DOI: 10.1002/adsc.200505190

The Direct, Enantioselective, One-Pot, Three-Component, Cross-Mannich Reaction of Aldehydes: The Reason for the Higher Reactivity of Aldimine *versus* Aldehyde in Proline-Mediated Mannich and Aldol Reactions

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Received: May 8, 2005; Accepted: July 27, 2005

Abstract: In the proline-mediated Mannich and aldol reactions of propanal as a nucleophile, the aldimine prepared from benzaldehyde and *p*-anisidine is about 7 times more reactive than the corresponding aldehyde, benzaldehyde, as an electrophile. This higher reactivity of aldimine over aldehyde is attributed to the carboxylic acid of proline protonating the basic nitrogen atom of the aldimine more effectively than the oxygen atom of the aldehyde, an explanation which has been both experimentally and theoretically verified.

Keywords: asymmetric synthesis; imines; Mannich reaction; organocatalysis; proline

Introduction

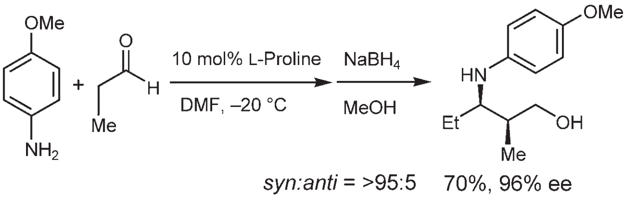
Aldehydes and aldimines are both important electrophiles in organic synthesis, and addition reactions to these electrophiles constitute some of the most useful and fundamental organic transformations. It is generally accepted that an aldimine is less reactive toward nucleophilic addition than its corresponding aldehyde owing to the difference in electronegativity between O and N, and the steric hindrance present in the aldimine.[1] Recently, however, an aldimine has been found to be more reactive than the corresponding aldehyde in the following reactions. In the Mukaiyama aldol and Mannich reactions, Kobayashi and co-workers have reported that a silyl enol ether reacts preferentially with aldimines over aldehydes in the presence of $Yb(OTf)_3$,[2] which is in marked contrast to conventional Lewis acids such as $TiCl_4$ or TMSOTf, which afford the aldol product selectively. In the presence of $PdCl_2(PPh_3)_2$ the reactivity of allylstannanes with aldimines is higher than that with aldehydes.[3] Akiyama and co-workers have reported that the aldimine was activated chemoselectively by HBF_4, or a small loading of the conventional Lewis acid or the combination of $BF_3 \cdot OEt_2$ and water.[4] In reductive amination using $NaBH_3CN$, the imine is more reactive than the corresponding carbonyl compound.[5] However, as far as we are aware, these have been the only examples in which the aldimine is more reactive than aldehyde.

The catalytic, asymmetric Mannich reaction is one of the most powerful methods for the construction of chiral nitrogen-containing molecules. Recently several excellent results have been reported in this area, some of which are based on catalytic asymmetric additions of a preformed enolate to aldimines.[6] In addition to such Mannich reactions of preformed enolates, direct, catalytic asymmetric Mannich reactions have also been developed recently.[7] Chiral organometallic catalysts of this reaction have been developed by Shibasaki,[8] Jørgensen,[9] and Trost,[10] while a chiral Brønsted acid catalyst was devised by Terada.[11] List's[12] and Barbas'[13] groups have independently developed the asymmetric, direct three-component Mannich reaction catalyzed by proline,[14] and now organocatalysis-mediated asymmetric Mannich reactions have been investigated by the several groups.[15]

We have been studying organic reactions under high pressure induced by water-freezing,[16] and recently found that this high pressure effectively promotes the List–Barbas–Mannich reaction between aldehyde, anisidine and proline, affording the Mannich adducts in good yield and excellent enantioselectivities, even for substrates which cannot be obtained at ambient pressure.[17] During the application of high pressure induced by water-freezing to the three-component cross-Mannich reaction of two different aldehydes, we found that the desired Mannich product was obtained in good yield with excellent enantioselectivity at –20 °C, and soon discovered that high pressure is not necessary.[18] That is, a direct and enantioselective, one-pot, three-component cross-Mannich reaction of two different aldehydes proceeded at ambient pressure. A Mannich reaction in which one aldehyde is employed as the Mannich donor, and the other aldehyde is utilized as a component of the Mannich acceptor, affording a synthetically versatile intermediate, a β-amino aldehyde. A similar reaction was reported by Barbas'[13g] and Cordova's[19] groups independently.

The corresponding cross-aldol reaction of two different aldehydes has been reported to proceed at 4 °C by Northrup and MacMillan.[20] The fact that the Mannich reaction proceeds at lower temperature (–20 °C) than the aldol reaction (4 °C) indicates that the aldimine is more electrophilic than the parent aldehyde.

