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ALDOL REACTIONS OF A CYCLOBUTANONE ENOLATE

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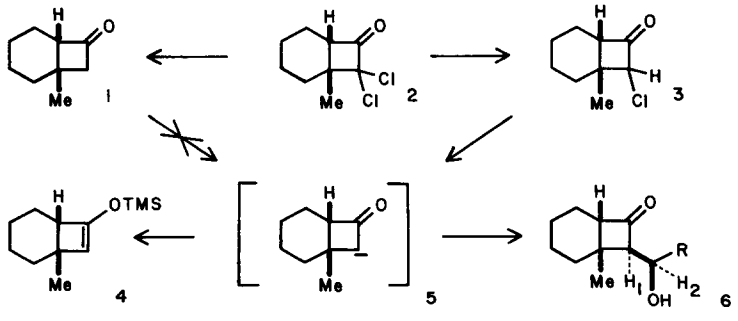
Addition of an aldehyde and zinc chloride to a cyclobutanone enolate, prepared by the reaction of an α-chlorocyclobutanone with dimethylcopperlithium, gave an aldol adduct in good yield.

Although cyclobutanones are extremely useful intermediates in synthesis,[1] their utility is limited by their accessibility.[2,3,4] The thermal (2 + 2) cycloaddition of an olefin with dichloroketene generally proceeds in high yields.[4,5] Therefore, the accessibility would be improved if dichlorocyclobutanones so produced could be functionalized.

Enolate generation and subsequent bond-forming reactions might provide a general route to a wide variety of cyclobutanones. The reduction of **2** with zinc in acetic acid[5] leads to the parent cyclobutanone **1**, which upon deprotonation with an amide base might yield a cyclobutanone enolate. In our hands, this gave a reaction product with many components regardless of the trapping protocol. Greene et al.[6] reported that methyl iodide can alkylate an α-chlorocyclobutanone enolate, generated by reduction of a dichlorocyclobutanone with dimethylcopperlithium. In our hands, a similar enolate was trapped with trifluoroacetic acid (5 equiv., -78°C) to give the monochlorocyclobutanone **3**.[7] A second application of dimethylcopperlithium gave the parent enolate **5**. This was trapped (-78°C to 23°C, 24 hr., Et_2O/Me_2S) by chlorotrimethylsilane (2.5 equiv.) in the presence of hexamethylphosphoric triamide (2 equiv.).[8] Thus, one should be able to functionalize cyclobutanones using the library of reactions of silyl enol ethers.[9]

Scheme



The directed aldol reaction[10] is a powerful method for forming carbon-carbon bonds and for generating stereochemistry[11] in a controlled fashion. If a cyclobutanone enolate gives a reasonable yield of aldol adduct, the sequence of thermal (2 + 2) cycloaddition-aldol reac-

tion is a potentially general method for elaborating an olefin. When the silyl ether **4** was treated sequentially with methyllithium and the aldehyde **7**, an aldol product was isolated in low yield. Similarly disappointing results were obtained following treatment of the silyl ether **4** with the dimethyl acetal of 2-ethylhexanal under the conditions of Noyori.[12] Enolates generated by the 1,4-addition of dimethylcopperlithium to enones have been used in aldol reactions[13] when either hexamethylphosphoric triamide[14] (1.2 equiv.) or zinc chloride[15] (1.3 equiv.) was added. These conditions were compared using the aldehyde **7** (Table 1). The results

Table 1. Aldol Condensations of **7** and **5** to give **8**

entry	conditions	yield
1	-78°C to rt, 24 h	no reaction
2	-78°C to rt, HMPA, 24 h	52%
3	-78°C, HMPA, 15 sec	75%
4	-78°C, $ZnCl_2$, 15 min	70%

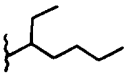
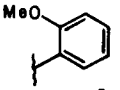
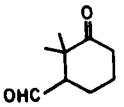
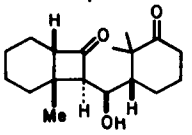
show that both sets of conditions give an aldol product in a useful yield. Since the yields are about equal and because hexamethylphosphoric triamide is a potential carcinogen,[16] we explored briefly the range of aldehydes which can undergo the aldol reaction in the presence of zinc chloride. The results are shown in Table 2.[17]

