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Diaminomethylenemalononitrile as a Chiral Single Hydrogen Bond Catalyst: Application to Enantioselective Conjugate Addition of α-Branched Aldehydes

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Abstract: An improved diaminomethylenemalononitrile organocatalyst, bearing a *N,N*-disubstituted structure, promoted enantioselective conjugate addition reaction of α-branched aldehydes with vinyl sulfone, affording adducts with excellent enantioselectivities (up to 96% ee). Mechanistic studies revealed that the diaminomethylenemalononitrile motif holds the vinyl sulfone substrate using a single hydrogen bond accompanied by multiple weak interactions, including electrostatic C–H···O interactions.

In molecular recognition and supramolecular chemistry, hydrogen bond (H-bond) and non-covalent interactions, including a C–H···O interaction, are key factors for the host-guest complexation.[1] Although each non-covalent interaction is not strong, it makes the complex favorable in multiple bonding conditions. The organocatalyst attracted attention in the past decades because of its advantages, including environmentally benign properties, high stereo- and chemo-selectivities, and easy handling.[2] *N,N'*-Disubstituted thioureas,[3] squaramides[4] are privileged structural motifs for several enantioselective molecular transformations. H-bond catalysts bearing two N–H moieties serve as double H-bond donors, yielding a characteristic complexation with reaction substrates, which is essential to attain excellent enantioselectivity, as well as reasonable catalytic activity. In our ongoing project, which focuses on developing organocatalysts bearing novel H-bond donor moiety, an organocatalyst **1** bearing *N,N'*-disubstituted diaminomethylenemalononitrile (DMM) structure instead of thiourea/squaramide motif has been found (Figure 1A). This catalyst shows excellent properties in enantioselective conjugate addition reactions of α-branched aldehydes with vinyl sulfones (Figure 1B).[5] We reported DMM-catalyzed aldol and other conjugate addition chemistry.[6–7]

We speculated that the two N–H moieties in the *N,N'*-disubstituted DMM motif serve as a double H-bond donor

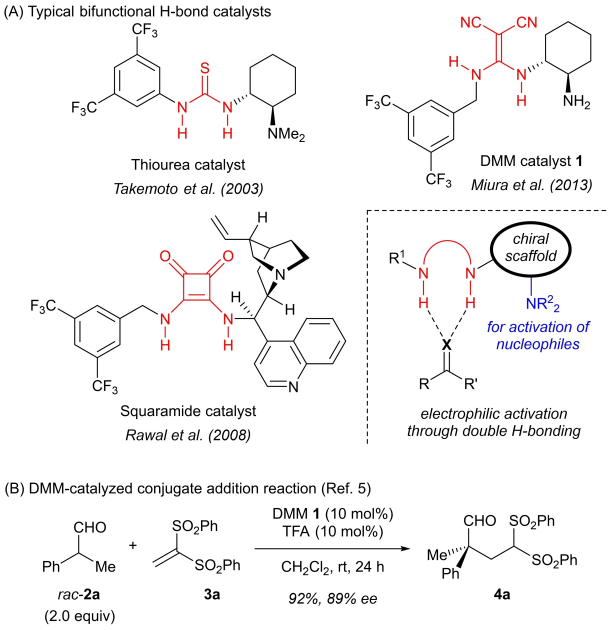

Figure 1. (A) Structures of typical bifunctional H-bond catalysts and their catalytic mechanism. (B) Previous DMM-catalyzed conjugate addition reaction.

similar to thiourea/squaramide motifs. However, in some reactions, DMM-derived catalysts exhibited better stereoselectivities than the corresponding thiourea/squaramide-derived catalysts.[7] To understand the differences in such structurally related catalysts, we have reinvestigated a relationship between the molecular structure of DMM-derived catalysts and the catalytic activity. Herein, we report *N,N,N'*-trisubstituted DMM derivatives, where the third substituent is introduced to one nitrogen atom, still catalyze the reaction in an enantioselective manner. In addition, a careful screening of the substituent helps in the development of an improved DMM catalyst, which caused better enantioselectivity compared with the reported organocatalysts, including our DMM catalyst **1**.[5,8] Experimental and theoretical analyses of this reaction have shown the importance of multiple non-covalent interactions, including the C–H···O interaction between enamine-bounding catalyst molecule and vinyl sulfone substrate.

