Determination of Relative Frequency of Carbanion Formation at α-Positions of Ketones under Aldol Reaction Catalysis Conditions

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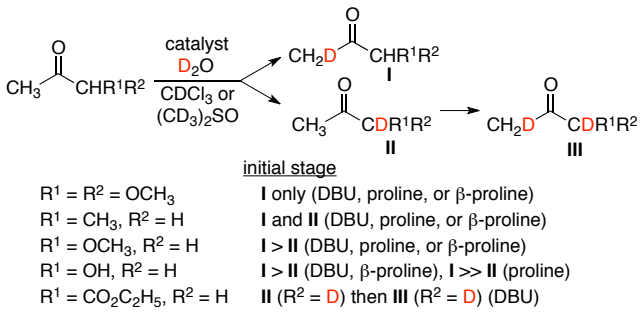
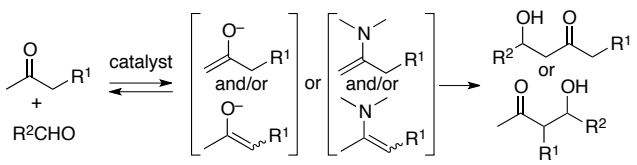
Supporting Information



ABSTRACT: To provide insight into aldol reaction catalysis, the relative frequencies of carbanion formation at each α-position of ketones under catalysis by DBU, proline, β-proline, and related catalysts were determined through the deuteration of the ketones in the presence of these catalysts. For selected cases, the deuteration rate was compared with the aldol reaction rate, and whether the generated enolate/enamine resulted in return to the ketone or product formation was estimated.

The reactions of ketones involving in situ formation of enolates and their equivalents (such as enamines) constitute important chemical transformations; an example is the aldol reaction.[1,2] In the reactions of preformed enolates and silyl enol ethers, reaction sites on the corresponding ketones are determined by the formation of the enolates and the enol ethers.[1] In the catalyzed reactions of ketones, however, the relationship between the formation of enolates or enamines and the formation of products, including regioselective formation of products, is not well understood.[2-6] When a ketone has two enolizable α-positions, the carbanion may form at both the α-positions or at either of the α-positions. Although the product-forming enolates/enamines can be deduced from the products, it has been rarely determined which enolates/enamines form and to what extent during the catalyzed reactions. Regioselectivities of aldol and related reactions may be the results of regioselective formation of an enolate/enamine or because a single type of enolates/enamines among those formed results in product formation (Scheme 1).

Scheme 1. Enolates/enamines in regioselective reactions.



Although it is often considered that the transition state of the C-C bond formation is the one controlling the product formation and the product stereochemistries,[7] extent of generation of the transition state and thus the formation of the product may be affected by concentrations of the enolates/enamines. Thus, frequency of the formation of the enolates/enamines, half-lives of the formed enolates/enamines, the rate of the formation of the enolates/enamines, and other factors all impact product formation.[8] Although transition states of the C-C bond formation have been computed or suggested in certain cases of catalyzed aldol and related reactions of ketones, including those of highly diastereo- and enantioselective versions of the reactions, the reported transition states are often derived only from the enolates/enamines that lead the generated products to address the *syn*/*anti*- and/or enantioselectivities.[2-5,6d,e,g,i,k,7a]

To understand mechanisms of the regioselectivities of the C-C bond formation in aldol and related reactions of ketones having two enolizable α-positions and to understand mechanisms of catalysis, sites of carbanion formation (i.e., which enolates/enamines form) and the frequencies with which these species form must be determined. This information may be combined with analyses of products formed to understand whether the enolates/enamines generated are used for the C-C bond formation or are returned to the ketone and to what degree the enolates/enamine formation is reversible during aldol and related reactions. Subsequent comparison to all possible transition states derived from each of all the forming enolates/enamines may be used to elucidate the mechanisms of regioselective formations of products and of the mechanisms of catalysis.