Several features merit comment. First, the α carbon of the aldehyde can be monosubstituted (entries 1, 4), disubstituted (entries 2,5,9), or trisubstituted (entry 3). Second, the electron-rich aldehyde *o*-anisaldehyde (entry 8) gave a good yield of aldol product. Third, the reaction showed good regioselectivity when an aldehyde and a (rather hindered) ketone were present in the same molecule (entry 9). Fourth, all of the aldol reactions gave almost exclusively a single diastereomer with the exception of entry 5 (2-ethylhexanal).

The stereochemistry of the adduct with the aldehyde **7** was determined from a single-crystal X-ray diffraction study.[18] The adduct was found to posess the stereochemistry indicated. Thus, it is the *threo*, Cram[19] product. This stereochemistry can be explained using the chelate model.[20,21,22] Only a single enolate face is accessible, thereby enforcing a particular conformation on the chelate chair. In this case, the angular methyl group probably enhances the *threo*/*erythro* selectivity: a severe 1,3-diaxial type of interaction results between the angular methyl and the alkyl group attached to the aldehyde in the chelate leading to the *erythro* product. The reaction between **5** and **7** gave the same aldol product, **8**, in all cases tried (Table 1), as determined by ^1H NMR at 300 MHz. At present, we are unable to

discern experimentally whether the reaction is controlled kinetically or thermodynamically. The rest of the adducts are assigned as threo by analogy with the stereochemistry observed in

Table 2. Condensation of 5 With Aldehydes

entry	aldehyde	product		yield (%)	mp (°C)	J H_1H_2 (Hz)
1	n-butyraldehyde	6, R = n-Pr	(6a)	86	37-38	6.6
2	iso-butyraldehyde	6, R = i-Pr	(6b)	85	oil	6.1
3	pivalaldehyde	6, R = t-Bu	(6c)	75	84-86	2.2
4	hexanal	6, R = n-pentyl	(6d)	86	oil	6.4
5	2-ethylhexanal	6, R = 	(6e)	73	oil	7.6
6	furfural	6, R = 	(6f)	80	49-51	7.8
7	benzaldehyde	6, R = Ph	(6g)	83	103-104	7.1
8	o-anisaldehyde	6, R = 	(6h)	92	98-100	6.3
9	 7	 8		70	116-117	9.0

entry 9, and by the magnitude of the vicinal coupling constant[21] between the cyclobutanone methine hydrogen atom (H-1) and the hydrogen atom (H-2) on the carbon bearing hydroxyl of **6** (Table 2).

Heathcock[22] has shown that racemic enolates can react with racemic aldehydes to give an aldol product which is very nearly a single diastereomer. This double stereodifferentiation[22] can fix still another chiral center. In entries 5 and 9 (Table 2), a racemic aldehyde was used. In entry 9, there was almost exclusively a single diastereomer. With 2-ethylhexanal, there was a 1:1 mixture (as indicated by ^{13}C NMR) of diastereomers. The aldol reaction with optically active 1,2:3,4-di-O-isopropylidene-α-D-galacto-1,6-dialdohexopyranose[23] was tried in hopes of effecting a kinetic resolution. Surprisingly, a 1: mixture of diastereomers resulted, even with a deficiency of aldehyde.

General Procedure for Aldol Reactions. At -78°C, a solution of **3** (164 mg, 0.95 mmol) in ether (2.8 mL) was added dropwise to Me_2CuLi[26] (2.05 mmol) under nitrogen. After 10 min, a

solution of fused zinc chloride (175 mg, 1.28 mmol) in ether[15] (5 mL) was added; 2 min later, a solution of the aldehyde (1.95 mmol) in ether (4 mL) was quickly added. The -78°C bath was exchanged for a 0°C bath. After 5 min, the cold reaction mixture was submitted to aqueous workup.[26]

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