This research began from an unexpected result in rescreening of the DMM-derived organocatalysts in enantioselective conjugate addition of α-branched aldehydes to a vinyl sulfone (Scheme 1): the reaction of racemic 2-phenylpropanal *rac*-**2a** with $(PhSO_2)_2C{=}CH_2$ **3a** in the presence of *N,N*-dibenzyl DMM

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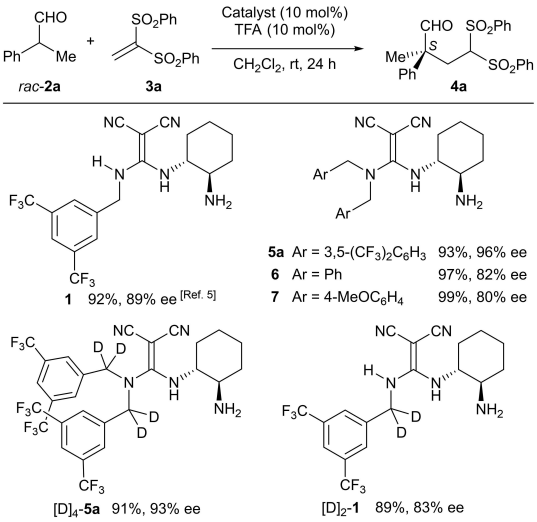
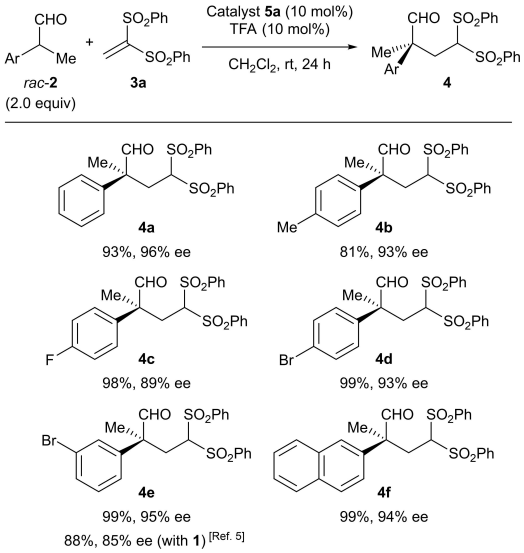


Scheme 1. Screening of DMM Catalysts.



Scheme 2. Enantioselective Conjugate Addition Reaction Using **5a**.

catalyst **5a** gave the adduct **4a** with better enantioselectivity than that by *N*-monobenzyl DMM catalyst **1**[5] (89% ee for **1** vs. 96% ee for **5a**). Although this reaction has been used as a kind of touchstone for primary amine organocatalysts,[8] the highest enantiomer excess has been achieved in this case. This observation was a surprise because the *N*,*N*-disubstitution in the DMM catalyst **5a** was contradictory to the conventional transition state model using double H-bonding with the sulfone substrate. The electronic behavior of pendant benzyl groups affected the enantioselectivity. The replacement of (3,5-bis (trifluoromethyl)phenyl)methyl groups with simple benzyl and (4-methoxyphenyl)methyl groups resulted in a decrease in the enantioselectivity (82% ee for **6**, 80% ee for **7**). Considering that a C–D···X interaction is weaker than the corresponding C–H···X interaction,[9] we examined the reaction in the presence of a catalyst [D]$_4$-**5a** in which benzylic positions of DMM catalyst **5a** were deuterated. Although the reaction occurred, the enantioselectivity dropped to 93% ee. Benzylic deuteration of the first-generation DMM catalyst **1** caused impairing of the enantioselectivity.[10]