Here, to take the first step, relative frequencies of the α-carbanion formation (formations of enolates/enamines) of ketones **1**-**5** (Figure 1) under the catalysis by DBU, proline, pyrrolidine-3-carboxylic acid (β-proline), and related molecules (Figure 2) were determined through the deuteration of the ketones in the presence of these catalysts. For selected cases, the frequencies of the enolate or enamine formation were compared with the aldol reaction rates. Ketones **1**-**5** were used in this study because regioselective reactions of these ketones are of interest.[3-6]

Carbanions and their equivalents of ketones readily react with D_2O.[9] Thus, deuteration may be correlated with the formation of the carbanions and their equivalents.[9] We reasoned that rates and sites of ketone deuteration in the presence of catalysts should correlate with the frequency of the formation of enolates/enamines.

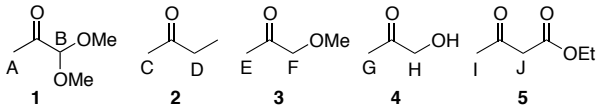


Figure 1. Ketones and their potential deuteration positions.

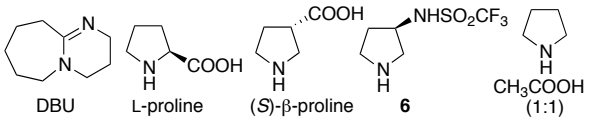


Figure 2. Catalysts used in the deuteration study.

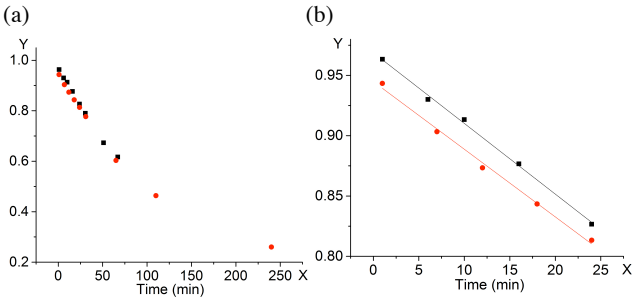


Figure 3. Time course of the deuteration of **1** in the presence of DBU. X = time after addition of DBU. Y = [integration of the CH_3 (including CH_2D and CHD_2) at position A]/{[integration of $(OCH_3)_2$] x 1/2}. (a) The full time range analyzed and (b) the time range corresponding to the initial stage of the reaction. Carried out twice: Black squares: Y = -0.00586X + 0.96(8); red circles: Y = -0.00561X + 0.94(4).

First, the deuteration reaction of 1,1-dimethoxypropan-2-one (**1**) was performed in the presence of DBU (0.1 equiv) and D_2O in $CDCl_3$. The reaction mixture was time-dependently monitored by ^1H NMR analyses and changes in the integration of the CH_3 (including CH_2D and CHD_2) at position A and of the CH at position B (Figure 1) were monitored. The initial rate of the deuteration was determined from the changes in the integration over time (Figure 3 and Table 1, entries 1 and 2, see also Supporting Information (SI)). The integration of the methyl group at position A was reduced by approximately half after 100 min under the conditions used, indicating that the methyl group was approximately 50% deuterated after 100 min (Figure 3). In contrast, the integration of the proton at position B was unchanged after 48 h (i.e., no deuteration of the methine group at position B). These results indicate that the carbanion is generated exclusively at the methyl group at position A of **1** or that the methyl group at position A is the enolizing site under the DBU catalysis conditions used.

In the DBU-catalyzed aldol reactions of ketone **1** with aryl trifluoromethyl ketones, the C-C bond formation occurred only at the methyl group at position A.[3b,c] Thus, the bond formation reaction site of the ketone in the aldol reactions matched to the site of the carbanion formation.

