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Design of Acid−Base Catalysis for the Asymmetric Direct Aldol Reaction

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ABSTRACT
Proper design of acid−base catalysis has been shown to be effective for achieving high reactivity and selectivity in the asymmetric direct aldol reaction during the development of diamine−Brønsted acid types of catalyst. In this study, two principal approaches have been implemented to create a new type of catalysis and high catalytic efficiency: one is the creation of a highly viable acidic function within acid−base catalysts; the other is the creation of rather complicated but more cooperatively arranged hydrogen-bond networks that would be expected to stabilize a transition state, thereby promoting new reactivity and selectivity.

Introduction

β-Hydroxy carbonyl and 1,3-diol units are frequently found in complex polyol architectures of natural products and have attracted a great deal of attention from synthetic organic chemists.[1] The aldol reaction is a useful and concise method for preparing these units from two carbonyl compounds such as a ketone and an aldehyde or an aldehyde and an aldehyde. Over the past half decade, rapid progress has been made in the development of enantioselective aldol reactions:[2] from the utilization of "preformed and stereodefined stable enolates"[2] (e.g., irreversibly generated metal enolates such as silyl, borane, titanium, and tin enolates) to "in situ formed labile enolate synthons"[3] (a reversible mixture of two species, e.g., keto−enolate or keto−enamine) (Figure 1).

There have been numerous reports on small-molecule-catalyzed direct aldol reactions using the latter enolate equivalents.[4−23] In particular, "the discovery of the versatile catalytic nature of proline occurring via enamine intermediates" has undoubtedly been the biggest breakthrough in this field of research (Figure 2).[8−23]

Because multiple-step acid−base catalysis is thought to be involved in the formation and reaction of enamine intermediates (see also Figure 5), we began our study by focusing on the fundamental nature of the amine−acid catalysis, namely, *that the acidic part of amine-acid catalysts seems to be largely responsible for, at least, rapidly promoting the steps of enamine and carbon−carbon bond formation*. The OH part of simple carboxylic acids have an intrinsic pK_a value of around ∼12 (in DMSO).[24] For example, proline has a carboxylic acid component with this level of acidity. We considered that an answer to the question of how the acidic function participates in aldol catalysis might be obtained by determining the effects of simply changing the acidic part to be more acidic or less acidic. Although our investigation has been done as a part of the continuous development of asymmetric aldol catalysis, another important aim of our studies is to discover a high catalytic efficiency (turnover number, TON) through the electronic tuning of the acid function.

From these viewpoints, the first stage of our research centered on the molecular design of simple diamine−acid types of catalyst possessing an acidic fragment of $(R_3N\cdots H^+)X^-$ (p$K_a \approx 10$ in DMSO; R = H or alkyl) (Figure 3, left). The second stage of our research was concerned with catalysts possessing a more ionic function, such as $R_2N^{\delta-}-H^{\delta+}$ types of acid (hopefully, p$K_a \approx 8$ in DMSO) (Figure 3, right). We also considered the possibility that Lewis acids (M^{n+}: M, metal; *n*, an integer) might act as an alternative to a proton (H^+).[25] Such catalyst candidates are readily accessible from molecular libraries of diamines derived from the 20 different naturally occurring amino acids. The combined use of diamines with commercially available Brønsted or Lewis acids facilitates both the structural and electronic tuning of catalysts and diversity-based[26] catalyst discovery.

In this study, we implemented two principal approaches to creating a new type of catalysis and high catalytic efficiency: one was the creation of unique acidic functions $(R_3N\cdots H^+)X^-$ and $R_2N^{\delta-}-H^{\delta+}$ acids, in place of the OH-type acids, within the acid−base catalysts; the other was the creation of rather complicated but more cooperatively arranged hydrogen-bond networks that would be expected to stabilize a transition state, thereby promoting new reactivity and selectivity. To make such a hydrogen-bond network, a catalyst should provide, at the least, an additional binding site for a proton (Figure 3, right). In general, protonated ROH groups ($H^+\cdots OH(R)$) have a pK_a value that is much smaller than that of protonated NR_3 groups ($(R_3N\cdots H^+)X^-$),[27] which suggests that a nitrogen lone pair has a considerably stronger affinity for protons. An NH-type acid (in this case not an

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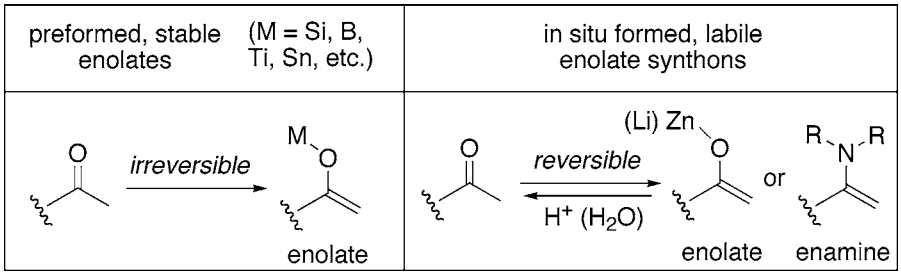


FIGURE 1. Two different enolate equivalents.

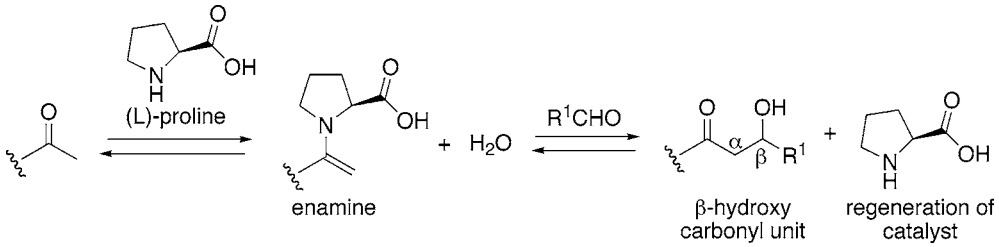


FIGURE 2. Summary of proline catalysis.

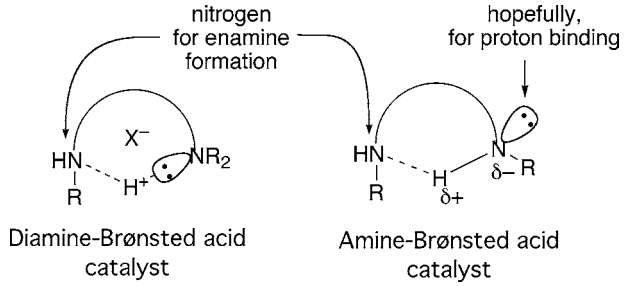


FIGURE 3. Molecular design of amine−acid catalysts.

$(R_3N\cdots H^+)X^-$ but an $(R_2N^{\delta-}-H^{\delta+})$ type of acid) preserves a lone pair on the nitrogen that can further accept a proton and, in this respect, is more suitable for catalysis than OH-type acids. We would therefore expect an $(H^+\cdot\cdot\cdot(R_2N^{\delta-})-H^{\delta+})$ type of interaction between the catalyst and its reaction partner. Although the argument is still speculative, we discuss it in detail in a forthcoming chapter.

