OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

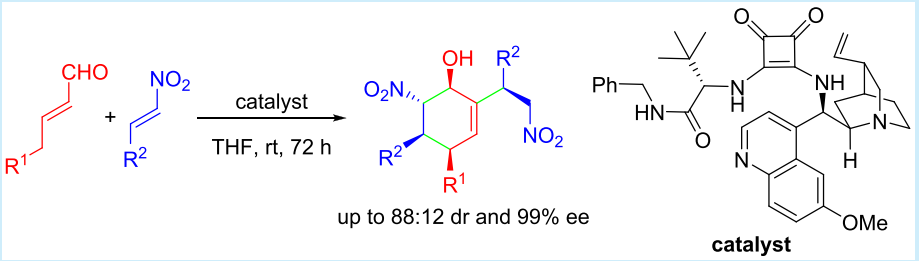
pubs.acs.org/OrgLett

# Enantioselective Synthesis of Cyclohexenol Derivatives from γ-Aryl-Substituted Enals via an Organocatalyzed Three-Component Reaction

Debashis Majee, Satish Jakkampudi, Hadi D. Arman, and John C.-G. Zhao*

Department of Chemistry, University of Texas at San Antonio, One UTSA Circle, San Antonio, Texas 78249-0698, United States

Supporting Information

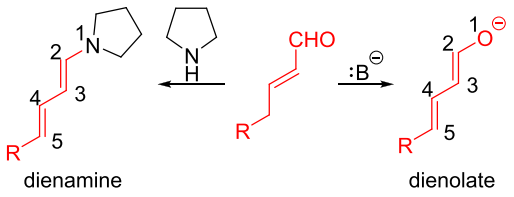



**ABSTRACT:** A three-component reaction between γ-aryl-substituted α,β-unsaturated aldehydes and nitroalkenes was realized by using cinchona alkaloid-derived (thio)ureas and squaramides via the dienolate intermediates. This unprecedented 1,3- and 1,5-reactivity of dienolates of the γ-aryl-α,β-unsaturated aldehydes led to the formation of cyclohexenol derivatives with four contiguous stereogenic centers and a chiral substituent at C2 with good diastereoselectivities and high ee values. Such reactivities of the dienolates are totally different from those of the corresponding dienamine intermediates.