With the improved DMM catalyst **5a**, the reactions of some α-branched aldehydes **2** were examined (Scheme 2). Aldehydes **2b–d** bearing *p*-substituted phenyl groups reacted with **3a** to afford the corresponding adducts **4b–d** in good yields with enhanced enantioselectivities. Although *m*-bromophenyl aldehyde **2e** was a problematic substrate in the reaction with the first-generation catalyst **1**, the enantioselectivity was increased to 95% ee using the improved catalyst **5a**. Moreover, aldehyde **2f** bearing 2-naphthyl group was converted to the product **4f** with 94% ee.[11]

To obtain mechanistic insights of the reaction catalyzed by improved DMM catalyst **5a**, we evaluated a correlation of enantiomer excess of product **4a** (ee$_P$) toward that of the DMM catalyst **5a** (ee$_{CAT}$). As shown in Figure 2A, a good linear relationship was observed. This fact proved that one catalyst molecule participates in the enantioselectivity-determining transition state of the reaction. Considering the reported

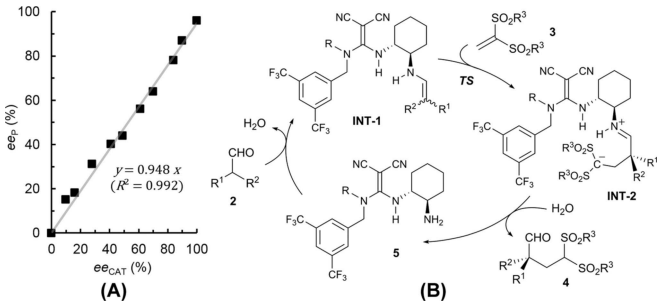


Figure 2. (A) A linear correlation between enantiomer excesses of catalyst **5a** (ee$_{CAT}$) and product **4a** (ee$_P$). (B) Proposed catalyst cycle for the improved DMM catalyzed reaction.

mechanism catalyzed by primary amines,[8] this reaction should include a catalytic cycle as shown in Figure 2B. TFA-mediated dehydrative condensation between the DMM catalyst **5** and aldehyde **2** produces a reactive enamine intermediate **INT-1**. In addition, the C–C bond-forming step with vinyl sulfone **3** produces iminium species **INT-2**, and its hydrolysis causes the formation of product **4** along with the regeneration of DMM catalyst **5**. Among each step, the C–C bond-forming step would be a rate/enantioselectivity-determining step.[12]

We conducted the density functional theory (DFT) simulation [PCM(CH_2Cl_2)-M06-2X/6-31+G(d) level of theory] of the reaction of 2-phenylpropanal **2a** with a vinyl sulfone **3b** (R^3 = Me) (Figure 2B). Here a catalyst **5b** in which one of the (3,5-bis (trifluoromethyl)phenyl)methyl groups in **5a** was replaced with a simple methyl group (R = Me) was adopted as a model. After many attempts (for detailed reaction profiles, see the ESI), transition state **TS-*S*** with the *E*-enamine structure and its *Z*-isomeric transition state **TS-*R*** were found as energetically acceptable transition states (Figures 3A–C). Here, the participation of TFA in the transition states are not considered.[13] Transition state **TS-*S*** gives experimentally obtained major