The self-Mannich reaction of propanal, *p*-anisidine and a catalytic amount of L-proline also proceeds when all three components are mixed together at –20 °C without preformation of the aldimine [Eq. (1)].[18] The success of this procedure also indicates that the self-Mannich reaction is faster than the self-aldol reaction.



syn:anti = >95:5 70%, 96% ee

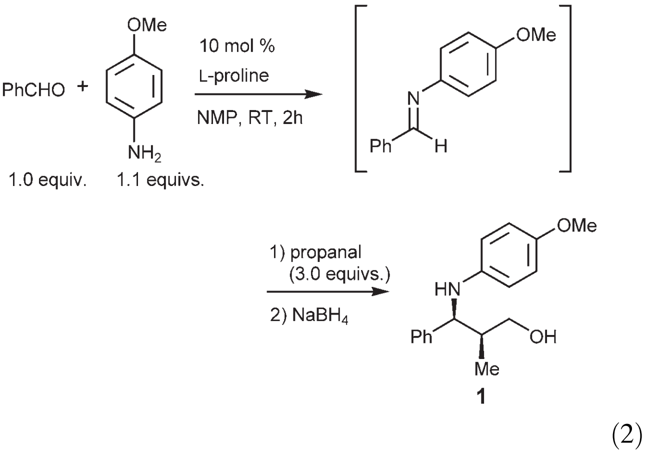
(1)

These results are contrary to the generally accepted notion mentioned above that an aldimine is less reactive toward nucleophilic addition than its parent aldehyde. In order to clarify the reason for the reactivity difference between aldimine and aldehyde in the proline-catalyzed Mannich and aldol reactions,[21] a systematic comparison of aldimine and aldehyde has been made, and theoretical calculations on these reactions performed, which will be disclosed in this full paper.

Results and Discussion

Optimization of the Conditions of the Mannich Reaction

As a typical three-component Mannich reaction, we selected that involving propanal, benzaldehyde and *p*-anisidine as the nucleophilic aldehyde, electrophilic aldehyde and amine, respectively. The reaction was performed as follows [Eq. (2)]: To the aldimine, generated by stirring *p*-anisidine (1.1 equivs.), benzaldehyde (1.0 equiv.), and proline (10 mol %) for 2 h in a given solvent at room temperature, was added propanal (3.0 equivs.) at a given temperature. The reaction was quenched after 20 h by the addition of $NaBH_4$ in order to reduce the β-amino aldehyde initially formed to the corresponding β-amino alcohol **1** because of the former's instability. Optimization of the reaction conditions was performed. Screening of solvents revealed that DMF and NMP (*N*-methyl-2-pyrrolidinone) were suitable, affording the product in good yield with high *syn*- and enantio-selectivities, while the reaction scarcely proceeded in CH_3CN, CH_2Cl_2, THF and toluene. The reaction was examined in NMP at three different temperatures, 0 °C, –10 °C and –20 °C with varying reaction times, the results being summarized in Figure 1. Although a high yield (86%) was obtained after 5 h at 0 °C, the yield decreased after 5 h owing to side-reactions of the initially generated Mannich adduct with propanal (*vide infra*). At –10 °C and –20 °C, however, good yields (85%) were obtained after 20 h and the yield did not decrease beyond a certain time. The following conclusions were drawn from these results. The progress of the reaction should be monitored carefully when it is carried out at 0 °C, because of the rapid over-reaction, and the best reaction time is dependent on the substrate. At –10 °C or –20 °C, however, careful monitoring of the reaction progress is not necessary and good yields are obtained even after long reaction times.



(2)

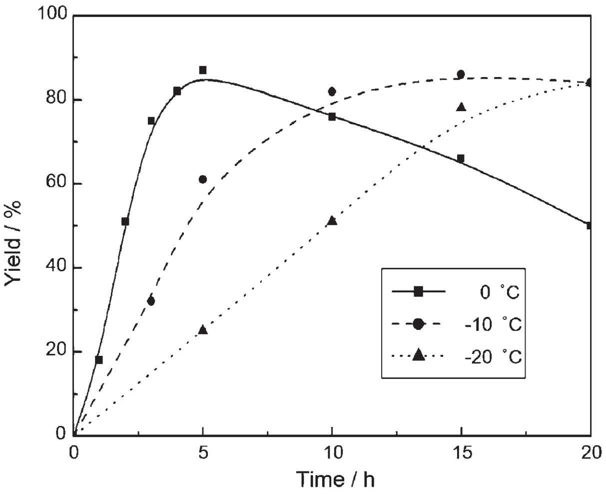
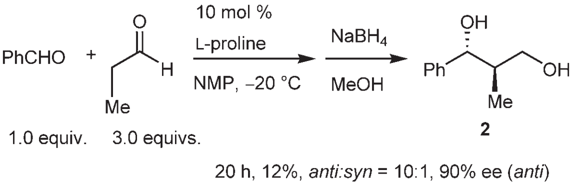


Figure 1. Effects of temperature and reaction time on the proline-mediated Mannich reaction.