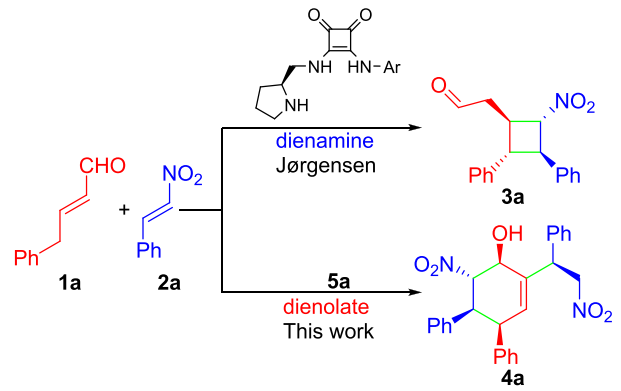


α,β-Unsaturated aldehydes are versatile substrates in amine-mediated organocatalysis.[1,2] In fact, the activation of these substrates via the formation of iminium intermediates with the amine catalysts was recognized in the beginning of organocatalysis,[3] and many useful synthetic methodologies based on this activation mode have been established since then.[1,2,4] In recent years, activation of enolizable α,β-unsaturated aldehydes via the formation of dienamine intermediates with the amine catalysts has also received considerable attention (Scheme 1).[5,6] The dienamine intermediate may have 1,3- (i.e., α-functionalization), 1,5- (i.e., γ-functionalization), 2,5- (i.e., [4 + 2] cycloadditions), or 4,5-reactivity (i.e., [2 + 2], [2 + 3], and [2 + 4] cycloadditions) depending on the electrophile or the catalyst.[5,6] For example, Jørgensen and co-workers reported that the dienamine of *trans*-4-phenylbut-2-enal (**1a**) reacts with *trans*-β-nitrostyrene (**2a**) to give the [2 + 2] cycloaddition product **3a** (Scheme 2, upper equation).[6d] Nonetheless, the reactivity of the corresponding dienolate intermediate of the enolizable α,β-unsaturated aldehyde was essentially unrecognized in organocatalysis. The single example that we found in the literature is the formation of dienolates from α,γ-diphenyl-substituted enals as reported by Xu and co-workers.[7] During our recent study of a reaction between **1a** and **2a** catalyzed by the modularly designed organocatalyst (MDO) self-assembled from quinidine thiourea (**5a**) (Figure 1) and L-proline,[8] the formation of an unexpected product **4a** was observed, albeit in very low yield (Scheme 2, lower equation). Subsequent control experiments revealed that the reaction was not catalyzed by the

**Scheme 1. Formation of Dienamine and Dienolate Intermediates of an Enolizable α,β-Unsaturated Aldehyde**




**Scheme 2. Comparison of Dienamine- and Dienolate-Mediated Reactions of 1a and 2a [Ar = 3,5-$(CF_3)_2C_6H_3$-]**




**Received:** October 6, 2019




DOI: 10.1021/acs.orglett.9b03532
Org. Lett. XXXX, XXX, XXX–XXX

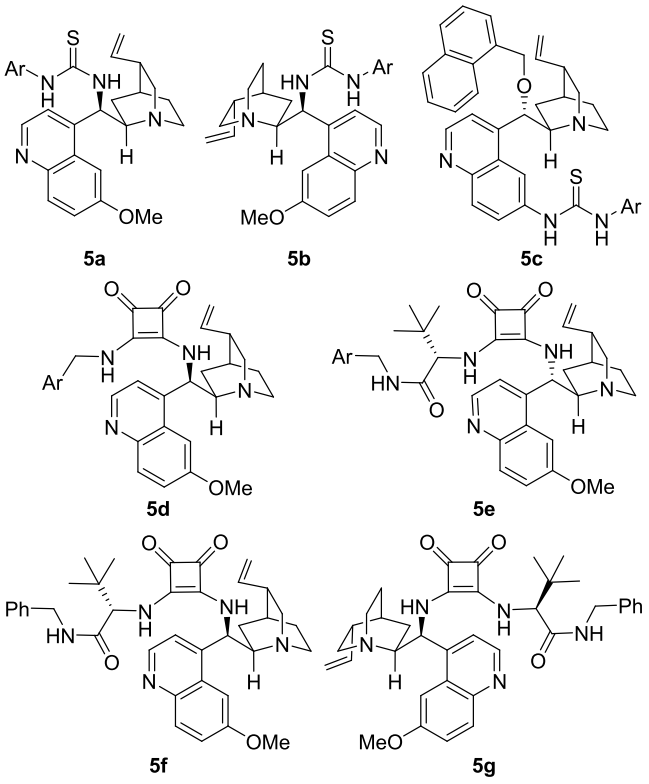


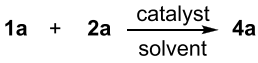

**Figure 1.** Structures of selected catalysts employed in this study [Ar = 3,5-$(CF_3)_2C_6H_3$-].

MDO but instead that **5a** was solely responsible for the formation of this product. Most likely, product **4a** is formed through a three-component reaction between **1a** and **2a** (two molecules of **2a** are involved) via domino[9] 1,3- and 1,5-dialkylation of the dienolate intermediate by the nitroalkene followed by an intramolecular Henry reaction. Herein we report a highly diastereo- and enantioselective three-component reaction between $\gamma$-aryl-substituted $\alpha,\beta$-unsaturated aldehydes and nitroalkenes that uses a cinchona alkaloid-derived (thio)urea or squaramide as the catalyst.

