

Asymmetric Vinylogous Aldol Reaction via H-Bond-Directing Dienamine Catalysis

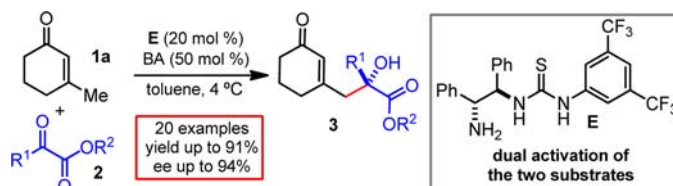
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ABSTRACT



The enantioselective direct vinylogous aldol reaction of 3-methyl 2-cyclohexen-1-one with α -keto esters has been developed. The key to success was the design of a bifunctional primary amine-thiourea catalyst that can combine H-bond-directing activation and dienamine catalysis. The simultaneous dual activation of the two reacting partners results in high reactivity while securing high levels of stereocontrol.

Asymmetric aminocatalysis has greatly improved chemists' ability to stereoselectively functionalize unmodified carbonyl compounds.¹ Recently, this strategy has shown potential for controlling the formation of remote stereocenters, which is a difficult synthetic goal.² Specifically, the propagation of the HOMO-raising electronic effect through a conjugated π -system of extended enamines,

such as dienamines³ and trienamines,⁴ has allowed the direct, stereoselective functionalization of unsaturated carbonyls at their γ and ϵ positions, respectively. While these aminocatalytic activation modes have been successfully exploited for the design of stereoselective pericyclic reactions,⁵ their use in nucleophilic addition/substitution manifolds has remained relatively underexplored.⁶

Herein, we describe the development of a direct vinylogous aldol reaction of 3-methyl 2-cyclohexen-1-one **1a** with α -keto esters **2**. The key to success was the design of a bifunctional primary amine-thiourea catalyst that can combine the H-bond-directing activation of the electrophilic substrate with the dienamine activation of the enone donor. The dual activation strategy secures direct access to aldol products **3** with high stereocontrol and perfect γ -site selectivity.

The vinylogous aldol reaction⁷ is a powerful way to directly construct densely adorned δ -hydroxylated α,β -unsaturated carbonyls, which are common structural motifs in biologically relevant natural molecules.^{8a} Traditionally,

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(3) For a review on dienamine activation, see: Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865.

(4) For an overview on trienamine activation, see: (a) Arceo, E.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 5290. For selected examples: (b) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638. (c) Liu, Y.-K.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212. (d) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310.

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(6) (a) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (b) Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmman, C.; Christmann, M. *Org. Lett.* **2011**, *13*, 70. (c) Silvi, M.; Cassani, C.; Moran, A.; Melchiorre, P. *Helv. Chim. Acta* **2012**, *95*, 1985.

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stereoselective, catalytic, vinylogous aldol reactions rely upon indirect Mukayama-type strategies, which require the preformation of stable dienolate equivalents.⁸ There has been only limited success in achieving the direct in situ activation of unmodified carbonyl substrates, which would greatly expand the synthetic potential and atom economy of this chemical transformation.⁹

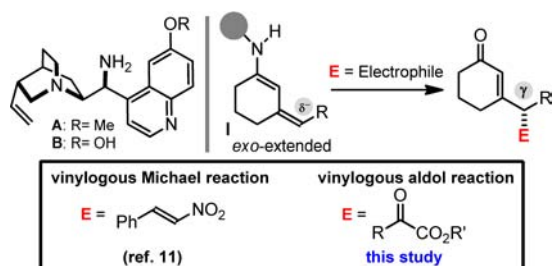


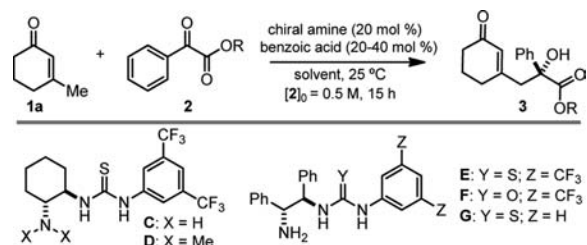
Figure 1. The design plan for developing a direct vinylogous aldol reaction under dienamine activation of cyclic enones: moving from a Michael to an aldol process by means of chiral primary amine catalysis. The gray circle represents the primary aminocatalyst scaffold.