Background

Simple amines and diamines, as well as their Brønsted acid salts, have been widely recognized as effective catalysts[28] for direct aldol reactions. A 1:1 mixture of pyrrolidine and benzoic acid also promotes the self-condensation of aldehydes.[29] Janda et al. demonstrated that the pyrrolidine−pyridine-type diamine metabolite, nornicotine, was able to catalyze the aldol reaction in water.[28c] Recently, new diamines have been developed as catalysts;[30] moreover, in their earlier reports, Barbas III et al.[12a,] and List et al.[11a] also mentioned, albeit briefly, the catalytic potential of chiral diamines and their Brønsted acid salts in asymmetric catalysis. Later, Barbas III et al. expanded the reaction scope of diamine catalysis to include the aldol reaction,[12d,e] the Mannich-type reaction,[12f−i] and other applications.[12b−c,12j] It has been also shown that L-proline is not very efficient (lower yields and enantiomeric excess (ee) values) as compared to diamines in the conjugate addition of aldehydes and ketones to nitrostyrene.[31] These fundamental investigations have stimulated intense research on recent solid-immobilized diamines and amines[32] and on the encapsulation of diamines within mesoporous materials.[33]

Notably, there were implications in an older study of enamine that acid salts of diamines (a 1:1 mixture of diamine and Brønsted acid) would be effective participants in aldol catalysis. During 1960−1980s, Hine exhaustively investigated[34] the role of acid in the formation of enamine. For instance, Hine effectively applied small diamine−Brønsted acid modules to the formation of

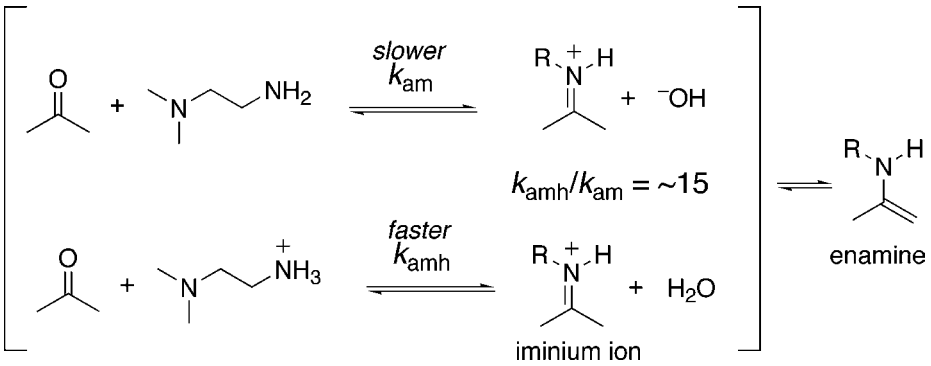


FIGURE 4. Effect of Brønsted acid on rapid formation of iminium ion.

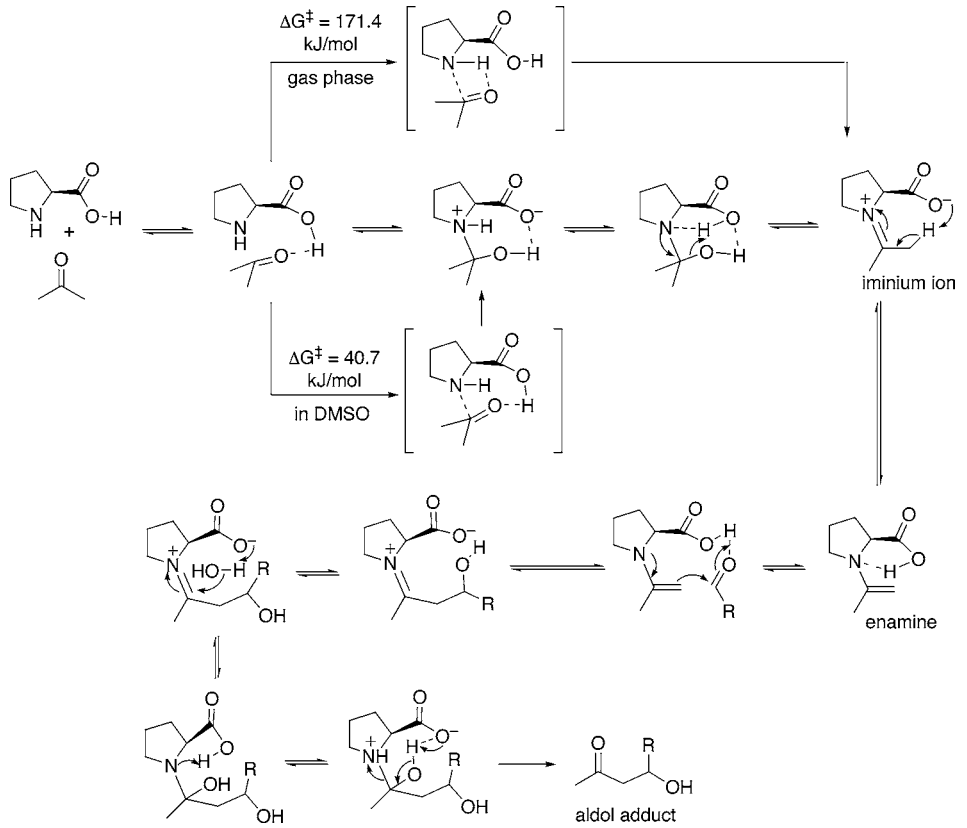


FIGURE 5. Plausible multistep proline catalyses (including Boyd's DFT calculations).[23]

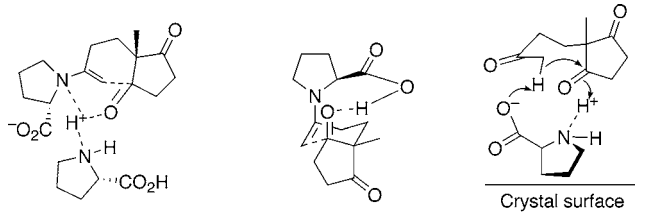


FIGURE 6. Possible mechanisms of Hajos–Parris–Eder–Sauer–Wiechert reaction.

iminium salts; in water, protonated diamines formed imines from the corresponding carbonyl compounds at a rate that was 15 times faster than that achieved by diamines alone (Figure 4). Thus, "acid" functioned "cooperatively" as part of the catalysis.

Indeed, proline-catalyzed reactions uniformly encompass a diverse set of acid–base catalyses (Figure 5); for example, Brønsted acid–carbonyl complexation and spontaneous attack of the amine fragment on the carbonyl carbon are accompanied by formation of an enamine as a key intermediate; the reaction results in the formation of water, which also plays a significant role in the reaction, including in regeneration of the catalyst.

Several mechanisms have been proposed for catalysis of the Hajos–Parrish–Eder–Sauer–Wiechert reaction by proline (Figure 6).[16–23] Jung[16] and later Eschenmoser et al.[17] first discussed a "one-proline mechanism" involving a side chain enamine intermediate. Subsequently, Agami et al.[18] proposed model **I**, in which a second proline molecule is invoked. Their kinetic studies, coupled with an observed nonlinear effect in asymmetric catalysis, supported the involvement of two proline molecules in the enantioselectivity-determining step.[19] However, a very recent theoretical approach[20] and experimental reinvestigations[21] achieved by List and Houk contradict the kinetic results of Agami et al. and support a one-proline mechanism such as, for example, model **II**.

Heterogeneous catalysis involving a concerted bifunctional acid–base mechanism (**III**) has also been suggested as a possible mechanism on the basis of the observation that proline is often not completely soluble in organic solvents.[22] Furthermore, from studies of biological catalysis occurring via enamine intermediates[35] and a set of relevant ab intio calculations performed by Houk[20] (e.g., **II**) and others,[23] valuable insight into mechanistic aspects of the fundamental nature of the catalysis has been gained. Previous studies of antibodies[35c] that function via an analogous mechanism indicate that enamine formation and/or C–C bond breaking/forming is rate limiting. As suggested by Boyd's density functional theory (DFT) calculations of proline catalysis,[23] however, the two processes require 29.9 and 57.2 kJ mol^{-1} of energy, respectively, which is not enough to inhibit the reaction. Boyd's results also indicate that the initial complexation (−13.3 kJ mol^{-1}) and subsequent formation of the transition structure (171.4 kJ mol^{-1}) between proline and acetone require a substantial amount of total energy (158.1 kJ mol^{-1} in the gas phase) (Figure 5). Fortunately, however, an alternative pathway involving lower energy (40.7 kJ mol^{-1}) is utilized when the ionizing solvent DMSO is present to assist formation and stabilization of the sepa-

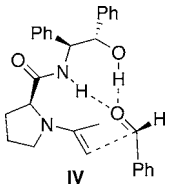


FIGURE 7. A transition model derived by Wu's DFT calculation.[36]

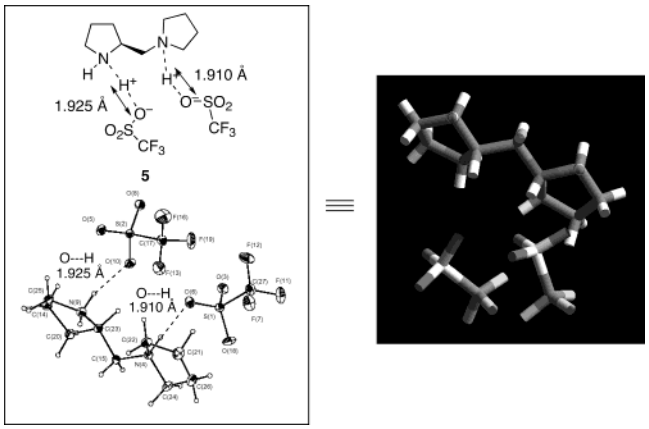


FIGURE 8. Structure of diamine **2**-2TfOH salt **5**.

rated charges of the transition state (Figure 5). In fact, it is clear from many other outstanding experimental results that the choice of solvents is a critical controlling factor by which the reaction can proceed.