Table 1. Relative deuteration rates per original proton.[a]

entry	ketone and position		relative deuteration rate per proton (min^{-1})		
			DBU in $CDCl_3$	proline in $(CD_3)_2SO$	β-proline in $(CD_3)_2SO$
1	**1**	CH_3, A	5.7×10^{-3}	1.2×10^{-4}	1.0×10^{-2}
2	**1**	CH, B	–[b]	–[b]	–[b]
3	**2**	CH_3, C	1.7×10^{-4}	1.4×10^{-4}	5.5×10^{-3}
4	**2**	CH_2, D	1.9×10^{-4}	2.1×10^{-5}	3.4×10^{-3}
5	**3**	CH_3, E	2.5×10^{-3}	3.6×10^{-4}	1.4×10^{-2}
6	**3**	CH_2, F	8.6×10^{-4}	1.1×10^{-4}	6.5×10^{-3}
7	**4**	CH_3, G	8.9×10^{-3}	1.1×10^{-4}	1.3×10^{-2}
8	**4**	CH_2, H	3.7×10^{-3}	$<1.3 \times 10^{-5}$	2.8×10^{-3}
9	**5**	CH_3, I	3.2×10^{-3}	–[c]	–[c]
10	**5**	CH_2, J	>0.7	>0.7	>0.7

[a] Conditions: Ketone (1.8 mmol), D_2O (8.0 mmol), and catalyst (0.18 mmol) in $CDCl_3$ (9.0 mL) or $(CD_3)_2SO$ (9.0 mL) as indicated at room temperature (25 °C). [b] Deuteration was not detected. [c] Deuterated in <5% after 24 h.

Deuteration of ketone **1** was also analyzed in the presence of proline under the same conditions, except that $(CD_3)_2SO$ was used instead of $CDCl_3$. In this case, deuteration was also detected only at the methyl group at position A. The previously reported regioselective C-C bond formation at the methyl group at position A in the proline-catalyzed aldol reactions of **1**[10] also matched to the deuteration site of **1**. The initial rate of the deuteration at the methyl group at position A in the presence of proline in $(CD_3)_2SO$ was approximately 50-fold slower than that in the presence of DBU in $CDCl_3$. Deuteration of **1** in the presence of proline was also tested in $CDCl_3$, but the mixture was not homogeneous and the initial rate of the deuteration was much slower than that in $(CD_3)_2SO$. The slow deuteration in the presence of proline compared to the deuteration in the presence of DBU is in accord with the slow reaction rates of the proline-catalyzed aldol reactions compared to DBU-catalyzed aldol reactions.[3b,c,10]

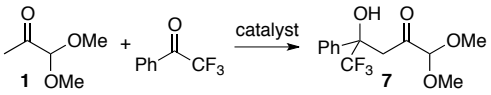
Deuteration of **1** was further tested in the presence of β-proline in $(CD_3)_2SO$. It has been demonstrated that β-proline catalyzes Mannich-type reactions of ketones, including those larger than acetone and those that are often not good substrates in proline-catalyzed reactions.[5] Deuteration of **1** by β-proline catalysis also occurred only at the methyl group at position A of **1**, and the initial rate of the deuteration by β-proline catalysis was approximately 100-fold faster than that by proline catalysis (Table 1, entry 1).

Deuteration of **1** in the presence of catalyst **6** in $(CD_3)_2SO$, pyrrolidine-CH_3COOH (1:1) in $(CD_3)_2SO$, and Et_3N in $CDCl_3$ were also analyzed. As Et_3N did not work as the catalyst for aldol reactions of **1** with phenyl trifluoromethyl ketone,[3c] no

deuteration of **1** was observed under the conditions with Et_3N. Deuteration at the methyl group was observed in the presence of **6** and pyrrolidine-CH_3COOH; the relative initial rates were 1.7 x 10^{-3} min^{-1} and 6.6 x 10^{-3} min^{-1}, respectively.

Next, aldol reactions of **1** affording **7** using the catalysts in neat conditions suitable for synthesis[3c] were performed and the conversion was analyzed over time (Table 2). Whereas the deuteration of ketone **1** using β-proline as catalyst was faster than that using **6** or pyrrolidine-CH_3COOH in $(CD_3)_2SO$, the aldol reaction to generate **7** using β-proline as catalyst was slower than that using **6** or pyrrolidine-CH_3COOH under neat conditions (Table 2, entry 3 versus entries 4 and 5). The deueteration of ketone **1** by β-proline was 100-fold faster than that by proline (Table 1, entry 1). In aldol reaction of **1**, however, the formation of the aldol product by β-proline catalysis was only 2 to 2.5-fold faster than that by proline catalysis (Table 2, entry 3 versus entry 2). Formation of the carbanion (or formation of enolate/enamine) was necessary for the generation of the aldol reaction product, but faster carbanion formation did not always result in faster aldol reaction. The enolates and enamines that do not lead to the bond-forming transition state to afford the products were abundant.