We selected the combination of the commercially available 3-methyl cyclohexenone **1a** and α -keto ester **2a** as a model for the vinylogous aldol reaction (Table 1). The choice was motivated by our previous experiences with vinylogous reactivity.^{6a,c,9b} Recently, we found that the cinchona-based primary amines **A** and **B**¹⁰ can promote vinylogous nucleophilicity upon selective activation of β -substituted cyclohexenones (Figure 1).¹¹ The transmission of the HOMO-raising effect through the transiently generated cyclic dienamine intermediate of type **I** allowed for intermolecular vinylogous Michael additions to proceed with high levels of enantioselectivity and exclusive γ -site selectivity. To be successful, the cinchona aminocatalyst needed to coax the regiocontrolled formation of the *exo*-cyclic extended dienamine intermediate **I**, resulting in the alkylation taking place selectively at the γ position.

This precedent¹¹ persuaded us to test these primary amine catalysts in the vinylogous aldol addition reaction. Despite extensive efforts, we have not succeeded in

translating the cyclic enone/cinchona-based catalyst system to the vinylogous aldol process. The use of 20 mol % of catalyst **A** or **B**, in combination with 40 mol % of benzoic acid as the cocatalyst, led to **3a** as the unique product, but with poor stereocontrol and very low reactivity (entries 1 and 2 in Table 1, reactions conducted in toluene at 60 °C).

Table 1. Development of the Direct Vinylogous Aldolization under Dienamine Activation of the Cyclic Enone **1a**^a



entry	amine	R	3	solvent	conv (%) ^b	ee (%) ^c
1 ^d	A	Et, 2a	3a	toluene	10	23
2 ^d	B	Et, 2a	3a	toluene	25	35
3	C	Et, 2a	3a	toluene	50	43
4	D	Et, 2a	3a	toluene	<5	—
5	E	Et, 2a	3a	toluene	43	89
6	F	Et, 2a	3a	toluene	53	68
7	G	Et, 2a	3a	toluene	32	77
8	E	Et, 2a	3a	CHCl ₃	19	89
9	E	Et, 2a	3a	THF	61	69
10	E	Et, 2a	3a	MTBE	40	81
11 ^e	E	Et, 2a	3a	toluene	70 ^f	89
12 ^e	E	Bn, 2b	3b	toluene	72 ^f	92
13 ^e	E	Me, 2c	3c	toluene	68 ^f	90
14 ^e	E	<i>i</i> -Pr, 2d	3d	toluene	65 ^f	88
15 ^e	E	<i>t</i> -Bu, 2e	3e	toluene	65 ^f	90
16 ^e	E	Anth, 2f	3f	toluene	80 ^f	94

^a BA: benzoic acid; MTBE: *tert*-butyl methyl ether; Anth: anthracen-9-ylmethyl. Catalyst **A** and **B** were used with 2 equiv of BA (40 mol %), while **C**–**G** required a 1:1 combination with the acid (20 mol %). Reactions on a 0.05 mmol scale using 2 equiv of **1a**. ^b Determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis on a chiral column. ^d Reaction at 60 °C. ^e Reaction performed with 5 equiv of **1a** and 50 mol % of BA at 4 °C over 48 h. ^f Value refers to the yield of the isolated compound **3** after chromatography.