Recently, Wu and co-workers reported[36] a small amide molecule that facilitated the asymmetric aldol reaction of acetone. Through DFT calculations, they proposed a mechanism involving two hydrogen bonds (model **IV**; Figure 7).

Taken together, these data clearly demonstrate that the fine-tuning of acid−base catalyses, that is, the proper arrangement of acid and base functions within the catalysts, widens their potential use in the direct aldol reaction. In this study, we describe the design and testing of acid−base catalysts based on this strategic way of thinking to enable their further application to the development of asymmetric synthesis.

Acid−Base Catalysts Derived from a Lewis Acid and Diamine

We started our investigation on the direct aldol reaction between acetone and *p*-nitrobenzaldehyde (**1a**) in DMF in the presence of (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (**2**; 0.06 equiv) and a lanthanide Lewis acid catalyst (0.03 equiv relative to **1a**).[30] Because water is inevitably generated during the direct aldol reaction, lanthanide triflates (OTf) are assumed to be a good choice of catalyst because of their water-stable nature and because their catalytic activity is preserved in water.[37] A rate enhancement was observed with most lanthanide catalysts. In particular, $Gd(OTf)_3$ showed an activity slightly higher than that of the other lanthanide triflates to give the *β*-hydroxycarbonyl product **3a** (83% yield, 85% ee) and its dehydrated product **4a** (for **3a** and **4a**, see Figure 9).

To identify essential features of catalysis leading to high productivity, an X-ray single crystallographic study of the $Gd(OTf)_3$−diamine **2** catalyst was undertaken. Unexpectedly, single crystals of the Gd(III)−**2** complex were not obtained, but single crystals of the diBrønsted acid salt **5** were eventually grown at −20 °C (Figure 8). The structure of **5** was established by X-ray crystallography at low temperature (208 K) and showed two typical hydrogen bonds (1.925 Å and 1.910 Å) between R_3NH^+ and ^-OTf. This result implies that TfOH may catalyze the reaction instead of the triflate salt even in this Lewis acid-diamine system; thus, triflate salts are not stable under these conditions, being presumably decomposed by a small amount of water and the diamine, and eventually function in catalysis as a TfOH source.[30]

Acid−Base Catalysts Derived from a Brønsted Acid and Diamine

We therefore turned our attention to diamine−Brønsted acid catalysts.[30] For comparison, catalysis of **1a** in acetone and similar reaction conditions described above was examined (Figure 9). As expected, the diamine−diBrønsted acid complex **5** did not work at all as an effective catalyst. By contrast, a 1:1 mixture of **5** and **2** was capable of promoting the reaction. This suggests that a 1:1 mixture of **2** and TfOH,[38] namely, catalyst **7** or presumably **6**, is the real active species.

Diamine **2** was further evaluated for catalysis of **1a** in the presence of a series of Brønsted acids. We found that, in general, the rate of the aldol reaction was more enhanced as the acidity of the Brønsted acid increased. The variations in acidity affected the enantioselectivity (18−84% ee). TfOH and Tf_3CH (**8**),[39,40] as well as acid **9**,

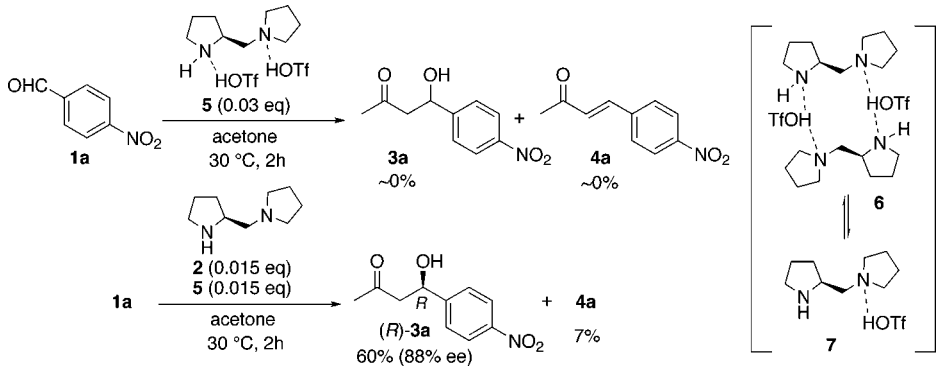


FIGURE 9. Real active species.

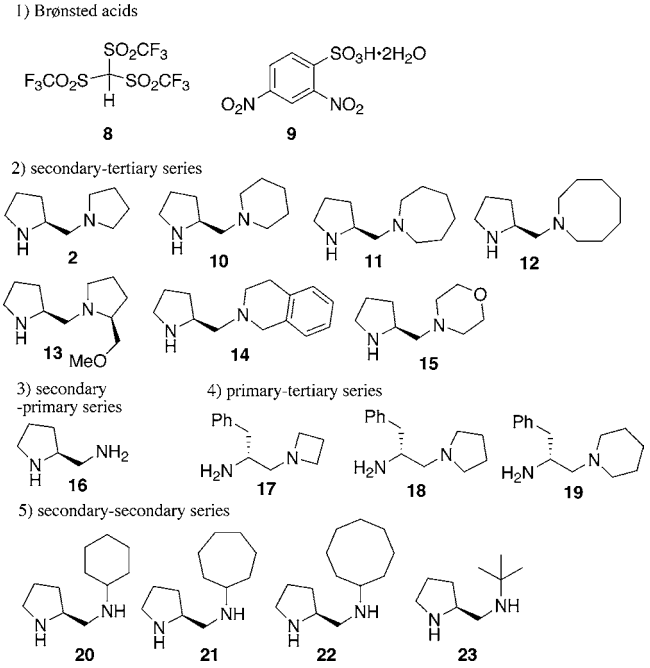


FIGURE 10. Bronsted acids and diamine libraries for reaction screening.

were shown to be superior Brønsted acids (Figure 10); we chose acid **9** for further tests owing to its commercial availability and easy handling. In parallel with these investigations, solvent effects were evaluated (THF, 7% yield, 79% ee; DMSO, 25%, 82% ee; MeOH, 6%, 75% ee; CH_3CN, 30%, 80% ee), and acetone was shown to be the best solvent (63%, 83% ee).

Twelve different diamines (secondary−primary, −secondary, and −tertiary diamines) with a consistent secondary amino structure derived from L-proline, as well as three different diamines (primary−tertiary diamines) derived from D-phenylalanine, were synthesized (Figure 10) and screened for their catalytic properties against a range of aldehydes. Reactions were carried out at 20−43 °C in acetone under conditions employing 0.01−0.2 equiv of catalyst relative to aldehyde.

Library 1. Our preliminary design of diamines focused on the secondary-tertiary diamines **2** and **10**−**15**. Each of these seven diamines were screened in the reaction of aldehydes **1a**−**1c** (Figure 11). Diamine **11** was found to be the best catalyst for obtaining a high ee (TON = 24) in the reaction of **1a**, although the reaction rate decreased in the order **2**, **11** > **10** > **12** > **13**∼**15** as the tertiary amine moiety became bulkier. The TON values ranged from 73 to 20 with a 0.01−0.03 equiv of **2**. When the reactions of **1b** and **1c** were carried out using secondary−tertiary diamines, the extensive formation of dehydration products (**4b** and **4c)** posed serious limitations.