Table 2. Aldol reaction conversion and yield.[a]



entry	catalyst	conversion (%)[b]	isolated yield (%)
1[c]	DBU	>95 (1.5 h)	84 (1.5 h)
2	proline	7 (3 h), 30 (22 h), 73 (93 h)	62 (96 h)
3	β-proline	15 (3 h), 69 (22 h)	68 (30 h)
4	**6**	55 (1 h), 80 (2 h), 91 (3 h)	88 (5 h)
5	pyrrolidine-CH_3COOH	60 (1 h), 86 (2 h), 91 (3 h)	91 (5 h)

[a] Conditions: **1** (5.0 mmol), phenyl trifluoromethyl ketone (0.5 mmol), and catalyst (0.05 mmol) at rt (25 °C) (neat). [b] Determined by ^1H NMR. [c] Data from ref 3c.

For the DBU and proline catalysis, the aldol reaction of **1** to afford **7** was also performed under the conditions that were the same as those used in the deuteration reaction except that phenyl trifluoromethyl ketone was used instead of D_2O. The initial rates of the formation of **7** were analyzed (Table 3, entry 1). Aldol reaction rates were also determined under the conditions with less (0.9 mmol compared to 8.0 mmol) phenyl trifluoromethyl ketone in the absence and presence of H_2O (Table 3, entries 2 and 3). In these cases, the added water did not affect the rate of the aldol reaction. Based on this result, by comparing the aldol reaction rates with the deuteration rates that are expected to reflect the frequency of the enolate/enamine formation, the extent of the conversion of the enolate/enamine to the aldol product was estimated. For the DBU catalysis, the aldol reaction rate was approximately 1/7 of the deuteration rate (Table 3, entry 1), indicating that approximately one in every seven enolates formed reacted with the acceptor ketone to afford aldol product **7**, and that the remaining six enolates were returned to the ketone. For the proline catalysis, the aldol reaction rate was approximately 2/3 of, or similar to the deuteration rate (Table 3, entry 4), indicating that approximately two in three enamines formed were used for the formation of the aldol product. Thus, although the frequency of enamine formation does not provide the information about the half-life or stability of the enamine, the product formation rate does depend on the enamine formation in the proline catalysis.

Table 3. Relative rates of aldol reaction of **1** to afford **7** and relative rates of deuteration of **1**.

entry	catalyst in solvent	relative rate of aldol reaction per molecule (min^{-1})[a]	relative rate of deuteration at position A per molecule (min^{-1})[b]
1	DBU in $CDCl_3$	2.4 x 10^{-3}	1.7 x 10^{-2}
2[c]	DBU in $CDCl_3$	2.5 x 10^{-4}	-
3[c,d]	DBU in $CDCl_3$	2.5 x 10^{-4}	-
4	proline in $(CD_3)_2SO$	2.2 x 10^{-4}	3.5 x 10^{-4}

[a] Aldol reaction conditions: **1** (1.8 mmol), phenyl trifluoromethyl ketone (8.0 mmol), and catalyst (0.18 mmol) in $CDCl_3$ (9.0 mL) or $(CD_3)_2SO$ (9.0 mL) as indicated at rt (25 °C). Full conversion of **1** to **7** in 1.0 minute = 1.0 min^{-1}. [b] Relative deuteration rate per proton shown in Table 1 was multiplied by 3 because of CH_3. [c] For the aldol reaction, phenyl trifluoromethyl ketone (0.9 mmol). [d] For the aldol reaction, H_2O (8.0 mmol) was added.

The deuteration of ketones **2**-**5** was also analyzed (Table 1, see also SI). For 2-butanone (**2**), under DBU catalysis, the initial rate of the deuteration per proton at the methyl group at position C was similar to that per proton at the methylene group at position D. Under proline catalysis, deuteration at the methyl group at position C was faster than that of the methylene group at position D (Table 1, entries 3 and 4).