Experimental Comparison of the Reactivity between Aldimine and Aldehyde

Next, the cross-aldol reaction of benzaldehyde and propanal was examined using NMP as solvent [Eq. (3)]. When the reaction was performed at 0 °C, several products were obtained; the cross-aldol product, the self-aldol product of propanal, and the aldol product of the initially generated cross- and self-aldol products with propanal. On the other hand, when the reaction was carried out at –20 °C, the reaction was rather clean, though its progress was slow. After 20 h at –20 °C, the *anti*-aldol product was obtained in 12% yield with good diastereoselectivity (*anti:syn* = 10:1) and excellent enantioselectivity (90% ee). The yield of the cross-aldol product versus reaction time is summarized in Figure 2. We also performed another experiment in which the self-aldol reaction of propanal was investigated at –20 °C, the results of which are also summarized in Figure 2. Figure 2 shows that reaction rates of the cross- and self-aldol reactions are similar.



(3)

From Figures 1 and 2, it was found that *N*-benzylidene-*p*-anisidine is about 7 times more reactive than the parent aldehyde, benzaldehyde, in the proline-mediated reaction with propanal at –20 °C.

The reactivity difference between aldimine and aldehyde was also investigated by direct *in situ* comparison. The reaction was performed as follows: benzaldehyde (1.0 M) and *p*-anisidine (0.50 M) were stirred in NMP for 2 h in the presence of proline (0.1 M), affording *N*-benzylidene-*p*-anisidine (0.50 M) and benzaldehyde (0.50 M), as checked by ^{1}H NMR. To this mixture was added propanal (3.0 M) at –20 °C, and the reaction was quenched after a certain period of time by the addition of $NaBH_4$ or $LiAlH_4$ [Eq. (4)]. Yields of the Mannich and aldol products were determined after isolation of β-amino alcohol **1** and 1,3-diol **2**. The results are summarized in Figure 3. From this *in situ* comparison, *N*-benzylidene-*p*-anisidine is found to be 6.8 times more reactive than benzaldehyde, which is in good agreement with the reactivity difference determined by the individual experiments.

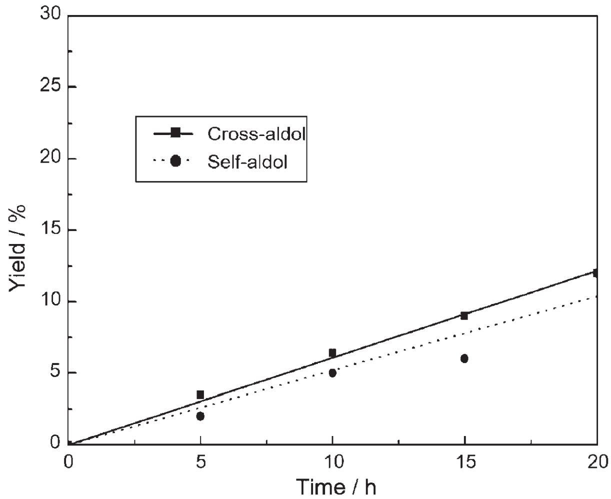
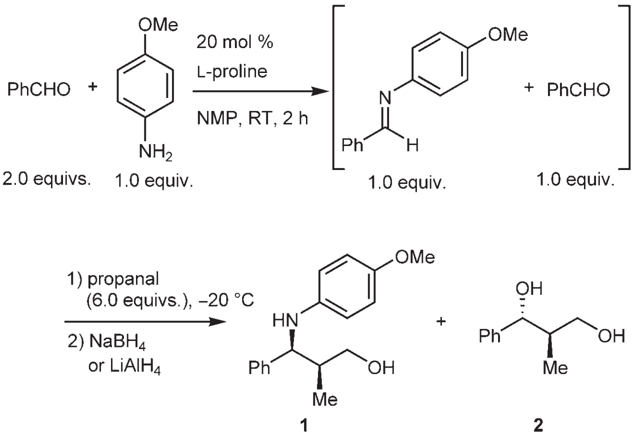


Figure 2. Relationship between yield and reaction time in the proline-mediated cross-aldol reaction of benzaldehyde and propanal and self aldol reaction of propanal at –20 °C.



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Theoretical Calculations

In order to explain the reactivity difference between aldimine and aldehyde as electrophiles in the proline-

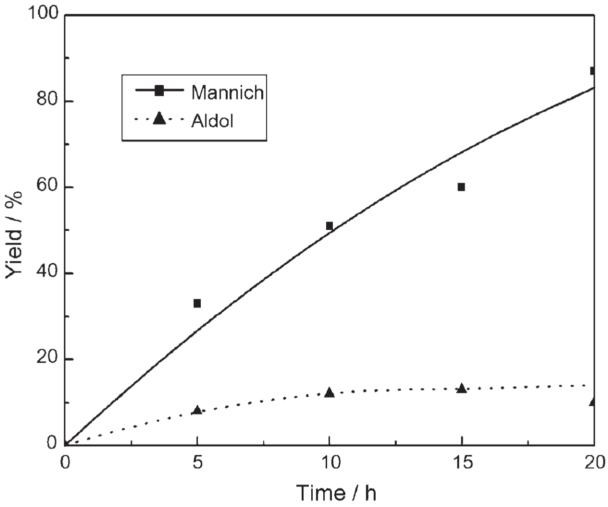


Figure 3. Reactivity difference of proline-mediated Mannich and aldol reactions by direct *in situ* comparison at −20 °C.