While catalyst **5a** led to the formation of **4a**, the yield, dr, and ee obtained for this product were low (Table 1, entry 1). In order to find an optimal catalyst for this reaction, many cinchona alkaloid-derived (thio)urea and squaramide catalysts were screened. The results for some representative catalysts (Figure 1) are collected in Table 1 (for more details, see Table S-1). As shown in Table 1, quinine-derived thiourea **5b** also led to low yield and stereoselectivities of **4a** (entry 2). Using urea instead of thiourea, changing the hydrogen-bonding capability of the (thio)urea moiety, or increasing the steric hindrance on the thiourea moiety of the catalyst all failed to improve the stereoselectivities of this reaction (for details, see the Supporting Information). On the other hand, the 6′-thiourea catalyst **5c** failed to catalyze the desired reaction completely (entry 3). Improved diastereoselectivity (79:21) and much improved enantioselectivity (95% ee) were obtained when the quinidine-derived squaramide catalyst **5d** was employed (entry 4). These results indicate that a squaramide moiety at C9 is more effective in stereocontrol than a thiourea moiety at the same location. Previously, Jacobsen and co-workers showed that the introduction of a secondary hydrogen-bonding site with a chiral substituent on the thiourea moiety is helpful for improving the stereoselectivities,[10] and therefore, we synthesized several new cinchona alkaloid squaramide catalysts containing a secondary hydrogen-bonding site and a chiral substituent, such as **5e**, **5f**, and **5g** (Figure 1). When the quinidine-derived squaramide **5e** was applied, the product enantioselectivity was slightly increased to 97% ee, but the product yield was much lower than that with **5d**, and the diastereoselectivity was also slightly inferior (entry 5). To our pleasure, when the 3,5-bis(trifluoromethyl)benzyl group on the amide moiety of the catalyst was replaced by a benzyl group, as in catalyst **5f**, the product yield increased to 80% with a dr of 88:12 and 99% ee (entry 6). In addition, when quinine-derived **5g** was applied, the opposite enantiomer of **4a** was obtained in good yield with similarly high ee (entry 7). Thus, this screening identified the quinidine-derived squaramide catalyst **5f** as the best catalyst for obtaining the three-component reaction product **4a**. Its enantiomer may be obtained by using catalyst **5g**. From the screening results, it is also obvious that the reaction, especially the reactivity, is highly sensitive to subtle changes in the catalyst structure.

Next, some common organic solvents were screened. As the results in Table 1 show, the enantioselectivity of the reaction was not much changed when different solvents were used, including polar and protic solvents (entries 8−15). However, the product yield and diastereoselectivity were more susceptible to the solvent used (entries 8−15), with methanol giving the lowest yield and diastereoselectivity of **4a** (entry 15). Of all the solvents screened, THF (entry 6) produced the highest yield and stereoselectivities for **4a**. We also found that

**Table 1. Catalyst Screening and Optimization of the Conditions for the Three-Component Reaction[a]**




| entry | catalyst | solvent | yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **5a** | THF | 41 | 60:40 | 53 |
| 2 | **5b** | THF | 53 | 65:35 | 64[e] |
| 3 | **5c** | THF | 0 | – | – |
| 4 | **5d** | THF | 51 | 79:21 | 95 |
| 5 | **5e** | THF | 34 | 70:30 | 97 |
| 6 | **5f** | THF | 80 | 88:12 | 99 |
| 7 | **5g** | THF | 75 | 81:19 | 97[e] |
| 8 | **5f** | 1,4-Dioxane | 62 | 78:22 | 98 |
| 9 | **5f** | Ether | 46 | 81:19 | 97 |
| 10 | **5f** | Toluene | 40 | 83:17 | 97 |
| 11 | **5f** | Benzene | 60 | 82:18 | 97 |
| 12 | **5f** | $CH_2Cl_2$ | 42 | 88:12 | 99 |
| 13 | **5f** | $CHCl_3$ | 40 | 82:18 | 98 |
| 14 | **5f** | $CH_3CN$ | 72 | 85:15 | 98 |
| 15 | **5f** | MeOH | 36 | 54:46 | 97 |
| 16[f] | **5f** | THF | 62 | 85:15 | 96 |
| 17[g] | **5f** | THF | 70 | 85:15 | 99 |
| 18[h] | **5f** | THF | 21 | 82:18 | 98 |
| 19[i] | **5f** | THF | 34 | 87:13 | 99 |