Library 2. In an effort to expand the range of aldehydes that the diamines could catalyze, we examined the reaction of aldehydes **1a**, **1b**, and **1c** with a range of catalysts, **16**−**23** (Figure 11). The primary−tertiary diamines **18** and **19** were found to be superb structural modules that avoided the formation of dehydration products. Secondary−primary diamine **16** was totally ineffective, regarding

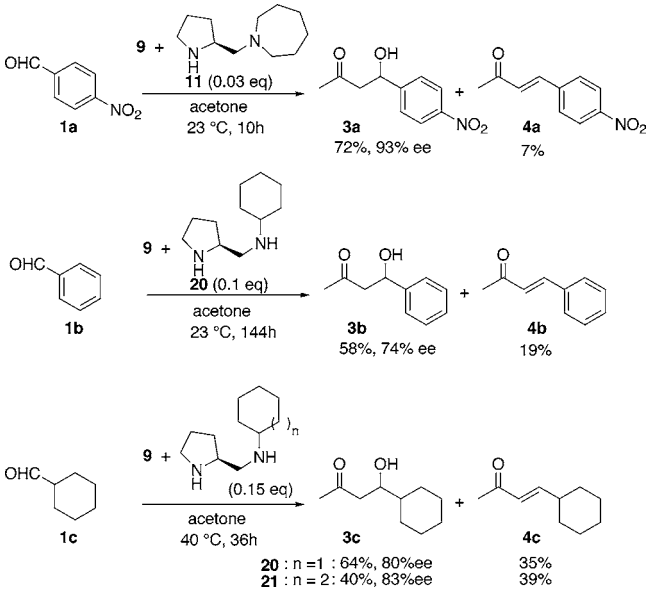


FIGURE 11. Some of the optimal results.

both productivity and efficiency. Secondary−secondary diamine **20** gave the most optimal results, albeit accompanied by the formation of a considerable amount of dehydration products. The best result afforded **3b** in 58% yield with 74% ee and **3c** in 64% yield with 80% ee (Figure 11). Unfortunately, the rate of the aldol reaction with primary−tertiary and secondary−secondary diamines was much slower than that with secondary−tertiary diamines.

Proposed Plausible Mechanism of Diamine−Acid Catalysis

The mechanism of the diamine−Brønsted-acid-catalyzed aldol addition is the subject of an extensive, ongoing investigation, but it remains unsolved. For the purposes of the discussion below, the catalytic cycle is based on a proline-catalyzed process (Figure 12). The reaction should proceed through a six-membered chairlike transition structure (model **V**), formed between the enamine derived from a diamine−acid catalyst and the aldehyde, in which the phenyl (Ph) group of PhCHO, as shown in Figure 12, for example, is adopted at the equatorial position. In addition, the pathway to dehydration might involve an aldimine species, which undergoes a Mannich-type reaction with acetone (or its enamine form) to give a β-aminoketone, followed by subsequent elimination (Figure 12, lower scheme). As suggested by Houk,[20] however, the formation of a hydrogen bond between the nitrogen and proton does not lower the energy of the transition state, which might therefore be advanced to model **VI**.

Advanced Acid−Base Catalyst with a Tetrazole Functionality: Implications of the Involvement of Hydrogen-Bond Networks

As demonstrated previously,[30] the acidity of the Brønsted acid[41] is an important factor in achieving high reactivity. Our ongoing research is now centered on a future genera-

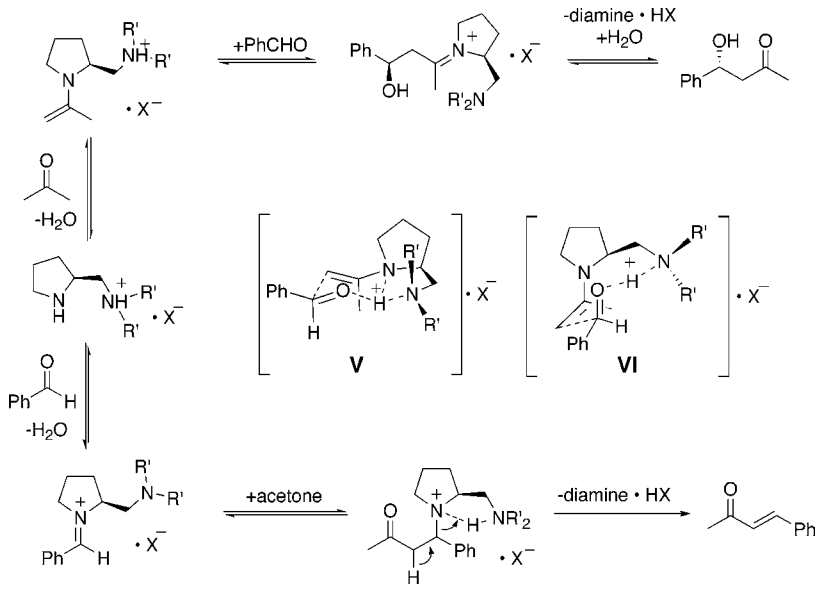


FIGURE 12. Possible catalytic pathways and transition states.

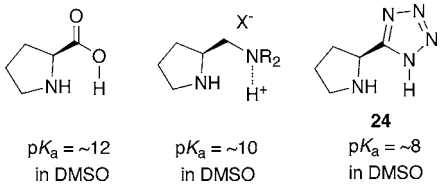


FIGURE 13. Variations in acid−base catalysts.

tion of catalysts based on acid−amines. These must possess both acidic and basic functions: the former comparable or hopefully superior to that of proline, the latter capable of binding the Brønsted acid function of a reaction substrate. Assuming that effective hydrogen-bond networks create a structurally tight transition state, a high ee and reactivity would be expected from catalysts that can form such networks.

In this regard, the acidic and basic functions of proline and diamine−Brønsted acid catalysts are unlikely to be suitable; although the oxygen of the hydroxy group of the carboxylic acid has an electron lone pair that can accept a proton, the affinity of a proton for this oxygen is expected to be rather low because, in addition to the arguments described in the Introduction, the basicity of the hydroxy group of the carboxylic acid must be attenuated by a resonance interaction;[42] however, the amine−Brønsted acid system $(R_3N\cdots H^+)X^-$ no longer has a lone pair on the nitrogen available for accepting an additional proton.

By contrast, more ionic $R_2N^{\delta-}-H^{\delta+}$ types of acid (Figure 3) seem best suited as both the proton acceptor and donor because a lone pair of electrons on the nitrogen remains available for possibly binding a proton (see also Introduction). Given these potential requirements for the optimal design of a new catalyst, we considered that the tetrazole structure[43] may be among the most suitable of the *N*-containing heterocycles (Figure 13). *N*-unsubstituted tetrazoles are moderately strong acids; the pK_a values of tetrazoles in water lie in the range of −0.8 to about 6, depending on the electronic properties of the substituent at position 5 of the tetrazole ring.[44] For example, the pK_a value in water of pyrrole, imidazole, pyrazole, 1,2,4-triazole 1,2,3-triazole, and tetrazole decreases in the order 16.5, 14.5, 14.0 10.0, 9.4, and 4.9, respectively.[45] By contrast, the pK_a values of carboxylic acids (that do not contain halogens or a nitro group at the α carbon) range from about 3.7 to 5.7.[46] Although each nitrogen of tetrazole is apparently less basic than normal sp^3 nitrogens, each one may help to accept a proton that approaches adjacent to the tetrazole ring if other hydrogen bonds are present that all are cooperatively arranged to stabilize the transition state. Furthermore, tetrazoles are mimics of carboxylic acids, whose structures are frequently used as a pivotal fragment of enzyme inhibitors.[47]

We tested this idea by using the tetrazole **24** to catalyze the aldol reaction.[43] When cyclopentanone **25** in a MeCN solution was subjected to chloral and **24** (0.05 equiv relative to chloral) at room temperature (Figure 14, upper), the reaction was far from complete (<1%), even after a prolonged reaction time (60 h) (Figure 14, triangle symbols). In sharp contrast, when chloral was replaced by its monohydrate, the reaction proceeded smoothly to give the aldol product in reasonable yield (83%, 82% ee and 76% diastereomeric excess (de) (*syn*-**26** major)). The addition of water (1 equiv) to a mixture of chloral and catalyst **24** gave a similar level of productivity (85%) and selectivity (84% ee and 80% de (*syn*-**26** major)). The ee of *anti*-**26** was also exceedingly high (>98% ee). By contrast, catalytic amounts of water (0.2 or 0.5 equiv) uniformly disabled the catalytic cycle (~5%). When proline (0.05 equiv) was used instead of **24** with either chloral or its monohydrate in $CHCl_3$ or MeCN, the reaction was sluggish (**26**, ~10% after 46 h). In general, a lower amount of catalyst and ketone is possible with **24**.