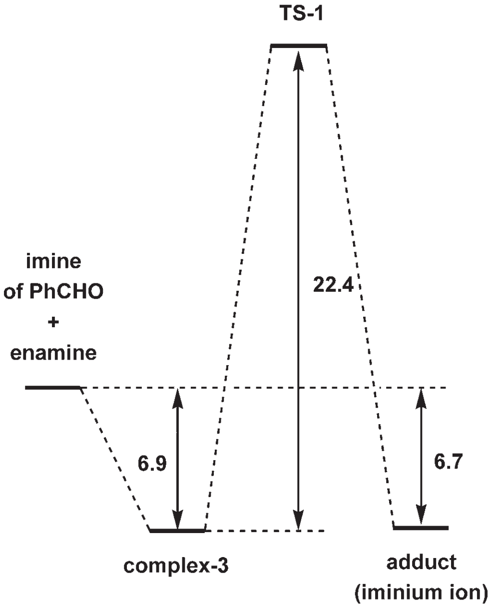


Figure 4. Potential energy profile for the Mannich reaction.

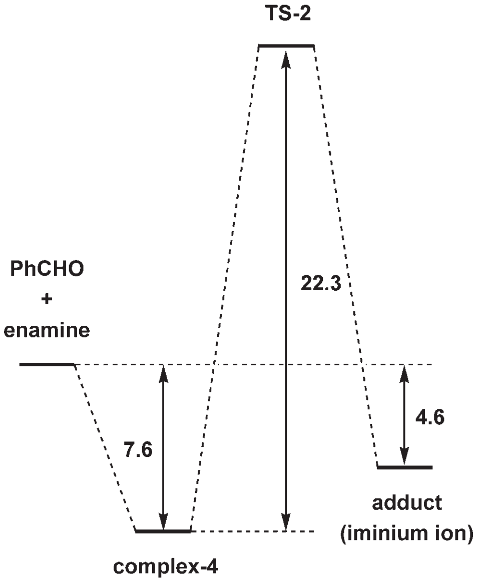


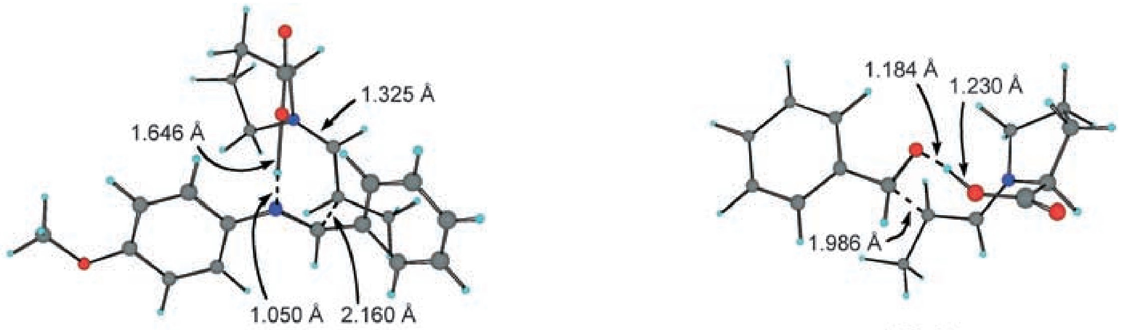
Figure 5. Potential energy profile for the aldol reaction.

mediated reaction with propanal, we have calculated the Mannich reaction of *N*-benzylidene-*p*-anisidine and propanal catalyzed by proline, and the aldol reaction of benzaldehyde and propanal catalyzed by proline using density functional theory (B3LYP/6-31G*).[22] Houk and Bahmanyar have already calculated the much simpler systems such as the Mannich reaction of *N*-ethylideneaniline and acetone[23] and the aldol reaction of acetone.[24]

In the Mannich reaction, the enamine interacts with the aldimine to generate a stable intermediate **3**, which is stabilized by 6.9 kcal/mol.[25] From this intermediate **3**, the Mannich reaction proceeds *via* **TS-1** with a TS energy of 22.4 kcal/mol. In the aldol reaction, benzaldehyde and the enamine interact to generate a stable intermediate **4**, which is stabilized by 7.6 kcal/mol.[25] From this intermediate **4**, the aldol reaction proceeds *via* **TS-2**, with a TS energy of 22.3 kcal/mol.