[a]Unless otherwise indicated, all of the reactions were carried out with **1a** (0.20 mmol), **2a** (0.60 mmol), and catalyst **5** (0.04 mmol, 20 mol %) in the specified solvent (0.7 mL) at room temperature for 72 h. [b]Yields of the isolated products after column chromatography. [c]Determined by $^1$H NMR analysis of the crude reaction mixtures. [d]Determined by HPLC analysis. [e]The opposite enantiomer was obtained as the major product. [f]The solvent amount was 1.2 mL. [g]The solvent amount was 0.5 mL. [h]The reaction was carried out at 0 °C. [i]The catalyst loading was 10 mol %.

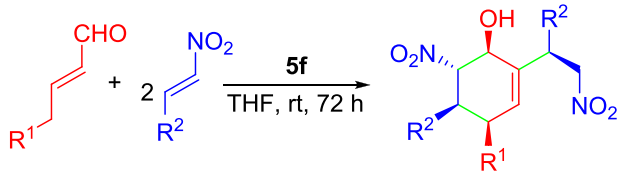


DOI: 10.1021/acs.orglett.9b03532
Org. Lett. XXXX, XXX, XXX−XXX

the product yield was very sensitive to the concentration of the starting materials. The latter also affected the stereoselectivities, albeit to a much lesser extent (entries 16 and 17). The optimal loading of THF was 0.7 mL for a 0.20 mmol loading of **1a** (entry 6). Both a higher and a lower amount of solvent led to inferior product yields and stereoselectivities (entries 16 and 17 vs entry 6). Furthermore, carrying out the reaction at 0 °C (entry 18) or with a reduced catalyst loading (i.e., 10 mol %; entry 19) led to much lower product yields.

Once the reaction conditions were optimized, the scope of this three-component reaction was evaluated. As the results in Table 2 show, besides *trans*-β-nitrostyrene (**2a**) (entry 1),

**Table 2. Substrate Scope of the Three-Component Reaction**[a]




**1** **2** **4**

| entry | $R^1$ | $R^2$ | 4/yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | **4a**/80 | 88:12 | 99 |
| 2 | Ph | 4-$MeC_6H_4$ | **4b**/73 | 84:16 | 99 |
| 3 | Ph | 4-$FC_6H_4$ | **4c**/70 | 80:20 | 98 |
| 4 | Ph | 4-$ClC_6H_4$ | **4d**/70 | 78:22 | 99 |
| 5 | Ph | 4-$BrC_6H_4$ | **4e**/75 | 85:15 | 99 |
| 6 | Ph | 2-$BrC_6H_4$ | **4f**/65 | 76:24 | 98 |
| 7 | Ph | 3-$BrC_6H_4$ | **4g**/68 | 80:20 | 98 |
| 8 | Ph | 2-Thiophenyl | **4h**/68 | 92:8 | 98 |
| 9 | Ph | *i*-Pr | 0 | – | – |
| 10 | 4-$MeOC_6H_4$ | Ph | **4i**/68 | 85:15 | 99 |
| 11 | 4-$FC_6H_4$ | Ph | **4j**/63 | 80:20 | 95 |
| 12 | 4-$ClC_6H_4$ | Ph | **4k**/61 | 84:16 | 98 |
| 13 | 4-$BrC_6H_4$ | Ph | **4l**/62 | 85:15 | 99 |
| 14 | 4-$MeOC_6H_4$ | 4-$BrC_6H_4$ | **4m**/65 | 80:20 | 99 |
| 15 | *i*-Pr | Ph | 0 | – | – |
| 16[e] | Ph | Ph | **4a**/70 | 87:13 | 99 |

