.: 275° C; column condition 2: initial time: 3 min, intial temp.: 250° C, rate: 10° C/min, final temp.: 275° C. Retention times for benzaldehyde derived products under column condition 1: **10** (R = Ph, t_R = 4.14), **11** (R = Ph, t_R = 4.82), **12** (R = Ph, t_R = 5.88 min), **13** (R = Ph, t_R = 6.72 min), **14** (R = Ph, t_R = 8.13 min), **15** (t_R = 9.11 min). Retention times for hydrocinnamaldehyde derived products under column condition 2: **10** (R = CH_2CH_2Ph, t_R = 4.31), **11** (R = CH_2CH_2Ph, t_R = 4.92), **12** (R = CH_2CH_2Ph, t_R = 6.35 min), **13** (R = CH_2CH_2Ph, t_R = 7.20 min), **14** (R = CH_2CH_2Ph, t_R = 8.98 min), **15** (R = CH_2CH_2Ph, t_R = 10.30 min).

7 This rate difference has been noted in several studies; for an example, see reference 3.

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