Homogeneous catalysis. Mechanisms of the catalysed Mukaiyama cross-aldol reaction

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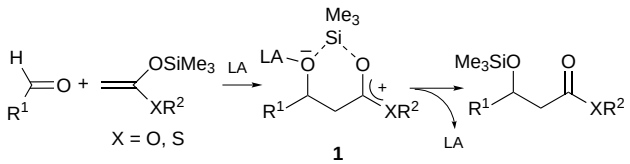
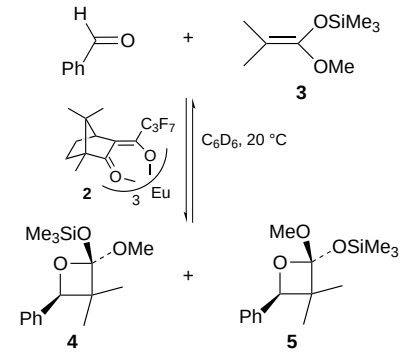
It is shown that [2 + 2] addition intermediates can form reversibly in the catalysed Mukaiyama reaction; these serve to prevent formation of the catalyst Me_3Si^+ and the reactivities of the [2 + 2] intermediates can affect the enantioselectivity of the reaction.

The Mukaiyama cross-aldol reaction is a versatile carbon–carbon bond-forming reaction which is catalysed by a variety of Lewis acids.[1] It is generally assumed to proceed by way of a cyclic intermediate **1** which allows for transfer of the silyl group (Scheme 1). For certain Lewis acids, however, intramolecular silicon transfer does not occur, rather the trimethylsilyl group is captured by the carbonyl substrate[2,3] and catalysis occurs by means of the powerful Me_3Si^+ catalyst.[2] Despite the possible widespread intervention of the (achiral) Me_3Si^+ catalytic path, there are a number of reports of chiral Lewis acid catalysts which give excellent enantiomeric excesses (ees),[4] indicating that for these catalysts, the unwanted Me_3Si^+ path is suppressed. The question then arises as to which type of Lewis acids will allow for one or other of the possible catalytic paths. It is probable that if the Lewis acid–oxygen bond of the aldolate **1** is weak and the bound oxygen atom is a good nucleophile, the rate of the silyl transfer step will be enhanced and consequently the capture of the Me_3Si^+ group by external nucleophiles will be suppressed. The direct silyl transfer path as illustrated in Scheme 1, however, may not be the only component of the mechanism because it is possible that an oxetane could form by capture of the carbenium ion of the intermediate. It is known that oxetanes are formed by Lewis acid-catalysed coupling of aldehydes and dialkyl ketene acetals.[5] The formation of the oxetane would be the equivalent of the Mukaiyama reaction, as an acidic workup would provide the desired aldol product. We report here on the detection of oxetanes in the Mukaiyama reaction using lanthanide and zinc complexes, both of which were expected to form aldolate intermediates with weak metal–oxygen bonds.

In benzene solution at 20 °C, the catalyst [Eu(hfc)$_3$] **2** (4 mol%) promotes the reaction between benzaldehyde and the ketene acetal **3** to give initially the two oxetane isomers **4** and **5** (Scheme 2). We have not been able to isolate these oxetanes in pure form but they have been characterized by their ^{1}H and ^{13}C NMR spectra, although the identity of the isomers **4** and **5** was not established.† The initial (kinetic) ratio of the isomers is 48 : 52 which slowly reaches an equilibrium ratio of 38 : 62. At 1 M concentration of each of the substrates, a maximum yield of 56% for the two oxetanes is obtained after 1 h in benzene solution at 20 °C using 4 mol% catalyst. Isomer equilibrium occurs over 2 h. The maximum yield of oxetanes (**4** and **5**) decreases upon dilution of the reaction solution, indicating that