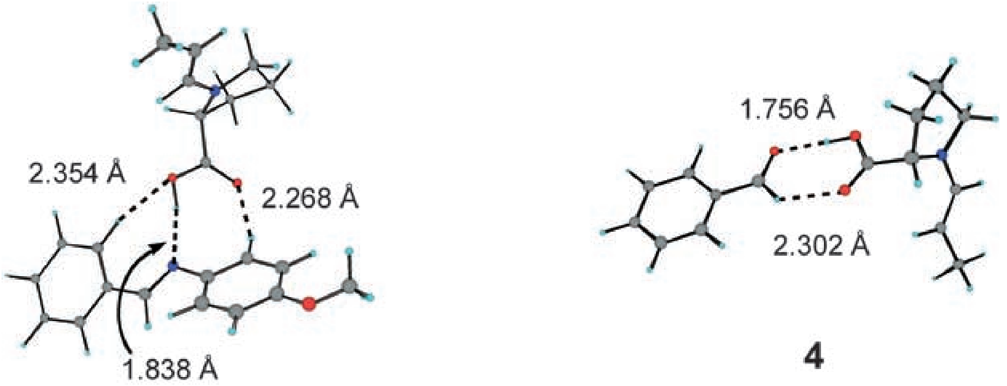
This theoretical comparison of the Mannich and aldol reactions revealed the following phenomena: the timing of the carboxylic acid proton transfer from proline to aldimine and aldehyde is completely different, which was originally observed in the Houk's calculation of the simpler system.[23] In the Mannich reaction, the carboxylic acid proton is mostly transferred to the aldimine, with the newly formed C–C single bond length is 2.160 Å, the newly formed N–C iminium bond length is 1.325 Å, the newly formed N–H bond length is 1.050 Å and the cleaved RCO_2–H bond length is 1.646 Å (**TS-1**). In the aldol reaction, however, proton transfer from the carboxylic acid to aldehyde and C–C single-bond formation occur nearly simultaneously with the newly forming O–H bond length being 1.184 Å and the cleaving RCO_2–H bond length is 1.230 Å in the transition state (**TS-2**). In other words, in the Mannich reaction initially protonation occurs on the basic nitrogen of the aldimine, which strongly activates it. This activation is much more effective than the activation by protonation of the less basic aldehyde. As the aldimine is more effectively activated by carboxylic acid protonation than the aldehyde, it is more electrophilic than the aldehyde in proline-mediated reactions.

Moreover, as the proton was mostly transferred on the nitrogen of the imine in the transition state, the charge density at the transition state is more localized in the Mannich reaction than in the aldol reaction. Because the solvent stabilizes the more charge-separated transition state, decreasing the activation energy, it would be



TS-1 TS-2

Figure 6. Transition state structure for the proline-catalyzed Mannich and aldol reactions.



3 4

Figure 7. The structures of the complexes in the Mannich and aldol reactions.

reasonable that the Mannich reaction is faster than the aldol reaction in a polar solvent such as NMP.[26]

^{1}H and ^{13}C NMR Study of Aldimine and Aldehyde in the Presence of Acid

To confirm this conclusion further, ^{1}H and ^{13}C NMR experiments[27] were carried out on the three samples; *N*-benzylidene-*p*-anisidine (sample A), benzaldehyde (sample B), and an equimolar mixture of *N*-benzylidene-*p*-anisidine and benzaldehyde (sample C). A certain amount of CF_3CO_2H was added little by little to $(CD_3)_2SO$ solutions of these three samples at 300 K. The variations in chemical shift of the aldimine and/or aldehyde proton and carbon (Figures 8 and 9) *versus* the amount of CF_3CO_2H were measured, with results summarized in Figures 10 and 11, respectively.

There is a good correlation between the ^{1}H NMR and ^{13}C NMR data, and moreover the experiments on aldehyde and aldimine separately (samples A and B), and on direct *in situ* comparison (sample C), gave the same results. Shifts to lower field were observed for the aldimine carbon and hydrogen in accordance with the amount of CF_3CO_2H. In the case of the aldehyde, however, only small down field shifts were observed. These results clearly indicate that the aldimine is protonated effectively, while the aldehyde is not.

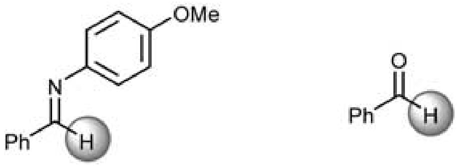


Figure 8. A proton examined in ^{1}H NMR.

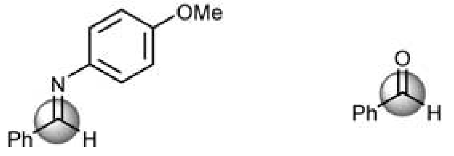


Figure 9. A carbon examined in ^{13}C NMR.