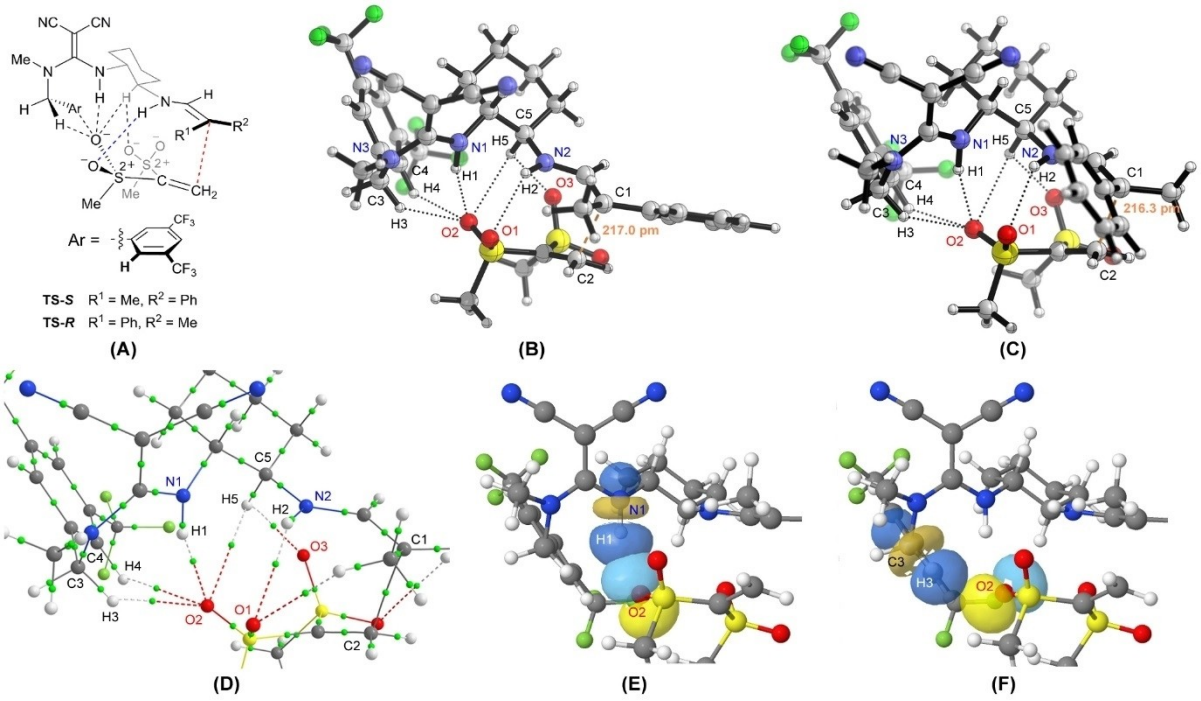


Figure 3. (A) Line-bond projections of **TS-*S*** and **TS-*R***. Sulfur-oxygen bonds are drawn as charge-separated resonance structure because of their pronounced single covalent bond character.[18] (B) Ball-stick projection of **TS-*S***. (C) Ball-stick projection of **TS-*R***. (D) QTAIM bond paths. BCPs are shown by green small spheres. (E) Strong N1–H1···$O2_{LP1}$ NBO interaction, and (F) Weak C3–H3···$O2_{LP2}$ NBO interaction.

enantiomer and it was preferable than **TS-*R*** ($\Delta\Delta G^{\ddagger}$ = 2.7 kcal mol^{-1} at 298 K).