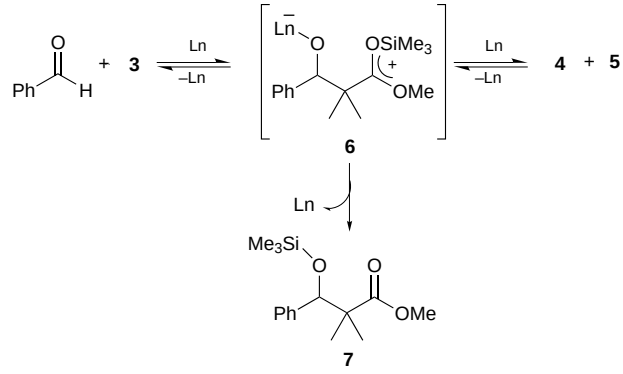
Scheme 1



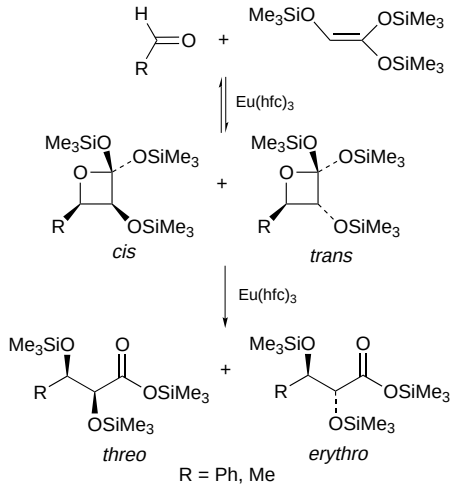
Scheme 2

the equilibrium illustrated in Scheme 2 obtains ($K \approx 3$ at 20 °C). Addition of 1 M pyridine quenches catalysis, but the addition of the hindered base, 2,6-di-*tert*-butyl-4-methylpyridine, does not affect the rate of catalysis. This latter observation indicates that the reaction in Scheme 2 is neither proton-initiated nor proton-catalysed. Under these conditions—4 mol% catalyst, 1 M each of substrates, benzene solution, 20 °C—the Mukaiyama product begins to appear after several hours and, after seven days, all of the substrates and intermediates are converted to this product. The Mukaiyama product is irreversibly formed because a 15% ee (*S*)[6] was found using the (+)-hfc catalyst, and the ee of the product did not change in the presence of the catalyst after two weeks. It was found that, after equilibration of the two oxetanes, their hydrolysed product had 0% ee using the (+)-hfc catalyst but a 5% ee (*S*) was observed for the hydrolysed products derived from the kinetically formed oxetanes (*ca.* 10% conversion to oxetanes).‡ This observation also supports the view that equilibration between substrates and oxetanes exists (Scheme 2).

The results are consistent with the mechanism outlined in Scheme 3 (Ln = **2**). In this case, the rate of production of the oxetanes by carbenium ion capture and the reverse reaction are faster than silyl transfer to produce the Mukaiyama product **7**. As might be expected, these relative rates vary according to the nature of the substrates and the catalyst. This is illustrated by a



Scheme 3



Scheme 4

comparison of the reactions shown in Scheme 4, where it is found that in catalysis of benzaldehyde, a *cis*:*trans* ratio of 80:20 is observed for the Mukaiyama product. For 1 mol% catalyst at 20 °C in benzene solution, the benzaldehyde reaction gives a *cis*:*trans* ratio of 75:25 at 40% conversion to the two oxetanes and 55:45 after 60% conversion.§ This change in isomer ratio occurs before significant amounts of the Mukaiyama products are formed, indicating that equilibration between the substrates and oxetanes occurs. Final equilibrium may not be established under these conditions, however, because a constant *cis*:*trans* ratio was not observed before the Mukaiyama product began to appear. For the analogous reaction with acetaldehyde (Scheme 4), under the same conditions, the rates of formation of the oxetanes and the Mukaiyama product are comparable. Similarly, the [Zn(facac)$_2$·2H$_2$O] (facac = hexafluoroacetylacetonate) complex catalyses the coupling between benzaldehyde and **3** but the equilibrium **4** ⇌ **5** is not established before significant amounts of the Mukaiyama product is formed (Scheme 2). With this zinc catalyst, no [2 + 2] addition products are observed in the coupling of benzaldehyde and CH$_2$=C(OSiMe$_3$)SBu^t indicating that catalysis proceeds either wholly by direct silyl transfer or, if [2 + 2] products are formed, their concentrations are very low. We note that neither the Eu nor the Zn catalysts lead to coupling of ketones with silyl ketene acetals nor coupling of silyl enol ethers with aldehydes or ketones.