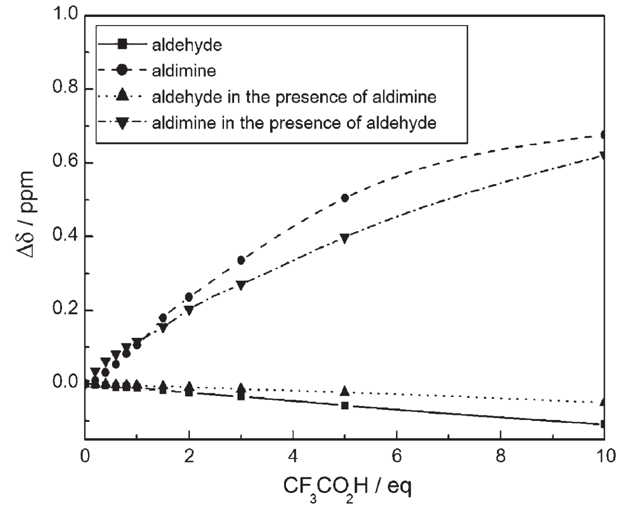


Figure 10. Correlation between the amount of CF_3CO_2H and ^1H NMR chemical shift.

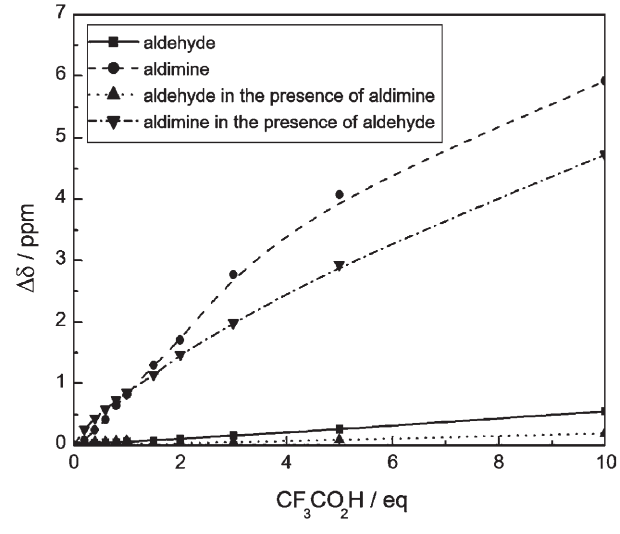
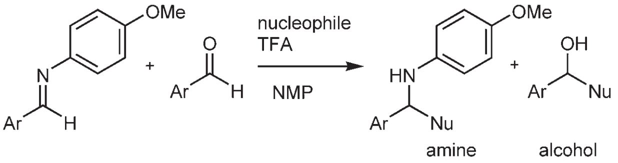


Figure 11. Correlation between the amount of CF_3CO_2H and ^{13}C NMR chemical shift.

The higher reactivity of aldimine over aldehyde is attributed to the effective protonation by acid of the aldimine basic nitrogen, which is supported by NMR experiments. This concept should be applied not only to the proline-mediated Mannich and aldol reactions but also to other Brønsted acid-mediated reactions. Thus, we investigated the reactivity difference between aldimine and aldehyde in the presence of Brønsted acid in the addition reaction of silyl enol ether, and allyltin and reduction by the use of Bu_3SnH. The equimolar amounts of aldimine and aldehyde were treated with 1-phenyl-1-trimethylsiloxyethene,[4d] allyltributhyltin,[4b] or Bu_3SnH in the presence of an equimolar amount of CF_3CO_2H with the results summarized in Table 1. All these nucleophiles selectively add to aldimine, affording the corresponding amine with a trace amount of alcohol generated by the reaction with aldehyde. These results clearly indicate that Brønsted acid selectively activates imine over aldehyde.[4]



(5)

Conclusion

The reason for the higher reactivity of aldimine over aldehyde in the asymmetric, direct, one-pot, three-component, cross-Mannich reaction of two different aldehydes has been experimentally and theoretically investigated with the conclusion that the effective protonation by acid of the aldimine basic nitrogen is the key. The generally accepted notion that aldehyde is more reactive than aldimine would be applicable to nucleophilic addition reactions under basic conditions (Figure 12). In the Brønsted acid-mediated reaction, however, aldimine is more reactive than aldehyde. A related phenomenon was reported by Yamamoto and co-workers in the reversal of the reactivity between electron-rich and electron-deficient aldehydes by the use of Lewis acid:[28] that is, electron-deficient aldehydes were more reactive in the reaction with basic nucleophiles, while nucleophiles reacted preferentially with electron-rich aldehydes in the

Table 1. Reactivity difference between aldimine and aldehyde in the presence of Brønsted acid.[a]

Entry	Ar	Nucleophile	T [°C]	Yield [%][b]		Amine : Alcohol
				Amine	Alcohol	
1	Ph	$H_2C{=}C(OTMS)Ph$	–40 to –25	95	trace	>95:5
2	Ph	$Bu_3SnCH_2CH{=}CH_2$	–25	80	trace	>95:5
3	2-Naph	Bu_3SnH	–25	95	trace	>95:5

[a] The reaction was performed in the presence of equimolar amount of aldehyde, aldimine and CF_3CO_2H.
[b] Yield of isolated product.