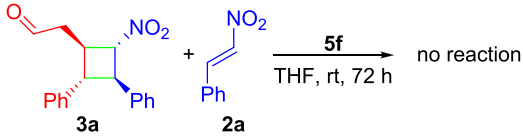
[a]Unless otherwise indicated, all of the reactions were carried out with **1** (0.20 mmol), **2** (0.60 mmol), and catalyst **5f** (0.04 mmol, 20 mol %) in THF (0.7 mL) at room temperature for 72 h. [b]Yields of the isolated products after column chromatography. [c]Determined by $^1H$ NMR analysis of the crude reaction mixtures. [d]Determined by HPLC analysis. [e]Carried out with 1.0 mmol of **1a**, 3.0 mmol of **2a**, and 0.20 mmol of **5f** (20 mol %) in THF (3.5 mL).

substituted *trans*-β-nitrostyrenes are also good substrates for this reaction, and the desired products (**4b**–**g**) were obtained in good yields and diastereoselectivities with excellent enantioselectivities (entries 2–7). The electronic nature of the substituent and its location on the phenyl ring have only minimal influence on the stereoselectivity of this reaction. A heteroaryl-substituted (2-thiophenyl) nitroalkene also led to the formation of the expected product **4h** with excellent diastereoselectivity and enantioselectivity (entry 8). However, an alkyl-substituted nitroalkene failed to react under the optimized conditions (entry 9). On the other hand, different aryl-substituted enals participated in the desired reaction and led to the formation of the expected products (**4i**–**m**) in good yields and diastereoselectivities with excellent enantioselectivities (entries 10–14). Again, the electronic nature of the substituent on the phenyl ring of the enal has a negligible influence on the reactivity and stereoselectivities of this reaction. However, no reaction was observed when an alkyl-substituted enal was applied (entry 15). The reaction carried out on a 1.0 mmol scale of enal **1a** yielded the desired product **4a** with similar stereoselectivities and yield (entry 16).

The absolute stereochemistry of the major product was determined by X-ray crystallographic analysis of compound **4a** (for details, see the Supporting Information).

In order to understand the reaction mechanism, we synthesized cyclobutane derivative **3a** using the reported method[6d] and attempted the reaction of **3a** with **2a** using **5f** as the catalyst under the optimized conditions. Nonetheless, no reaction between **3a** and **2a** was observed (Scheme 3). This

**Scheme 3. Control Reaction Conducted with Compound 3a**




negative result rules out the possible involvement of **3a** as an intermediate of this reaction. We previously demonstrated that cinchona alkaloid (thio)ureas can be used as organocatalysts to deprotonate weakly acidic substrates,[11] such as α-styrylacetate.[11f] Xu and co-workers also demonstrated that cinchona alkaloid derivatives can deprotonate α,γ-diphenyl-substituted enals.[7] On the basis of these results, we believe that the reaction proceeds through the enolate mechanism via consecutive α-functionalization (i.e., 1,3-reaction) and γ-functionalization (i.e., 1,5-reaction). As shown in Scheme 4, enal **1a** is enolized by catalyst **5f** to form dienolate **8**, which is associated with the catalyst via ionic interactions. The reaction of **8** with **2a** yields intermediate **9**, which is an α-functionalization (i.e., 1,3-reaction) product, via a transition state similar to the one proposed for the formation of intermediate **11** (Scheme 4, bottom). Intermediate **9** is again enolized to form dienolate **10** by catalyst **5f**. According to the double-bond stereochemistry in the final product, this dienolate most likely adopts an *s-cis* conformation (**10**) instead of the *s-trans* conformation (**12**). The reaction of **10** with **2a** yields the γ-functionalization (i.e., 1,5-reaction) product **11** via the proposed transition state (Scheme 4, bottom), in which the *Si*–*Si* attack of the dienolate to the nitrostyrene leads to the observed stereochemistry of the major stereoisomer. Finally, an intramolecular Henry reaction yields the desired product **4a**. Alternatively, the reaction can also proceed with the γ-functionalization first and then the α-functionalization (for details, see the Supporting Information). According to this mechanism, the failure of the 4-isopropyl-substituted enal to participate in this reaction (Table 2, entry 15) most likely occurs because this substrate cannot be enolized by **5f**.

