Diastereoselective and enantioselective Mukaiyama aldol reactions of α-ketoesters using hydrogen bond catalysis†‡

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Hydrogen bond catalyzed Mukaiyama aldol reactions of α-ketoesters proceed in high diastereo- and enantioselectivities, giving products possessing two chiral centers, of which one is a tertiary alcohol.

The Mukaiyama aldol is one of the work-horse reactions in organic synthesis. A fundamental C–C bond-forming process, it gives β-hydroxy carbonyl compounds, often as their *O*-silyl ether derivatives, with up to two chiral centers. Given the prevalence of the aldol motif in natural products, much effort has been devoted to the development of catalytic enantioselective versions of this reaction, and numerous successes have been recorded, primarily with metal based catalysts.[1] While the catalytic, enantioselective Mukaiyama aldol reaction of aldehydes has been developed extensively, the corresponding reaction of ketones has proven more challenging, with only a handful of reports on this front.[2,3]

The difficulty in developing the enantioselective ketone Mukaiyama aldol reaction can be attributed to the lower intrinsic electrophilicity of ketones over aldehydes, combined with the smaller steric difference between the two groups flanking the carbonyl moiety. An effective solution to this problem is provided by pyruvate esters, in which the ketone carbonyl is rendered more electron-deficient by the neighboring carboxylate group.[4,5] Moreover, the aldol products of pyruvates are of special interest, since the resulting chiral tertiary alcohols[2] adjacent to the versatile carboxylate functionality are found in natural products and other compounds of biomedical relevance.[6] When this reaction is performed using α-substituted nucleophiles, aldol products possessing two chiral centers are produced. To our knowledge, the seminal work of Evans, using metal-based complexes, provides the only reports of diastereo- and enantioselective Mukaiyama aldol reactions using substoichiometric amounts of a catalyst.[7] We report here the first hydrogen-bond promoted diastereo- and enantioselective Mukaiyama aldol reactions of ketones.[8–10]

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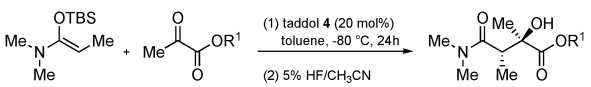
Based on the considerations stated above, we focused our efforts on the hydrogen bond promoted Mukaiyama aldol reaction of pyruvate esters. In initial studies, the *N*,*O*-ketene acetal **1** was reacted with methyl pyruvate at −78 °C in the presence of the commercially available naphthyl-taddol, **4**. Under these conditions, a smooth reaction took place to produce the expected aldol product **3a** in good yield, as a 15 : 1 mixture of diastereomers, with the major isomer having been formed in 80% ee (Table 1, entry 1). An examination of several related pyruvates showed the *tert*-butyl ester to provide optimal results in this reaction (entry 4): 22 : 1 diastereoselectivity and 93% ee for the major diastereomer.

The effectiveness of the above hydrogen bond promoted enantioselective reaction combined with the usefulness of the aldol products prompted us to investigate the capability of this transformation (Table 2). Several ketene acetal nucleophiles were selected for the study to not only assess the scope of the reaction but also the ability of the methodology to produce aldol adducts substituted with commonly encountered groups. Ketene acetals with alkyl substituents larger than methyl reacted well under the standard reaction protocol, giving aldol products in high diastereoselectivities (15 : 1 to 99 : 1) and useful enantioselectivities. In general, higher selectivities were observed with *tert*-butyl pyruvate than methyl pyruvate (entries 1–5). In contrast to the useful results obtained with the isobutyl-substituted *N*,*O*-ketene acetal, the isopropyl-substituted ketene acetal (not shown) was essentially

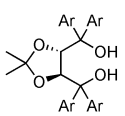
Table 1 Hydrogen bond promoted diastereo- and enantioselective Mukaiyama aldol reactions of representative esters of pyruvic acid



1 2 3 (major)

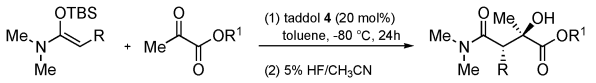
Entry	R^1	Yield (%)	dr	ee (%) *anti*/*syn*	Product
1	Me	80	15	85/60	**3a**
2	Et	72	17	80/70	**3b**
3	*i*Pr	67	14	89	**3c**
4	*t*Bu	80	22	93	**3d**
5	Bn	60	15	78	**3e**
6	Ph	40	17	59	**3f**

[a] All reactions were performed at 0.3 M concentration with 1.5 equiv. of the *N*,*O*-ketene acetal.