To understand better these findings, we determined the kinetic profile of the reactions of cyclopentanone **25** in anhydrous and monohydrated chloral. (Figure 14, lower).[43] The reaction was obviously initiated and accelerated at

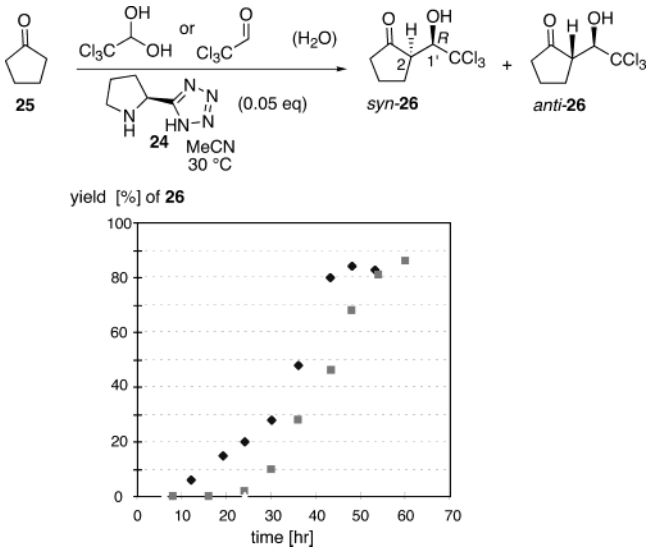
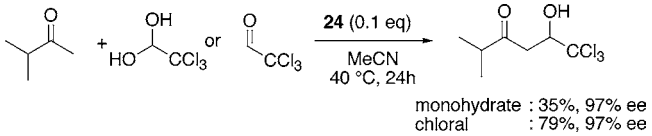
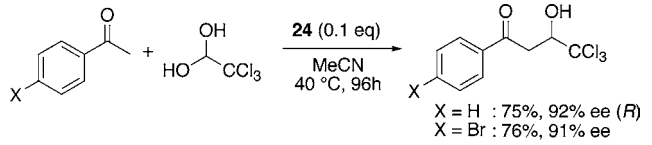


FIGURE 14. Reaction of **25** (2 equiv) using **24** (0.05 equiv) in MeCN. ♦, chloral monohydrate; ■, anhydrous chloral, then added water (100 mol %) at the 24 h period; △, anhydrous chloral.

Scheme 1. Aldol Reaction of 3-Methyl-2-butanone Promoted by Catalyst 24



Scheme 2. Aldol Reaction of Aromatic Ketones Promoted by Catalyst 24

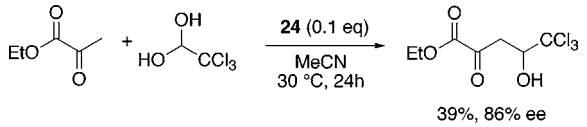


the point where water participated (square symbols). For the reaction with anhydrous chloral, the yield of product gradually increased after the addition of water (square symbols**)** at a rate comparable to that exhibited in the reaction with chloral monohydrate (diamond symbols).

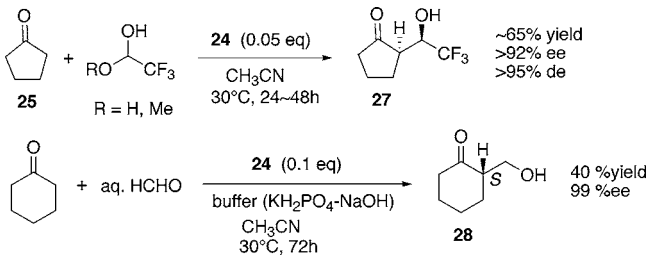
We tested both chloral and its monohydrate with other ketones to determine the substrate scope of this reaction.[43] Several examples highlight the characteristic nature of the reaction: (1) Methyl and aromatic ketones, which showed low reactivity in reactions with catalytic amounts of proline, exhibited sufficient reactivity and gave high enantioselectivities (82−97% ee). (2) In general, reactions with aliphatic ketones were better with chloral than with its monohydrate in terms of both reactivity and selectivity (Scheme 1). By contrast, aromatic ketones showed higher selectivity and reactivity in reactions with chloral monohydrate (Scheme 2). (3) Although prone to self-dimerization, the pyruvate afforded a crossed-aldol product in good enantioselectivity (86% ee) (Scheme 3).

This method was further extended to other aldehydes with a high affinity for water.[43] The monohydrate and ethanol hemiacetal of trifluoroacetaldehyde were both subjected to the catalytic cycle to give the identical

Scheme 3. Aldol Reaction of Ethyl Pyruvate Promoted by Catalyst 24



Scheme 4. Aldol Reaction of Aldehydes Having High Affinity with Water



product **27** (~65%) with high enantioselectivity (94 and 92% ee, respectively) and diastereoselectivity (>95% de, syn major). Even more striking was the level of ee (**28**, 99% ee) obtained in reaction of aqueous formaldehyde, although the TON was still modest (Scheme 4).

Possibility of Hydrogen-Bond Networks in the Transition Structure

As a step toward elucidating the mechanism of tetrazole catalysis, we considered the effects of water, although the following arguments are still speculative.[43] Although water effects that shift the aldehyde−iminium ion equilibrium to the formation of aldehydes through the decomposition of iminium ions might be possible, we were unable to identify ^{1}H NMR peaks corresponding to formation of the iminium ion or aminal during the reaction (Figure 15).

We also could not exclude the following role of water, that is, that generation of the hydrated form of chloral might prevent formation of the iminium ion from **24** and chloral (Figure 15). In fact, a catalytic amount of water (0.2 or 0.5 equiv) totally disabled the catalytic cycle, indicating that the remaining chloral poisoned the catalyst's activity; by contrast, 1 equiv of water markedly improved the catalysis, as described above. The experimental K_{eq} value evaluated from the investigation of a chloral−monohydrate equilibrium also suggests the highly preferential formation of the monohydrate form.[48] In addition, the following, as well as other,[49] findings support involvement of the monohydrate in the catalysis: *N*-(1-cyclopentenyl)pyrrolidine was subjected to the reaction with chloral or its monohydrate at 30 °C for ~50 h. With chloral, almost no reaction took place, but with its monohydrate, ~36% of the product was obtained, suggesting the importance of hydrogen bonding between the nitrogen and the hydroxy group (Figure 16). The real hydrogen-bond networks are most probably spread over complex aggregates of multiple monohydrates.

On the basis of this model, we can propose a putative description of tetrazole-based catalysis by the simpler alignment of at least two hydrogen bonds (Figure 17).

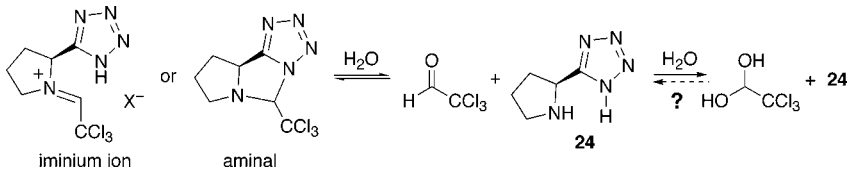


FIGURE 15. Catalyst poisoning and inhibition of this poisoning.