The discovery of the [2 + 2] addition path for the catalysed Mukaiyama is significant in a number of respects. For cases where silyl transfer is slow in the intermediate **6** (Scheme 3), the more rapid oxetane formation will reduce the life-time of this intermediate. Consequently, the probability of Me_3Si^+ capture in **6** by external nucleophiles will be reduced. The Me_3Si^+ group is stable in the oxetanes. As was noted earlier, the mechanism illustrated in Scheme 3 is more likely to occur when the Lewis acid–alkoxide bond of the intermediate **6** is weak. Intermediates having strong alkoxide–Lewis acid bonds are unlikely to lead to oxetane formation or to silyl transfer. This appears to be the case for many catalysts which only serve as initiators for the production of Me_3Si^+ catalyst.[2]

These results suggest that identification of the enantioselective step can be a complicated problem because the ee will depend on the relative rates of formation of the various species. If equilibration between the substrates and oxetanes is much faster than formation of the Mukaiyama product, the ee will depend on the relative rates of silyl transfer which lead to the formation of the two enantiomers of the product. If, however, the rates of equilibration and product formation are comparable, the ee will depend on a complex mix of rates associated with all of the diastereomeric species in the mechanism. Under these circumstances, there would not be a single chirality-controlling step. The observations presented here may help in the design of effective enantioselective catalysts for the Mukaiyama reaction.

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Footnotes and References

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† *Selected spectroscopic data* for the major and minor oxetanes (at equilibrium): δ_H (400 MHz, C_6D_6) (major isomer) 7.3–7.1 (m, 5 H), 4.95 (s, 1 H), 3.26 (s, 3 H), 1.27 (s, 3 H), 0.76 (s, 3 H), 0.29 (s, 9 H); (minor isomer) 7.3–7.1 (m, 5 H), 4.99 (s, 1 H), 3.34 (s, 3 H), 1.25 (s, 3 H), 0.76 (s, 3 H), 0.23 (s, 9 H); δ_C (125 MHz, $CDCl_3$) (major isomer) 139.0 (s), 127.7 (d), 127.2 (d), 125.1 (d), 116.2 (s), 82.6 (d), 49.4 (s), 48.8 (q), 23.5 (q), 21.1 (q), 1.05 (q); (minor isomer) 138.5 (s), 127.7 (d), 127.0, 125.6 (d), 115.7 (s), 81.8 (q), 50.7 (s), 49.0 (q), 19.0 (q), 18.1 (q), 1.06 (q).

‡ Mild acid hydrolysis of the mixture of oxetanes leads to the formation of the β-hydroxy ester. Enantiomeric excesses of the hydrooxy ester were determined using Eu(tfc)$_3$ as a chiral shift reagent.

§ The *cis* and *trans* oxetanes where R = Ph and Me were identified by conversion of mixtures of these compounds to mixtures of their respective *threo* and *erythro* 2,3-dihydroxyalkanoic acids according to the reported procedure (ref. 7). In both cases, where R = Ph or Me, it is noted that hydrolysis of the *cis* and *trans* oxetanes leads to formation of the *threo* and *erythro* products, respectively, which were identified by comparison with spectroscopic data from the literature (ref. 8).

Selected spectroscopic data for the oxetanes: δ_H (400 MHz, C_6D_6) (R = Ph, *threo*) 7.47 (m, 2 H), 7.2–7.0 (m, 3 H), 5.18 (d, *J* 6.2, 1 H), 4.69 (d, *J* 6.2, 1 H), 0.29 (s, 9 H), 0.27 (s, 9 H), −0.22 (s, 9 H); (R = Ph, *erythro*) 7.43 (m, 2 H), 7.2–7.0 (m, 3 H), 4.98 (d, *J* 4.9, 1 H), 4.35 (d, *J* 4.8, 1 H), 0.35 (s, 9 H), 0.26 (s, 9 H), 0.01 (s, 9 H); (R = Me, *threo*) 4.42 (d, *J* 6.3, 1 H), 4.28 (m, 1 H), 1.25 (d, *J* 6.4, 3 H); (R = Me, *erythro*) 4.10 (m, 1 H), 4.02 (d, *J* 4.8, 1 H), 1.21 (d, *J* 6.2, 3 H). The OSi(CH_3)$_3$ resonances for R = Me were left unassigned due to the complexity of this region in the ^{1}H NMR spectrum of the reaction mixture.

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