Ar = 1-naphthyl (**4**)

Table 2 H-bond promoted diastereo- and enantioselective Mukaiyama aldol reactions of representative substituted *N*,*O*-ketene acetals



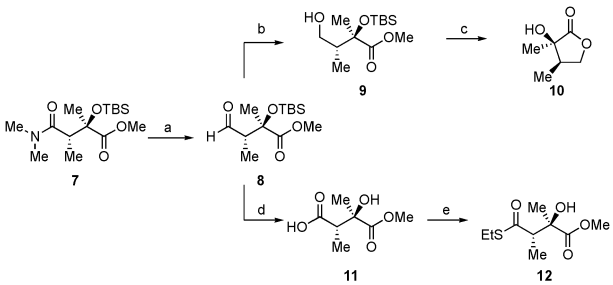
Entry	*R*	R^1	Product	Yield (%)	dr	ee (%)
1	Et	Me	**6a**	85	19 : 1	78
2	Et	*t*Bu	**6b**	44	15 : 1	84
3	Bn	Me	**6c**	73	24 : 1	88
4	*i*Bu	Me	**6d**	74	75 : 1	90
5	*i*Bu	*t*Bu	**6e**	48	99 : 1	93
6	OMe	Me	**6f**	78	99 : 1	88
7	OMe	*t*Bu	**6g**	63	99 : 1	92
8	OPh	Me	**6h**	84	99 : 1	97
9	OPh	*t*Bu	**6i**	61	99 : 1	95
10	OPMP	Me	**6j**	76	72 : 1	89
11	OPMP	*t*Bu	**6k**	80	77 : 1	95
12	SMe	Me	**6l**	51	33 : 1	91
13	Cl	Me	**6m**	84	99 : 1	88

[a] All the reactions were performed at 0.3 M concentration with 1.5 equiv. of the *N*,*O*-ketene acetal.

unreactive under the standard reaction conditions, presumably due to steric hindrance.

Several hetero-atom substituted ketene acetals were examined in the taddol catalyzed pyruvate aldol reaction and all worked well (entries 6–13). The high diastereo- and enantioselectivities observed for these substrates are of particular interest, since the Lewis basic functionalities in the reactants, some of which are capable of forming hydrogen bonds, could have altered the pyruvate-catalyst interactions required for good selectivities. Alkoxy substituted reactants gave the aldol products as essentially single diastereomers, formed in high enantioselectivities (entries 6–11). The *para*-methoxy phenyl (PMP) substituted ketene acetal was examined, as it would provide an orthogonally protected diol product prior to removal of the TBS group. The aldol adducts of the PMP substrates were obtained in high diastereoselectivities and excellent enantioselectivities. Sulfur and chlorine substituted ketene acetals were also effectively used in this reaction and provided the expected products in excellent selectivities (entries 12, 13).

The absolute and the relative configuration of the aldol products derived from this methodology were determined through correlation with known compounds. The aldol products possess an amide and an ester, two carboxyl groups known to have dramatically different reactivity. Most nucleophilic reagents are known to react preferentially with an ester carbonyl over an amide. A notable exception is the Schwartz reagent, which has been shown to selectively reduce a wide range of simple, tertiary amides to aldehydes.[11] In a recent report we showed not only that Schwartz's reagent reduces α-substituted tertiary amides to the corresponding aldehydes, but that it does so without epimerizing the α-position.[10e] Thus, treatment of aldol product **7**, a 15 : 1 mixture of diastereomers, with the Schwartz reagent afforded aldehyde **8** in essentially the same ratio of diastereomers. Further transformations converted **8** into the known γ-lactone **10**, which was used to confirm the relative configuration of the product.[7c]