The quest for a more stereoselective and reactive system prompted us to undertake an extensive catalyst screening (Figure S1, Supporting Information (SI)). We wondered if the application of chiral bifunctional H-bond-directing amine catalysts could provide a suitable solution (Table 1). A bifunctional primary amine-thiourea catalyst, which can combine H-bond-directing activation of the α -ketoester **2** and dienamine catalysis, might result in the simultaneous dual activation of the two reacting partners while

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(12) For selected examples of primary amine-thiourea catalysts in enamine and iminium ion activations, see: (a) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451. (b) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (c) Galzerano, P.; Bencivenni, G.; Pesciaoli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.—Eur. J.* **2009**, *15*, 7846. (d) Yu, F.; Jin, Z.; Huang, H.; Ye, T.; Liang, X.; Ye, J. *Org. Biol. Chem.* **2010**, *8*, 4767.

positioning them in a proper 3-D molecular assembly. This could lead to higher levels of both reactivity and stereoselectivity.^{12,13}

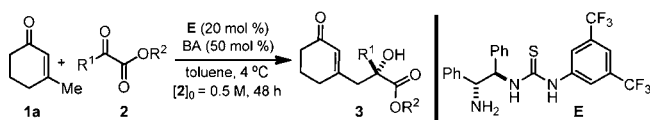
Pursuing this dual activation prospect, we explored the potential of bifunctional primary amine-thiourea catalysts **C** and **E**, easily available from commercially available chiral diamines, to promote the model reaction. Both bifunctional catalysts induced a great acceleration of the reaction rate, even at ambient temperature (entries 3 and 5). To our delight, the simple bifunctional catalyst **E** inferred a satisfactory level of stereoselection (89% ee, entry 5). We then initiated a catalyst structure/reactivity and stereoselectivity correlation study, using modified amine-thiourea derivatives. This was to identify a role for each functional group of the catalyst scaffold and to gain preliminary insight into the mechanism of stereoselection. Replacing the primary amine in **C** with the corresponding *N,N*-dimethyl tertiary amine (the Takemoto catalyst,¹⁴ **D**, entry 4) completely suppressed the reactivity. This is in agreement with a mechanistic scenario requiring the formation of a dienamine reactive intermediate. The urea catalyst **F** was slightly more reactive but slightly less stereoselective than its thiourea analogue **E** (compare entries 5 and 6). This indicates that the catalysts likely operate by similar mechanisms as H-bond donors; that is, the Lewis basicity of sulfur in **E** probably does not play a direct role during the catalysis. In addition, the absence of the electron-withdrawing trifluoromethyl group, which substantially reduces both the acidity and the H-bond donor propensity of the thiourea moiety, resulted in a lower reactivity and stereoselectivity (catalyst **G**, entry 7). All these results suggest a cooperative mechanism of catalysis of the thiourea and the primary amino moiety, which synergistically channel the process toward a highly stereoselective vinylogous pathway by concomitant activation of both the electro- and nucleophilic partners.

To further improve the efficiency of the catalysis by amine **E**, different reaction parameters were studied. Examination of the acid cocatalyst (Table S1) and reaction media (entries 8–10 in Table 1 and Table S2) identified benzoic acid and toluene as the more effective combination (entry 5). A second cycle of optimization using these conditions revealed that an excess of the benzoic acid (50 mol %)

and of the enone **1a** (5 equiv) substantially increased the reactivity, allowing the process to be conducted at 4 °C.¹⁵ These conditions provided the product **3a** with synthetically useful results over a 48-h reaction time (entry 11 in Table 1: **3a** isolated in 70% yield, and 89% ee) and were selected to evaluate the scope of the vinylogous aldol process.

The size of the ester moiety did not alter the stereochemical outcome of the reaction. The corresponding aldol adducts **3b–f** were produced with similar optical purity and chemical yield (entries 12–16 in Table 1, ee ranging from 88% to 94%). The scope of the aromatic α -keto ester derivatives **2** is detailed in Table 2. Different substitution patterns were well-tolerated, regardless of their position on the phenyl ring (entries 1–7). The presence of an electron-donating group or of a heteroaromatic moiety partially affected the efficiency of the catalytic system (entries 8 and 9). Aliphatic α -keto esters proved to be competent electrophiles of the vinylogous aldol reaction, providing the corresponding aldol adducts **3q–t** with synthetically useful results (entries 11–14).