The Bader's Quantum Theory of Atoms In Molecules (QTAIM) analysis,[14] which represents the chemical bond by the bond path defined by an electron density function between atoms, visualizes the interatomic interactions in **TS-*S*** (Figure 3D). Here, two bond paths for the N–H···O interaction (N1–H1···O2 and N2-H2···O1) are found. In addition, the sulfonic oxygen atoms interact with three hydrogen atoms in enamine-bounding catalyst, including H3 on benzylic C3, H4 on aromatic C4, and H5 on C5 in the cyclohexane backbone.[15] The QTAIM parameters of N1–H1···O2 interaction, such as electron density (ρ_{BCP}) and Laplacian ($\nabla^2\rho_{BCP}$) at the bond critical point (BCP), imply that the bond may be classified into common H-bond (ρ_{BCP} = 0.0211 *e* bohr^{-3}; $\nabla^2\rho_{BCP}$ = +0.0691 *e* bohr^{-5}).[16] However, ρ_{BCP} (0.0131 *e* bohr^{-3}) and $\nabla^2\rho_{BCP}$ (+0.0468 *e* bohr^{-5}) in N2–H2···O1 interaction are notably reduced. In all C–H···O interactions, QTAIM parameters confirmed the importance of electrostatic factor (for more details, see the ESI). This conclusion is consistent with the Natural Bond Orbital (NBO) analysis[17] which is used as an orbital-based bond descriptor linked to the Lewis structure (Figures 3E and 3F). The sum of the second perturbation energies [*E*(2)] in N1–H1···O2 interaction is much larger than that in N2–H2···O1 interaction (11.7 kcal mol^{-1} vs. 2.6 kcal mol^{-1}). Moreover, *E*(2) values in four C–H···O interactions are similar in magnitude to the weak N2–H2···O1 interaction (2.2 kcal mol^{-1} for C3–H3···O2, 1.9 kcal mol^{-1} for C4–H4···O2, 2.2 kcal mol^{-1} for C5–H5···O2, and 3.1 kcal mol^{-1} for C5–H5···O3). A clear single bond character of the push-pull C_α-C_β bond in the catalyst molecule (Figure 4) should be noted. Two covalent-bond indices, Natural Localized Molecular Orbital (NLMO)/Natural Population Analysis (NPA) bond order and delocalization index (DI) are 1.27 and 1.15, respectively. The highly charge-separated character of this partial double bond is supported as follows: 1) NPA charges of C_α (−0.51 *e*) and C_β (+0.57 *e*), and 2) highly twisted geometry around C_α–C_β bond axis in **TS-*S***.[18] Consequently, the relatively heavy contribution of the charge-separated resonance structure **II** in this push-pull system[19] enhances C3–H3···O2 interaction, as well as N1–H1···O2 bonding.[20,21] Relatively large *E*(2) value of the N1–H1···O2 interaction plays a central role in stabilizing the transition state complex. Therefore, we conclude that the *N*,*N*-dibenzyl DMM motif serves as a *single* H-bond donor. Despite weak stabilization by each C–H···O interaction, their cooperation assists to construct the suitable asymmetric reaction field, which is required for the highly enantioselective C–C bond formation. Such a DMM motif would favor the molecular design of tailor-made H-bond catalysts.

In conclusion, we successfully developed *N*,*N*-dibenzyl DMM organocatalyst **5a** for the enantio-selective conjugate addition

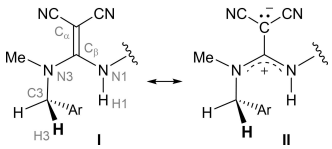


Figure 4. Resonance structures in the push-pull system.

reaction of α-branched aldehydes with vinyl sulfone. Compared with previous reports, the new DMM catalyst realized higher enantioselectivity. The DFT calculation revealed that the *N*,*N*-dibenzyl DMM motif served as a single H-bond donor, but the transition states were secondary stabilized by multiple non-covalent interactions, including the C–H···O interaction. Push-pull effects in the DMM backbone are key factors for enhancing such weak interactions. Currently, the developments of novel organocatalysts bearing the *N*,*N*-dialkyl DMM motif and applications to other asymmetric reactions are being investigated in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: organocatalyst · multiple interactions · vinyl sulfone · conjugate addition · hydrogen bond

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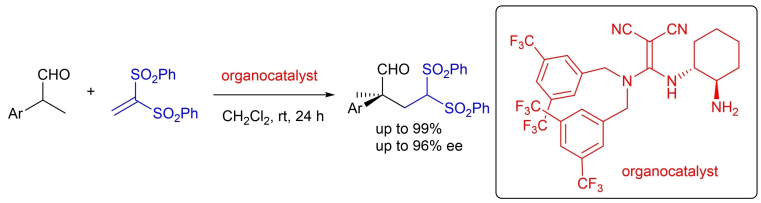

A novel organocatalyst using single hydrogen-bond and multiple non-covalent interactions (including C–H···O interactions) effectively promoted asymmetric conjugate additions of α-branched aldehydes to vinyl sulfone, affording the addition products with excellent enantioselectivities (up to 96% ee).

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