Reaction Conditions: (a) $Cp_2Zr(H)Cl$ (2 equiv.), CH_2Cl_2, rt, 30 min, yield = 70%; (b) $NaBH_3CN$ (1 equiv.), CH_3COOH, THF, 0 °C, 15 min. yield = 84%; (c) 50% aq. HF:CH_3CN (1:1), 70 °C, 14 h, yield = 70%; (d) (i) Jones oxidation; (ii) 5% aq. HF/CH_3CN, rt, 12 h, yield = 80%; (e) (i) CDI, CH_3CN, rt, 2h; (ii) EtSH, 12h, rt , yield = 32%.

Scheme 1 Determination of relative and absolute configuration.

The correlation confirmed the major product of the hydrogen bond catalyzed Mukaiyama aldol to be the *anti*, as shown. The other products shown in Table 2 are expected to possess congruent stereochemistry. The absolute stereochemistry of the products was also established through chemical correlation to the known compound, ester-thioester **12**. The structure of **12** was unambiguously assigned based on comparison of its ^{1}H NMR, ^{13}C NMR and optical rotation with that reported in the literature (Scheme 1).[7]

The high enantioselectivity observed in the above reactions can be understood by considering a transition state in which the ketone carbonyl group is activated by the taddol catalyst through a single-point hydrogen bond. The enantioselectivities observed for the taddol catalyzed Mukaiyama aldol reactions of aldehydes were rationalized through such a model,[10b] further support for which was provided by a crystal structure of a complex between a taddol and an aldehyde.[10e]

The scope of this hydrogen bonding mediated reaction was expanded further to include benzoyl formates (phenylglyoxylates) as electrophiles. A search of the literature revealed no reports on catalytic diastereoselective and enantioselective Mukaiyama aldol reactions of these electrophiles. When *N*,*O*-ketene acetal **1** was reacted with methyl benzoyl formate using taddol catalysis, the aldol product was obtained as a 3 : 1 ratio of diastereomers, with each isomer being formed in comparable ee (Table 3, entry 1). As with pyruvates, the *tert*-butyl ester of benzoyl formate provided higher diastereoselectivity (entry 2). The ethyl substituted ketene acetal was more selective in terms of dr and ee than the parent nucleophile (entry 4). Alkoxy substituted ketene acetals afforded modest to very good diastereoselectivity, with both diastereomers being formed in high ee (entries 5–7).

The results above provide the first examples of hydrogen bond promoted diastereo- and enantioselective Mukaiyama aldol reactions of activated ketones with various *N*,*O*-ketene acetals. The reactions are catalyzed by the commercially available chiral hydrogen bond donor molecule, naphthyl taddol **4**. Pyruvates and benzoyl formates function well as electrophiles in these reactions, giving aldol products possessing two chiral centers in good to excellent diastereo- and enantioselectivities. This simple method produces richly functionalized subunits and should prove useful for natural product synthesis.

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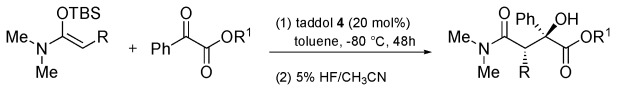
Table 3 Diastereo- and enantioselective Mukaiyama aldol reactions with methyl benzoyl formate[a]



5 13 (major)

Entry	*R*	R^1	Product	Yield (%)	dr	ee (%) *anti*/*syn*
1	Me	Me	**13a**	81	3 : 1	76, 71
2	Me	*t*Bu	**13b**	75	5 : 1	73, 86
3	Et	Me	**13c**	90	10 : 1	87, —
4	OMe	Me	**13d**	76	2 : 1	83, 88
5	OPh	Me	**13e**	76	9 : 1	86, 92
6	OPMP	Me	**13f**	87	9 : 1	88, 87

[a] All reactions were performed at 0.3 M concentration using 1.5 equiv. of *N*,*O*-ketene. The stereochemistry assigned to the products is tentative.

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