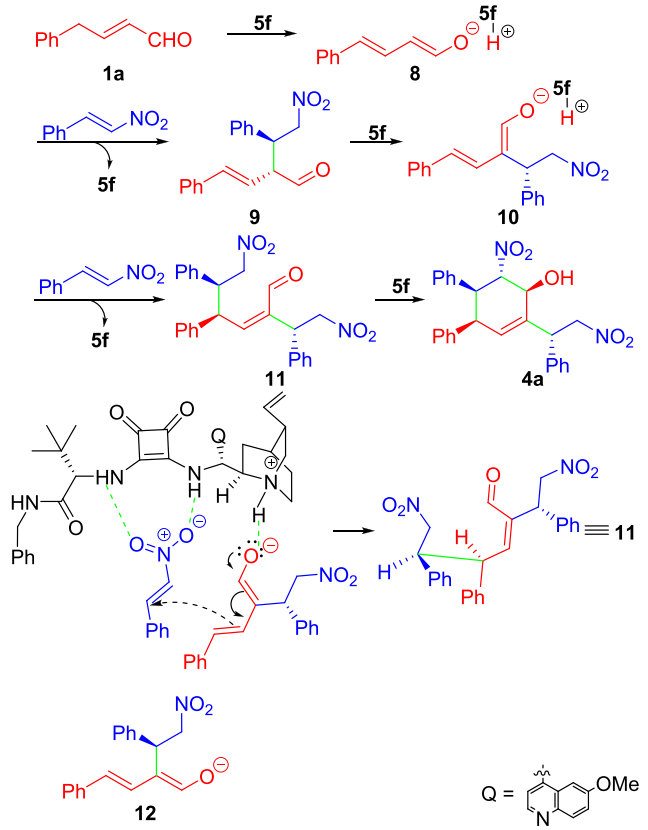
The obtained cyclohexenol product **4a** can be readily converted to the corresponding *O*-acetyl derivative **6** and the enone derivative **7** in high yields with complete retention of the stereochemistry (Scheme 5).

In summary, we have discovered a distinct reactivity of the dienolates of γ-aryl-substituted enals catalyzed by cinchona alkaloid-derived thioureas and squaramides, which participate in three-component reactions with nitroalkenes via an α,γ-dialkylation and ensuing intramolecular Henry reaction. When squaramide **5f** is used as the catalyst, the reaction yields the

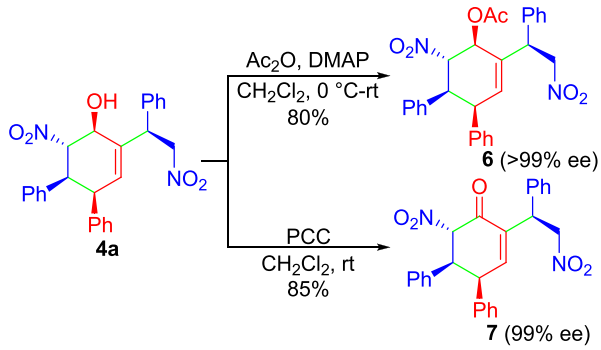


DOI: 10.1021/acs.orglett.9b03532
Org. Lett. XXXX, XXX, XXX–XXX

**Scheme 4. Proposed Reaction Mechanism**



**Scheme 5. Synthetic Transformations of the Reaction Product 4a**



cyclohexanol products with five stereogenic centers in good yields and diastereoselectivities with high enantioselectivities.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03532.