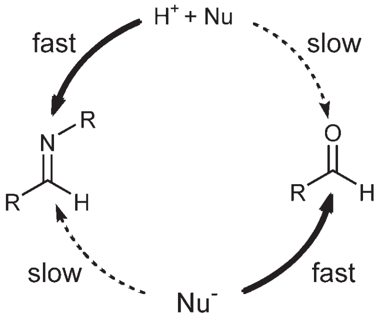


Figure 12. Reactivity difference between aldimine and aldehyde.

presence of Lewis acid owing to the facile coordination of the electron-rich aldehydes to the Lewis acid. The idea of effective aldimine activation by Brønsted acid is important, and should find wide use and application in synthetic organic chemistry. Indeed it has already been utilized in the recent elegant asymmetric catalytic reaction of aldimine promoted by chiral Brønsted acid described independently by Akiyama's[6p] and Terada's[11,29] groups.

Experimental Section

General Remarks

All reactions were carried out under an argon atmosphere and monitored by thin-layer chromatography covered with silica gel 60 F$_{254}$. Preparative thin-layer chromatography was performed using silica gel 60 F$_{254}$ and B-5F. Flash chromatography was performed using silica gel 60 and silica gel 60N. ^{1}H and ^{13}C NMR spectra were obtained as solutions in deuterated solvents, referred to undeuterated solvents for ^{1}H NMR and deuterated solvents for ^{13}C NMR.

Experimental Procedure for the Investigation of Temperature Effect in the Mannich Reaction (Figure 1)

After stirring a solution of benzaldehyde (510 μL, 5.0 mmol), *p*-anisidine (677.0 mg, 5.5 mmol) and L-proline (57.6 mg, 0.1 mmol) in NMP (5.0 mL) for 2 h at room temperature, propanal (1.1 mL, 15.0 mmol) was added to the reaction mixture at –20 °C, and stirring was continued for a certain period at the same temperature. The reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3), and the organic phases were combined and washed with brine, and dried over Na$_2$SO$_4$. After removal of the volatile materials under reduced pressure, the residue was dissolved in MeOH (3.0 mL), and then NaBH$_4$ (3.0 mmol) was added at 0 °C. After stirring the mixture for 30 minutes, the reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3). The organic phases were then combined and dried over Na$_2$SO$_4$. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography and afforded (2*S*,3*S*)-3-(*p*-anisidino)-2-methyl-3-phenylpropan-1-ol (**1**).[19b]

Experimental Procedures for the Cross- and Self-Aldol Reactions

Cross-aldol reaction (Figure 2): To an NMP (1.0 mL) solution of benzaldehyde (106.0 μL, 1.0 mmol) and L-proline (11.5 mg, 0.1 mmol) was added propanal (216.0 μL, 3.0 mmol) at –20 °C, and stirring was continued for a certain period at the same temperature. The reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3), and the organic phases were combined and washed with brine, and dried over Na$_2$SO$_4$. After removal of the volatile materials under reduced pressure, the residue was dissolved in THF (3.0 mL), and then LiAlH$_4$ (114.0 mg, 3.0 mmol) was added at 0 °C. After stirring the mixture for 30 minutes, the reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3). The organic phases were then combined and dried over Na$_2$SO$_4$. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography, which afforded (1*R*,2*R*)-2-methyl-1-phenylpropane-1,3-diol (**2**).[20]

Self-aldol reaction (Figure 2): To an NMP (1.0 mL) solution of L-proline (11.5 mg, 0.1 mmol) was added propanal (216.0 μL, 3.0 mmol) at –20 °C, and stirring was continued for a certain period at the same temperature. The reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3), and the organic phases were combined and washed with brine, and dried over Na$_2$SO$_4$. After removal of the volatile materials under reduced pressure, the residue was dissolved in MeOH (3.0 mL), and then NaBH$_4$ (113.0 mg, 3.0 mmol) was added at 0 °C. After stirring the mixture for 30 minutes, the reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3). The organic phases were then combined and dried over Na$_2$SO$_4$. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography, which afforded 2-methylpentane-1,3-diol (**2**).[20]

Experimental Procedure for the *in situ* Comparison of the Reactivity Difference between Aldimine and Aldehyde (Figure 3)

After stirring a solution of benzaldehyde (106.0 μL, 1.0 mmol), *p*-anisidine (62.0 mg, 0.5 mmol) and L-proline (11.5 mg, 0.1 mmol) in NMP (1.0 mL) for 2 h at room temperature, propanal (216.0 μL, 3.0 mmol) was added to the reaction mixture at –20 °C, and stirring was continued for 20 h at this temperature. The reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3), and the organic phases were combined and washed with brine, and dried over Na$_2$SO$_4$. After removal of the volatile materials under reduced pressure, the residue was dissolved in MeOH (3.0 mL), and then NaBH$_4$ (3.0 mmol) was added at 0 °C. After stirring the mixture for

30 minutes, the reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3). The organic phases were then combined and dried over Na_2SO_4. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography and afforded the β-amino alcohol **1** and the 1,3-diol **2**.