For methoxyacetone (**3**), the initial rate of the deuteration per proton at the methyl group at position E was 2- to 3-fold faster than that per proton at the methoxy-substituted methylene group at position F for all the cases of the catalysis by DBU, proline, and β-proline (Table 1, entries 5 and 6).

For hydroxyacetone (**4**), similar to the results of **3**, the initial rate of the deuteration per proton at the methyl group at position G was faster than that per proton at the hydroxyl group-substituted methylene group at position H for all the three catalysts (Table 1, entries 7 and 8). Under the proline catalysis, the initial velocity of the deuteration at the methyl group at position G of **4** was similar to that at the methyl group at position A of ketone **1**, and the deuteration rate of the hydroxyl group-substituted methylene group at position H was more than 10-times slower than that of the methyl group at position G. In reported proline-catalyzed aldol reactions of **4** with aldehydes, the C-C bond formation often exclusively occurred at the hydroxyl group-substituted methylene moiety at position H.[4] However, deuteration of this site was found to be slower than the deuteration of the methyl group that was not the bond-forming site. Deuteration at the methyl group at position G of **4** in the presence of β-proline was approximately 100-fold faster than that in the presence of proline.

For ethyl 3-oxobutanoate (**5**), the methylene group at position J was immediately (within a minute) deuterated in more

than 70% upon addition of DBU, proline, or β-proline (Table 1, entry 10). Deuteration of the methyl group at position I was also observed in the presence of DBU (Table 1, entry 9). This is in accord with the previous observation that DBU-catalyzed aldol reactions of **5** provide aldol products with the C-C bond formation at position I.[3c] For proline or β-proline catalysis, the deuteration of the methyl group at position I was less than 5% after 24 h.

For ketones **2**, **3**, **4**, and **5**, the positions favored for deuteration did not directly correlate with the C-C bond formation sites in aldol and related reactions (see SI, Table S22 for refs of reactions of each ketone). Formation of carbanions (or enolates/enamines) is necessary to be the reaction site and for fast reactions, rapid or frequent enolate/enamine formation is required. But, the results indicate that frequent carbanion formation site is not necessary to be the C-C bond formation site. To understand regioselectivities of the aldol reactions, transition states for the C-C bond formation involving each of all the enolates/enamines formed may need to be compared.

In summary, relative frequencies of the formation of carbanions (or enolates/enamines) of a set of ketones at each α-position under catalyzed reaction conditions were determined through deuteration. For selected cases, the consequences of the formed enolates/enamines during the catalyzed reactions were estimated by comparing the deuteration results and the aldol reaction results. With these experiments, mechanisms of regioselectivities of the reactions and mechanisms of catalysis were clarified to some degree. The strategies and the methods used in this study may be useful for elucidating mechanisms of other catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, deuteration results, and NMR spectra of deuteration experiments (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This study was supported by the Okinawa Institute of Science and Technology Graduate University and in part by the MEXT/JSPS (Japan) Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (No. 26105757).

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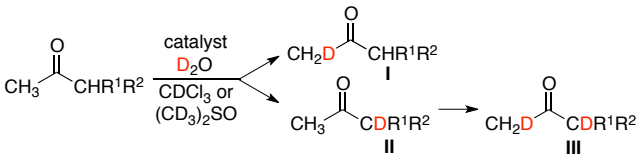

initial stage

$R^1 = R^2 = OCH_3$	**I** only (DBU, proline, or β-proline)
$R^1 = CH_3$, $R^2 = H$	**I** and **II** (DBU, proline, or β-proline)
$R^1 = OCH_3$, $R^2 = H$	**I** > **II** (DBU, proline, or β-proline)
$R^1 = OH$, $R^2 = H$	**I** > **II** (DBU, β-proline), **I** >> **II** (proline)
$R^1 = CO_2C_2H_5$, $R^2 = H$	**II** (R^2 = D) then **III** (R^2 = D) (DBU)