Detailed experimental procedures, ORTEP drawing of compound **4a**, compound characterization data, and copies of NMR spectra and HPLC chromatograms of the reaction products (PDF)

### Accession Codes

CCDC 1883852 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: cong.zhao@utsa.edu.

### ORCID

John C.-G. Zhao: 0000-0001-7174-5956


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The generous financial support of this research from the Welch Foundation (Grant AX-1593) and the National Science Foundation (Grant CHE-1664278) is gratefully acknowledged. The authors also thank Drs. Manisha Bihani and Sharada Swain for conducting some initial experiments.

## ■ REFERENCES


(1) (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005. (b) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2007.

(2) (a) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium Catalysis. *Chem. Rev.* **2007**, *107*, 5416−5470. (b) Tsogoeva, S. B. Recent Advances in Asymmetric Organocatalytic 1,4-Conjugate Additions. *Eur. J. Org. Chem.* **2007**, *2007*, 1701−1716.

(3) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels−Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244.

(4) *Comprehensive Asymmetric Catalysis, Volumes I−III and Supplements I and II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999.

(5) Marcos, V.; Alemán, J. Old Tricks, New Dogs: Organocatalytic Dienamine Activation of α,β-Unsaturated Aldehydes. *Chem. Soc. Rev.* **2016**, *45*, 6812−6832.

(6) (a) Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. Enantioselective α- and γ-Alkylation of α,β-Unsaturated Aldehydes Using Dienamine Activation. *Org. Lett.* **2011**, *13*, 70−73. (b) Silvi, M.; Cassani, C.; Moran, A.; Melchiorre, P. Secondary Amine-Catalyzed Asymmetric γ-Alkylation of α-Branched Enals via Dienamine Activation. *Helv. Chim. Acta* **2012**, *95*, 1985−2006. (c) Kutwal, M. S.; Appayee, C. Highly Regio- and Enantioselective γ-Alkylation of Linear α,β-Unsaturated Aldehydes. *Eur. J. Org. Chem.* **2017**, *2017*, 4230−4234. (d) Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. Asymmetric Organocatalytic Formal [2 + 2]-Cycloadditions via Bifunctional H-Bond Directing Dienamine Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 2543−2546. (e) Albrecht, Ł.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Escrich, C.; Jørgensen, K. A. Dienamine-Mediated Inverse-Electron-Demand Hetero-Diels−Alder Reaction by Using an Enantioselective H-Bond-Directing Strategy. *Angew. Chem., Int. Ed.* **2012**, *51*, 13109−13113. (f) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. Cooperative Dienamine/Hydrogen-Bonding Catalysis: Enantioselective Formal [2 + 2] Cycloaddition of Enals with Nitroalkenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 4104−4107. (g) Li, W.; Wei, J.; Jia, Q.; Du, Z.; Zhang, K.; Wang, J. Asymmetric Synthesis of Tetrahydroquinolines through a [3 + 2] Cycloaddition Controlled by Dienamine Catalysis. *Chem. - Eur. J.* **2014**, *20*, 6592−6596. (h) Qi, L.-W.; Yang, Y.; Gui, Y.-Y.; Zhang, Y.; Chen, F.; Tian, F.; Peng, L.; Wang, L.-X. Asymmetric Synthesis of 3,3′-Spirooxindoles Fused with Cyclobutanes through Organo-




DOI: 10.1021/acs.orglett.9b03532
*Org. Lett.* XXXX, XXX, XXX−XXX

catalytic Formal [2 + 2] Cycloadditions under H-Bond-Directing Dienamine Activation. *Org. Lett.* **2014**, *16*, 6436−6439. (i) Hejmanowska, J.; Jasiński, M.; Wojciechowski, J.; Mlostoń, G.; Albrecht, Ł. The First Organocatalytic, Ortho-Regioselective Inverse-Electron-Demand Hetero-Diels−Alder Reaction. *Chem. Commun.* **2017**, *53*, 11472−11475. (j) Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. Enantio- and Diastereoselective Synthesis of Substituted Tetrahydro-1*H*-isochromanes through a Dynamic Kinetic Resolution Proceeding under Dienamine Catalysis. *Org. Lett.* **2012**, *14*, 3740−3743.