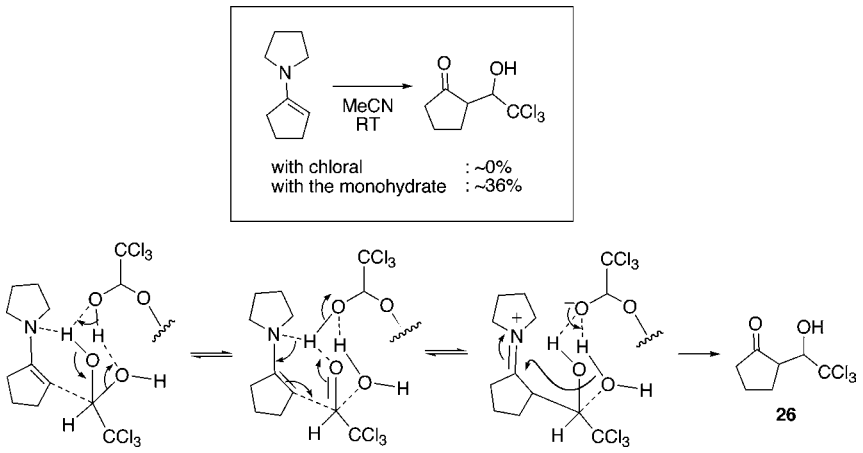


FIGURE 16. Possible hydrogen-bond networks created by interactions among multiple chloral hydrates.

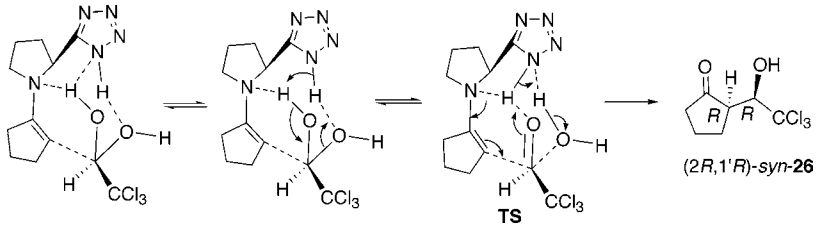


FIGURE 17. Proposed hydrogen-bond networks created by interactions between catalyst and chloral hydrate.

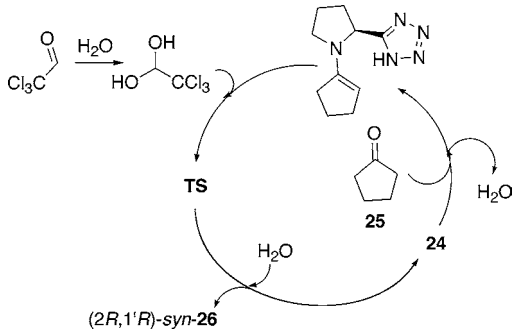


FIGURE 18. Possible catalytic cycle.

Although more research is needed to gain further understanding of the detailed mechanism, we have developed a current rationale to account best for this catalytic cycle (Figure 18).

Future Perspectives

Our results illustrate the importance and power of the molecular design of acid−base catalysts for the asymmetric direct aldol reaction. In some respects, tetrazole catalyst **24** far exceeded or matched the results derived from proline; its notable features are its ability to allow water to participate positively in the reaction and its effective hydrogen-bond networks that stabilize the transition state. Diamine−Brønsted acid **7** gave the lowest loading of catalyst (no more than 0.01 equiv) and the highest TON of 73. Each reaction course strongly depended on the acidic and basic nature, as well as the structure, of the catalyst, in addition to the correct adjustment of reaction conditions, including the solvent.

We are facing a turning point in research, in particular, how to gain higher catalytic efficiency, namely, a reasonably high TON (nothing less than 100) and turnover frequency (TOF: TON/time). The selectivities (ee and de) have been demonstrated to be under relatively perfect control by proline and other acid−base catalysts; however, improving the reactivity still remains a considerable challenge. Additional research might shed light on the reasons why 0.1 to 0.3 equiv of catalyst relative to substrate are usually needed for the efficient conversion of reaction substrates. What will take us beyond the catalytic functions of metal-based catalysts in the asymmetric direct aldol reaction seems closely related to this point. Thus, the design of acid−base catalysts strongly requires and will benefit from advanced molecular manipulations in the future.

References

(1) Rychnovsky, S. D. Oxo Polyene Macrolide Antibiotics. *Chem. Rev.* **1995**, *95*, 2021−2040.

(2) (a) Machajewski, T. D.; Wong, C.-H. The Catalytic Asymmetric Aldol Reaction. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374. (b) Arya, P.; Qin, H. Advances in Asymmetric Enolate Methodology. *Tetrahedron* **2000**, *56*, 917−947. (c) Denmark, S. E.; Stavenger, R. A. Asymmetric Catalysis of Aldol Reactions with Chiral Lewis Bases. *Acc. Chem. Res.* **2000**, *33*, 432−440.

(3) Saito, S.; Yamamoto, H. Directed Aldol Condensation. *Chem.−Eur. J.* **1999**, *5*, 1959−1962.

(4) Watanabe, K.; Yamada, Y.; Goto, K. New Type of Aldol Condensations Catalyzed by Metal (II) Complexes of α-Amino Acid Esters and that with Cyclodextrin System. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1401−1406.

(5) (a) Yamada, Y. M. A.; Yoshikawa. N.; Sasai, H.; Shibasaki, M. Direct Catalytic Adol Reactions of Aldehydes with Unmodified Ketones. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871−1873. (b) Shibasaki, M.; Kanai, M.; Funabashi, K. Recent Progress in Asymmetric Two-Centered Catalysis. *Chem. Commun.* **2002**, 1989−1999. (c) Shibasaki, M.; Yoshikawa, N. Lanthanide Complexes in Multifunctional Asymmetric Catalysis. *Chem. Rev.* **2002**, *102*, 2187−2209.

(6) (a) Trost, B. M.; Ito, H. A Direct Catalytic Enantioselective Aldol Reaction via a Novel Catalyst Design. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. (b) Trost B. M.; Ito, H.; Silcoff, E. R. Asymmetric Aldol Reaction via a Dinuclear Zinc Catalyst: α-Hydroxyketones as Donors. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368. (c) Trost, B. M.; Silcoff, E. R.; Ito, H. Direct Asymmetric Aldol Reactions of Acetone Using Bimetallic Zinc Catalysts. *Org. Lett.* **2001**, *3*, 2497−2501.

(7) Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. Catalytic Asymmetric Aldol Reaction of Ketones and Aldehydes Using Chiral Calcium Alkoxides. *Tetrahedron Lett.* **2001**, *42*, 4669−4673.

(8) Dalko, P. I.; Moisan, L. Enantioselective Organocatalysis. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748.

(9) (a) Yamada, S.; Hiroi, K.; Achiwa, K. Asymmetric Synthesis with Amino Acid I. Asymmetric Induction in the Alkylation of Keto-Enanine. *Tetrahedron Lett.* **1969**, 4233−4236. (b) Eder, U.; Sauer, G.; Wiechert, R. New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures. *Angew. Chem., Int. Ed.* **1971**, *10*, 496−497. (c) Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.* **1974**, *39*, 1615−1621.

(10) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (b) Notz, W.; List, B. Catalytic Asymmetric Synthesis of anti-1,2-Diols. *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387. (c) List, B.; Pojarliev, P.; Castello, C. Proline-Catalyzed Asymmetric Aldol Reactions between Ketones and α-Unsubstituted Aldehydes. *Org. Lett.* **2001**, *3*, 573−575. (d) List, B. Asymmetric Aminocatalysis. *Synlett* **2001**, 1675−1686. (e) List, B. Proline-Catalyzed Asymmetric Reactions. *Tetrahedron* **2002**, 58, 5573−5590. (f) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. Direct Catalytic Enolexo Aldolization. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785−2788.