Experimental Procedure of NMR Study

A: The NMR sample was prepared as follows: *N*-benzylidene-*p*-anisidine was synthesized according to the literature procedure.[30] To a $(CD_3)_2SO$ (0.5 mL) solution of *N*-benzylidene-*p*-anisidine (53.0 mg, 0.25 mmol) was added $(CD_3)_2SO$ solution containing CF_3CO_2H (5 M, 10 μL, 0.05 mmol) little by little.

B: The NMR sample was prepared as follows: to a $(CD_3)_2SO$ (0.5 mL) solution of benzaldehyde (25.5 μL, 0.25 mmol) was added $(CD_3)_2SO$ solution containing CF_3CO_2H (5 M, 10 μL, 0.05 mmol) little by little.

C: The NMR sample was prepared as follows: to a $(CD_3)_2SO$ (0.5 mL) solution of *N*-benzylidene-*p*-anisidine (26.0 mg, 0.125 mmol) and benzaldehyde (13 μL, 0.125 mmol) was added $(CD_3)_2SO$ solution containing CF_3CO_2H (2.5 M, 10 μL, 0.025 mmol) little by little.

Experimental Procedure of Table 1, Entry 1

To an NMP (0.6 mL) solution of *N*-benzylidene-*p*-anisidine (63.4 mg, 0.3 mmol), benzaldehyde (30.5 μL, 0.3 mmol) and CF_3CO_2H (23.1 μL, 0.3 mmol) was added 1-phenyl-1-trimethylsiloxyethene (61.5 μL, 0.3 mmol) at −40 °C. After stirring the mixture at from −40 °C to −25 °C for 3 h, the reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3). The organic phases were combined and dried over Na_2SO_4. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography (AcOEt:hexane = 1:3), affording 3-(*p*-anisidino)-1,3-diphenylpropan-1-one;[4d] yield: 95 mg (95%).

Experimental Procedure of Table 1, Entry 2

To an NMP (0.6 mL) solution of *N*-benzylidene-*p*-anisidine (63.4 mg, 0.3 mmol), benzaldehyde (30.5 μL, 0.3 mmol) and CF_3CO_2H (23.1 μL, 0.3 mmol) was added allyltributyltin (91.4 μL, 0.3 mmol) at −25 °C. After stirring the mixture for 1 h at that temperature, the reaction was quenched with 5% KF solution, and the organic materials were extracted with ethyl acetate (×3), and washed with brine (×3). The organic phases were combined and dried over Na_2SO_4. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography (AcOEt:hexane = 1:3), affording *N*-(1-phenylbut-3-enyl)-*p*-anisidine;[31] yield: 60.8 mg (80%).

Experimental Procedure of Table 1, Entry 3

To an NMP (0.6 mL) solution of *N*-naphthylidene-4-methoxyaniline (78.4 mg, 0.3 mmol), naphthaldehyde (46.9 mg, 0.3 mmol) and CF_3CO_2H (23.1 μL, 0.3 mmol) was added Bu_3SnH (81 μL, 0.3 mmol) at −25 °C. After stirring the mixture for 0.5 h at that temperature, the reaction was quenched with 5% KF solution, and the organic materials were extracted with ethyl acetate (×3), and washed with brine (×3). The organic phases were combined and dried over Na_2SO_4. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography (AcOEt:hexane = 1:3), affording *N*-(2-naphthyl)methyl-*p*-anisidine; yield: 75.1 mg (95%). ^1H NMR (600 MHz, $CDCl_3$): δ = 3.75 (3H, s), 4.44 (2H, s), 6.65 (2H, d, *J* = 2.8 Hz), 6.78–6.85 (2H, m), 7.45–7.53 (3H, m), 7.80–7.88 (3H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 49.3, 55.7, 114.1, 114.8, 125.6, 125.8, 125.9, 126.1, 127.6, 127.7, 128.2, 132.6, 133.4, 137.1, 142.3, 152.1; IR (neat): ν = 2832, 1516, 1464, 1296, 1240, 1126, 1119, 1038, 823, 748 cm^{-1}; HR-MS (FAB): calcd. for $C_{18}H_{17}NO$: 263.1310; found: 263.1282.

Acknowledgements

This work was partially supported by a Grand-in-Aid for Scientific Research on Priority Areas (A) "Creation of Biologically Functional Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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[25] By using the counterpoise method (S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553), we estimated the basis set superposition errors (BSSEs) for the reactant complexes **3** and **4** in the Mannich and aldol reactions. After taking BSSEs into account (3.7 and 3.2 kcal/mol for **3** and **4**, respectively), we obtained stabilization energies of 6.9 and 7.6 kcal/mol for the reactant complexes **3** and **4**.

[26] The Mannich reaction scarcely proceeded in CH_3CN, CH_2Cl_2 and toluene, while good yield was obtained in NMP and DMF, see ref.[18]

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