Table 2. Scope of the Direct Vinylogous Aldolization^a



entry	R ¹	R ²	3	yield (%) ^b	ee (%) ^c
1	4-Br-C ₆ H ₄	Bn	3i	68	88
2	4-Cl-C ₆ H ₄	Bn	3j^d	89	88
3	4-I-C ₆ H ₄	Bn	3k	77	90
4	4-F-C ₆ H ₄	Bn	3l	73	85
5	2-F-C ₆ H ₄	Bn	3m	91	82
6	2-F,4-Br-C ₆ H ₄	Bn	3n	87	80
7	4-Me-C ₆ H ₄	Bn	3g	65	87
8	4-MeO-C ₆ H ₄	Bn	3h	32	87
9	2-thiophenyl	Bn	3o	80	46
10	4-Cl-C ₆ H ₄	Anth ^d	3p^e	89	91
11	Ph	Bn	3q	65	79
12	Ph(CH ₂) ₂	Et	3r	87	90
13	<i>c</i> -C ₆ H ₁₁	Et	3s	71	83
14	(CH ₂) ₂ CO ₂ Bn	Bn	3t	86	91

(13) Recently, the H-bond-directing approach using chiral secondary amines has greatly expanded the potential of dienamine and trienamine catalysis in promoting asymmetric pericyclic reactions; see: (a) Albrecht, L.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Esrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543. (b) Ibrecht, L.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Esrich, C.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 13109. For the application in trienamine-mediated asymmetric reactions, see: (c) Albrecht, L.; Cruz Acosta, F.; Fraile, A.; Albrecht, A.; Christensen, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 9088. (d) Jiang, H.; Rodríguez-Esrich, C.; Johansen, T. K.; Davis, R. L.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10271.

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(15) Experimental observations, detailed in Figure S2 and Table S3 within the SI, revealed that prolonging the reaction time to obtain a higher conversion slightly affected the optical purity of the product **3**. The erosion of the enantiomeric excess was mainly ascribable to a retro-aldol pathway. An excess of the donor **1a** and of the benzoic acid and a lower reaction temperature were crucial to preserving the enantioselectivity, while the conversion of the process increased over time (Tables S4–S6).

^a BA: benzoic acid. Reactions performed on a 0.1 mmol scale using 5 equiv of **1a**. ^b Yield of the isolated products **3** after chromatographic purification. ^c Determined by HPLC analysis on a chiral column. ^d Anth: anthracen-9-ylmethyl. ^e The (*R*) absolute configuration for products **3j** and **3p** has been unambiguously inferred by X-ray crystallographic analysis; see ref 17.

As a limitation of the system, modifying the cyclic scaffold of the enone (i.e., 3-methyl 2-cyclopenten-1-one) resulted in a complete loss of reactivity.¹⁶ Crystals from chlorides **3j** and **3p** were suitable for anomalous dispersion X-ray analysis, which established an (*R*) absolute configuration at

(16) Attempts to forge two contiguous stereogenic centers at the λ and δ positions using differently β -substituted cyclohexanones have been unsuccessful. Linear enones also proved unreactive under the reported reaction conditions.

the newly formed γ -stereocenter of the vinylogous aldol adducts.¹⁷

Our experimental observations are consonant with a bifunctional mode of activation where the primary amine-thiourea catalyst **E** combines the H-bond activation of the α -keto ester and the dienamine activation of the enone **1a**. Modifications of the catalyst scaffold, as detailed in entries 4–7 of Table 1, revealed that the primary amine and the thiourea group play an active role during the catalysis. Figure 2 depicts a plausible catalytic machinery, which accounts for the observed stereochemical outcome. The relative spatial arrangement of the two reacting partners, as orchestrated by the bifunctional catalyst, determines the selective attack to the *Si*-face of the α -keto ester.

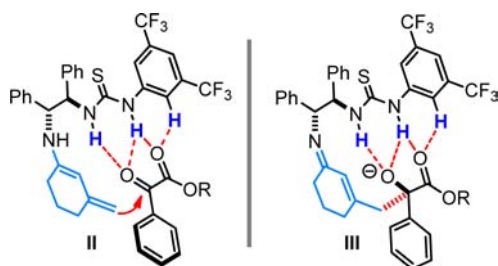


Figure 2. Plausible bifunctional mode of action of the primary amine thiourea catalyst **E**; possible ground-state association (**II**) and stabilization of the generating alkoxy anion (**III**).