(11) (a) List, B. The Direct Catalytic Asymmetric Three-Component Mannich Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337. (b) List, B.; Pojarliev, P.; Martin, H. J. Efficient Proline-Catalyzed Michael Additions of Unmodified Ketones to Nitro Olefins. *Org. Lett.* **2001**, *3*, 2423−2425. (c) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. The Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction: Scope, Optimization, and Application to the Highly Enantioselective Synthesis of 1,2-Amino Alcohols. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−834. (d) List, B. Direct Catalytic Asymmetric α-Amination of Aldehydes. *J. Am. Chem. Soc.* **2002**, *124*, 5656−5657.

(12) (a) Bui, T.; Barbas, C. F., III. A Proline-Catalyzed Asymmetric Robinson Annulation Reaction. *Tetrahedron Lett.* **2000**, *41*, 6951−6954. (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F. Catalytic Enantioselective Direct Michael Additions of Ketones to Alkylidene Malonates. III *Tetrahedron Lett.* **2001**, *42*, 4441−4444. (c) Betancort, J. M.; Barbas, C. F., III. Catalytic Direct Asymmetric Michael Reactions: Taming Naked Aldehyde Donors. *Org. Lett.* **2001**, *3*, 3737−3741. (d) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III Amino Acid-Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon−Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267. (e) Córdova, A.; Notz, W.; Barbas, C. F., III. Direct Organocatalytic Aldol Reactions in Buffered Aqueous Media. *Chem. Commun.* **2002**, 3024−3025. (f) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. Amine-catalyzed Direct Asymmetric Mannich-Type Reactions. *Tetrahedron Lett.* **2001**, *42*, 199−201. (g) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. A Highly Enantioselective Route to Either Enantiomer of Both α- and β-Amino Acid Derivatives. *J. Am. Chem. Soc.* **2002**, *124*, 1866−1867. (h) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. III. A Highly Enantioselective Amino Acid-Catalyzed Route to Functionalized α-Amino Acids. *J. Am. Chem. Soc.* **2002**, *124*, 1842−1843. (i) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. The Direct Organocatalytic Asymmetric Mannich Reaction: Unmodified Aldehydes as Nucleophiles. *J. Org. Chem.* **2003**, *68*, 9624−9634. (j) Mase, N.; Tanaka, F.; Barbas, C. F., III. Rapid Fluorescent Screening or Bifunctional Amine-Acid Catalysts: Efficient Syntheses of Quaternary Carbon-Containing Aldols under Organocatalysis. *Org. Lett.* **2003**, *5*, 4369−4372.

(13) (a) Northrup, A. B.; MacMillan, W. C. The First Direct and Enantioselective Cross-Aldol Reaction of Aldehydes. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6790. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. The Direct and Enantioselective Organocatalytic α-Oxidation of Aldehydes. *J. Am. Chem. Soc.* **2003**, *125*, 10808−10809.

(14) (a) Bogevig, A.; Kumaragurubaran, N.; Jorgensen, K. A. Direct Catalytic Asymmetric Aldol Reactions of Aldehydes. *Chem. Commun.* **2002**, 620−621. (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. Direct Organo-Catalytic Asymmetric α-Amination of Aldehydes- A Simple Approach to Optically Active α-Amino Aldehydes, α-Amino Alcohols, and α-Amino Acids. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790−1793. (c) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. Direct L-Proline-Catalyzed Asymmetric α-Amination of Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 6254−6255.

(15) (a) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. The Direct and Enantioselective, One-Pot, Three-Component, Cross-Mannich Reaction of Aldehydes. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677−3680. (b) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. Application of High-Pressure Induced by Water-Freezing to the Direct Catalytic Asymmetric Three-Component List-Barbas-Mannich Reaction. *J. Am. Chem. Soc.* **2003**, *125*, 11208−11209.

(16) Jung, M. E. A Review of Annulation. *Tetrahedron* **1976**, *32*, 3−31.

(17) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C. Structural Studies of Crystalline Enamines. *Helv. Chem. Acta* **1978**, *61*, 3108−3135.

(18) (a) Agami, C.; Meynier, F.; Puchot, C.; Guilhem, J.; Pascard, C. New Insights into the Mechanism of the Proline-Catalyzed Asymmetric Robinson Cyclization; Structure of Two Intermediates. Asymmetric Dehydration. *Tetrahedron* **1984**, *40*, 1031−1038. (b) Agami, C.; Puchot, C.; Sevestre, H. Is the Mechanism of the Proline-Catalyzed Enantioselective Aldol Reaction Related to Biochmical Processes? *Tetrahedron Lett.* **1986**, *27*, 1501−1504.

(19) Puchot, C.; Samuel, O.; Dunch, E.; Zhao, S.; Agami, C.; Kagan, H. B. Nonlinear Effects in Asymmetric Synthesis. Examples in Asymmetric Oxidation and Aldolization Reactions. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357.

(20) (a) Bahmanyar, S.; Houk, K. N. Transition States of Amine-Catalyzed Aldol Reactions Involving Enamine Intermediates: Theoretical Studies of Mechanism, Reactivity, and Stereoselectivity. *J. Am. Chem. Soc.* **2001**, *123*, 11273−11273. (b) Bahmanyar, S.; Houk, K. N. The Origin of Stereoselectivity in Proline-Catalyzed Intramolecular Aldol Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 12911−12912. (c) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. Quantum Mechanical Predictions of the Stereoselectivities of Proline-Catalyzed Asymmetric Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 2475−2479.

(21) (a) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. Kinetic and Stereochemical Evidence for the Involvement of Only One Proline Molecule in the Transition States of Proline-Catalyzed Intra- and Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 16−17. (b) List, B.; Hoang, L.; Martin, H. J. New Mechanistic Studies on the Proline-catalyzed Aldol Reaction. *Proc. Natl. Acad. Sci., U. S. A.* **2004**, *101*, 5839−5842.

(22) Rajagopal, D.; Moni, M. S.; Subramanian, S.; Swaminathan, S. Proline Mediated Asymmetric Ketol Cyclization: A Template Reaction. *Tetrahedron: Asymmetry* **1999**, *10*, 1631−1634.

(23) Rankin, K. N.; Gauld, J. W.; Boyd, R. J. Density Functional Study of the Proline-Catalyzed Direct Aldol Reaction. *J. Phys. Chem. A* **2002**, *106*, 5155−5159.

(24) Bordwell, F. G. Equilibrium Acidities in Dimethyl Sulfoxide Solution. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(25) Calter, M. A.; Orr, R. K. The Direct Aldol Reaction Using Bifunctional Catalysts. *Tetrahedron Lett.* **2003**, *44*, 5699−5701.

(26) Gennari, C.; Piarulli, U. Combinatorial Libraries of Chiral Ligands for Enantioselective Catalysis. *Chem. Rev.* **2003**, *103*, 3071−3100.