(7) Xie, J.-K.; Wang, Y.; Lin, J.-B.; Ren, X.-R.; Xu, P.-F. Direct Noncovalent Activation of *α,β*-Unsaturated Aldehydes for the Stereodivergent Synthesis of Substituted Cyclohexenes. *Chem. - Eur. J.* **2017**, *23*, 6752−6756.

(8) Mandal, T.; Zhao, C.-G. Modularly Designed Organocatalytic Assemblies for Direct Nitro-Michael Addition Reactions. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714−7717.

(9) (a) Chanda, T.; Zhao, J. C.-G. Recent Progress in Organocatalytic Asymmetric Domino Transformations. *Adv. Synth. Catal.* **2018**, *360*, 2−79. (b) Pellissier, H. Recent Developments in Asymmetric Organocatalytic Domino Reactions. *Adv. Synth. Catal.* **2012**, *354*, 237−294. (c) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. Bifunctional Amine-Squaramides: Powerful Hydrogen-Bonding Organocatalysts for Asymmetric Domino/Cascade Reactions. *Adv. Synth. Catal.* **2015**, *357*, 253−281.

(10) (a) Zuend, S. J.; Jacobsen, E. N. Cooperative Catalysis by Tertiary Amino-Thioureas: Mechanism and Basis for Enantioselectivity of Ketone Cyanosilylation. *J. Am. Chem. Soc.* **2007**, *129*, 15872−15883. (b) Vachal, P.; Jacobsen, E. N. Structure-Based Analysis and Optimization of a Highly Enantioselective Catalyst for the Strecker Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 10012−10014.

(11) (a) Guo, Q.; Bhanushali, M.; Zhao, C.-G. Quinidine Thiourea-Catalyzed Aldol Reaction of Unactivated Ketones: Highly Enantioselective Synthesis of 3-Alkyl-3-hydroxyindolin-2-ones. *Angew. Chem., Int. Ed.* **2010**, *49*, 9460−9464. (b) Guang, J.; Guo, Q.; Zhao, J. C.-G. Acetylphosphonate as a Surrogate of Acetate or Acetamide in Organocatalyzed Enantioselective Aldol Reactions. *Org. Lett.* **2012**, *14*, 3174−3177. (c) Guo, Q.; Zhao, J. C.-G. Highly Enantioselective Three-Component Direct Mannich Reactions of Unfunctionalized Ketones Catalyzed by Bifunctional Organocatalysts. *Org. Lett.* **2013**, *15*, 508−511. (d) Abbaraju, S.; Zhao, J. C.-G. Asymmetric Aldol Reaction of 3-Acetyl-2*H*-chromen-2-ones and Isatins Catalyzed by a Bifunctional Quinidine Urea Catalyst. *Adv. Synth. Catal.* **2014**, *356*, 237−241. (e) Guang, J.; Larson, A. J.; Zhao, J. C.-G. Stereoselective Mannich Reaction of *S*-Phenyl Thioesters Catalyzed by Bifunctional Organocatalysts. *Adv. Synth. Catal.* **2015**, *357*, 523−529. (f) Guang, J.; Rout, S.; Bihani, M.; Larson, A. J.; Arman, H. D.; Zhao, J. C. G. Organocatalyzed Enantioselective Direct Mannich Reaction of *α*-Styrylacetates. *Org. Lett.* **2016**, *18*, 2648−2651.



DOI: 10.1021/acs.orglett.9b03532
*Org. Lett.* XXXX, XXX, XXX−XXX