To further support the bifunctional activation mode, we investigated the possible association of the α -keto methyl ester **2c** with the catalyst **E** by means of NMR spectroscopic analyses. ¹H NMR titration studies of the catalytic system (amine **E** in the presence of 1 equiv of benzoic acid)¹⁸ were conducted in toluene-*d*₈ and with an increasing amount of **2c** (Figure S14). The low-field shifts of the NH thiourea protons clearly indicated the H-bonding complexation with the α -keto ester. In agreement with previous works,^{18,19} our NMR studies revealed how the *ortho* proton of the 3,5-bis(trifluoromethyl)phenyl catalyst moiety, acting as an H-bond donor, also participated in the catalyst–substrate **2c** interaction. In addition, the imine precursor of the dienamine intermediate was spectroscopically detected when mixing the aminocatalyst **E** with the enone **1a** in CDCl₃ and in the presence of 4 Å molecular sieves (Figures S3–S8).

(17) Crystallographic data for **3j** and **3p** are available free of charge from the Cambridge Crystallographic Data Centre, accession numbers CCDC 912144 and CCDC 912145, respectively.

(18) NMR spectroscopic studies of a catalyst **E**/benzoic acid mixture, detailed in Figures S9–S13, revealed the formation of a new molecular assembly, presumably as a result of the primary amine protonation. We note that a cooperative association of thiourea and a benzoic acid derivative has been reported; see: Zhang, Z.; Lippert, K. M.; Hausmann, H.; Kotke, M.; Schreiner, P. R. *J. Org. Chem.* **2011**, *76*, 9764.

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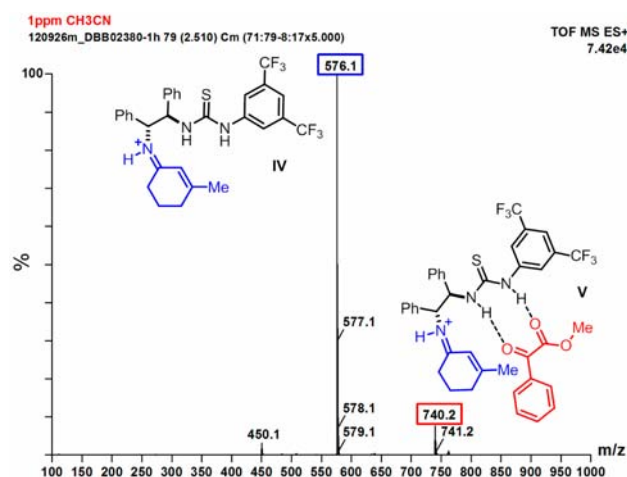


Figure 3. Detectable intermediates by ESI-MS analysis in positive mode of the catalytic vinylogous aldol reaction of **1a** and **2c**.

Further support for the proposed dual mode of activation was collected from mass spectrometry investigations.^{18,19b} As detailed in Figure 3, the ESI-MS spectrum in positive mode of the reaction mixture²⁰ showed the presence of the imine precursor **IV** at *m/z* 576.1 and of the complex **V** at *m/z* 740.2, where both reacting partners are brought together in close proximity.

In summary, we have reported a rare example of a direct vinylogous aldol reaction of an unmodified carbonyl compound. Key to the development of the chemistry was the design of a bifunctional primary amine-thiourea catalyst that can combine H-bond-directing activation and dienamine catalysis.

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Supporting Information Available. Experimental procedures, compound characterization, HPLC traces, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(20) The ESI-MS analysis refers to the reaction under the optimized conditions (20 mol % of **E**, 50 mol % of benzoic acid, 5 equiv of **1a**, and [**2c**]₀ = 0.5 M in toluene). The analyzed sample was collected 5 min after the start of the reaction. A concomitant ¹H NMR analysis did not show any detectable trace of the aldol product **3**, which would provide the same isotopic pattern of intermediate **V**. On the contrary, a trace amount of intermediate **V** was detected from the same NMR experiment; see Figures S15–S16 for full details.

The authors declare no competing financial interest.