(27) *Advanced Organic Chemistry*, 4th ed.; March, J., Ed.: John Wiley & Sons: New York, 1992; Chapter 8, pp 248−272.
(28) (a) Koshechkina, L. P.; Mel'nichenko, I. V. Aldol Condensation of Butyraldehyde in the Presence of Diamino Compounds. *Ukr. Khim. Zhur.* **1974**, *40*, 172−174. (b) Koshechkina, L. P.; Yasnikov, A. A. Catalysis with Diamines from the Aldol Condensation of Butyraldehyde. *Ukr. Khim. Zhur.* **1974**, *40*, 948−957. (c) Dickerson, T. J.; Janda, K. D. Aqueous Aldol Catalysis by a Nicotine Metabolite. *J. Am. Chem. Soc.* **2002**, *124*, 3220−3221.
(29) Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. Pyrrolidine-Catalyzed Homo-Aldol Condensation Reactions of Aldehydes. *Synlett* **1999**, 450−452.
(30) (a) Saito, S.; Nakadai, M.; Yamamoto, H. Diamine-Protonic Acid Catalysts for Catalytic Asymmetric Aldol Reaction. *Synlett* **2001**, 1245−1248. (b) Nakadai, M.; Saito, S.; Yamamoto, H. Diversity-Based Strategy for Discovery of Environmentally Benign Organocatalyst: Diamine-Protonic Acid Catalysts for Asymmetric Direct Aldol Reaction. *Tetrahedron* **2002**, *58*, 8167−8177.
(31) (a) Alexakis, A.; Andrey, O. Diamine-Catalyzed Asymmetric Michael Additions of Aldehydes and Ketones to Nitrostyrene. *Org. Lett.* **2002**, *4*, 3611−3614. (b) Andrey, O.; Alexakis, A.; Bernardinelli, G. Asymmetric Michael Addition of α-Hydroxyketones to Nitroolefins Catalyzed by Chiral Diamine. *Org. Lett.* **2003**, *5*, 2559−2561.
(32) (a) Angeletti, E.; Canepa, C.; Martinetti, G.; Venturello, P. Amino Groups Immobilized on Silica Gel: An Efficient and Reusable Heterogeneous Catalyst for the Knoevenagel Condensation. *J. Chem. Soc., Perkin Trans I* **1989**, 105. (b) Choudary, B. M.; Kantam, M. L.; Sreekanth, P.; Bandopadhay, T.; Figueras, F.; Tuel, A. Knoevenagel and Aldol Condensations Catalyzed by a New Diamino-Functionalized Mesoporous Material. *J. Mol. Catal. A: Chem.* **1999**, *142*, 361−365.
(33) Kubota, Y.; Goto, K.; Miyata, S.; Goto, Y.; Fukushima, Y.; Sugi, Y. Enhanced Effect of Mesoporous Silica on Base-Catalyzed Aldol Reaction. *Chem. Lett.* **2003**, 234−235.
(34) (a) Hine, J. Bifunctional Catalysis of α-Hydrogen Exchange of Aldehydes and Ketones. *Acc. Chem. Res.* **1978**, *11*, 1−7. (b) Hine, J.; Chou, Y. Rates of Imine Formation from Acetone and Some *N*,*N*-Dimethyl Vicinal Diamines. *J. Org. Chem.* **1981**, *46*, 649−652.
(35) (a) Wagner, J.; Lerner, R. A.; Barbas, C. F. III. Efficient Aldolase Catalytic Antibodies That Use the Enamine Mechanism of Natural Enzymes. *Science*, **1995**, *270*, 1797−1800. (b) Barbas, C. F.; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Björnestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I. A.; Lerner, R. A. Immune Versus Natural Selection: Antibody Aldolases with Enzymatic Rates but Broader Scope. *Science* **1997**, *278*, 2085−2092. (c) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F. III. Aldolase Antibodies of Remarkable Scope. *J. Am. Chem. Soc.* **1998**, *120*, 2768−2779. (d) Turner, J. M.; Bui, T.; Lerner, R. A.; Barbas, C. F., III; List, B. An Efficient Benchtop System for Multigram-Scale Kinetic Resolutions Using Aldolase Antibodies. *Chem.−Eur. J.* **2000**, *6*, 2772−2774. (e) Heine, A.; DeSantis, G.; Luz, J. G.; Mitchell, M.; Wong, C.-H.; Wilson, I. A. Observation of Covalent Intermediates in an Enzyme Mechanism at Atomic Resolution. *Science* **2001**, *294*, 369−374.
(36) Tang, Z.; Jiang, F.; Yu, L.-T.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. Novel Small Organic Molecules for a Highly Enantioselective Direct Aldol Reaction. *J. Am. Chem. Soc.* **2003**, *125*, 5262−5263.
(37) Kobayashi, S.; Nagayama, S.; Busujima, T. Lewis Acid Catalysts Stable in Water. Correlation between Catalytic Activity in Water and Hydrolysis Constants and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands. *J. Am. Chem. Soc.* **1998**, *120*, 8287−8288.
(38) Subramanian, L. R.; García, A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A. Ed.; John Wiley & Sons: New York, 1995; Vol. 7, pp 5142−5146.
(39) Waller, F. J.; Barrett, G. M.; Braddock, D. C.; Ramprasad, D.; McKinnell, R. M.; White, A. J. P.; Williams, D. J.; Ducray, R. Tris-(trifluoromethanesulfonyl)methide ("Triflide") Anion: Convenient Preparation, X-ray Crystal Structures, and Exceptional Catalytic Activity as a Counterion with Ytterbium(III) and Scandium(III). *J. Org. Chem.* **1999**, *64*, 2910−2913.
(40) Ishihara, K.; Hasegawa, A.; Yamamoto, H. Polystyrene-Bound Tetrafluorophenylbis(triflyl)methane as an Organic-Solvent-Swellable and Strong Brønsted Acid Catalyst. *Angew. Chem., Int. Ed.* **2001**, *40*, 4077−4079.
(41) Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignat'ev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P.-C. The Gas-Phase Acidities of Very Strong Neutral Brønsted Acids. *J. Am. Chem. Soc.* **1994**, *116*, 3047−3057.
(42) Wiberg, K. B. The Interaction of Carbonyl Groups with Substituents. *Acc. Chem. Res.* **1999**, *32*, 922−929.
(43) (a) Saito, S. JP Patent 2003-54197, 2003; The 83rd (Spring) Annual Meeting of the Chemical Society of Japan, 2003, Abstract II, p 1186. (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. Asymmetric Direct Aldol Reaction Assisted by Water and Proline-Derived Tetrazole Catalyst. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983−1986. (c) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *O*-Nitroso Aldol Synthesis: Catalytic Enantioselective Route to α-Aminooxy Carbonyl Compounds via Enamine Intermediate. *Proc. Natl. Acad. Sci., U. S. A.* **2004**, *101*, 5374−5378. (d) Cobb, A. J. A.; Shaw, D. M.; Ley, S. 5-Pyrrolidin-2-yltetrazole: A New, Catalytic, More Soluble Alternative to Proline in an Organocatalytic Asymmetric Mannich-Type Reaction. *Synlett* **2004**, 558−560.
(44) Boraei, A. A. A. Acidity Constants of Some Tetrazole Compounds in Various Aqueous−Organic Solvent Media. *J. Chem. Eng. Data* **2001**, *46*, 939−943.
(45) Catalan, J.; Menendez, M.; Elguero, J. On the Relationships between Basicity and Acidity in Azoles. *Bull. Soc. Chim. Fran.* **1985**, I-30−I-33.
(46) *March's Advanced Organic Chemistry*, 5th ed.; Smith, M. B., March, J., Eds.; John Wiley & Sons: New York, 2001; p343.
(47) Almquist, R. G.; Chao, W.-R.; Jennings-White, C. Synthesis and Biological Activity of Carboxylic Acid Replacement Analogues of the Potent Angiotestin Converting Enzyme Inhibitor. 5(*S*)-Benzamido-4-oxo-6-phenylhexanoyl-L-proline. *J. Med. Chem.* **1985**, *28*, 1067−1071.
(48) Greenzaid, P.; Luz, Z.; Samul, D. A Nuclear Magnetic Resonance Study of the Reversible Hydration of Aliphatic Aldehydes and Ketones I. Oxygen-17 and Proton Spectra and Equilibrium Constants. *J. Am. Chem. Soc.* **1967**, *89*, 749−756.
(49) (a) Funabiki, K.; Honma, N.; Hashimoto, W.; Matsui, M. Practical Asymmetric Synthesis of β-Trichloromethyl-β-hydroxy Ketones by the Reaction of Chloral Hydrate with Chiral Imines. *Org. Lett.* **2003**, *5*, 2059−2061. (b) Funabiki, K.; Matsunaga, K.; Nojiri, M.; Hashimoto, W.; Yamamoto, H.; Shibata, K.; Matsui, M. The Use of Trifluoroacetaldehyde Ethyl Hemiacetal or Hydrate in a Simple and Practical Regioselective Synthesis of β-Hydroxy-β-trifluoromethyl Ketones from Enamines and Imines. *J. Org. Chem.* **2003**, *68*, 2853−2860.

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