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

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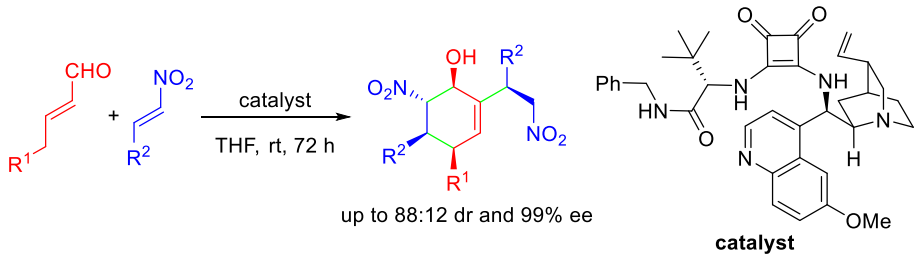
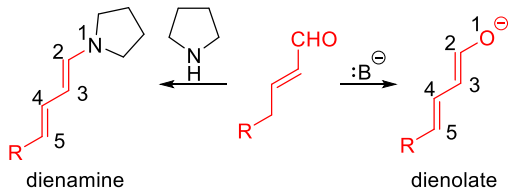
Supporting Information Placeholder



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 the C2 position in good diastereoselectivities and high ee values. Such reactivities of the dienolates are totally different from those of the corresponding dienamine intermediates.

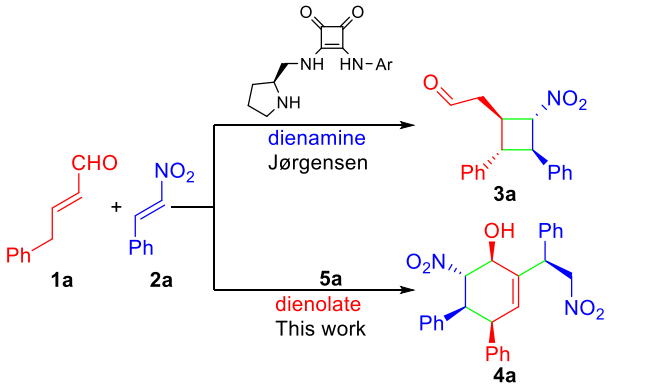
α,β-Unsaturated aldehydes are versatile substrates in amine-mediated organocatalysis.[1,2] In fact, the activation of these substrates via the formation of the iminium intermediates with the amine catalysts was recognized in the beginning of organocatalysis,[3] and many useful synthetic methodologies have been established since then based on this activation mode.[1,2,4] In recent years, activating enolizable α,β-unsaturated aldehydes via the formation of the dienamine intermediates with the amine catalysts have also received considerable attentions (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), and 4,5-reactivities (i.e., [2+2], [2+3], and [2+4] cycloadditions), depending on the electrophiles or the catalysts.[5,6] For example, Jørgensen and coworkers have reported that the dienamine of *trans*-4-phenylbut-2-enal (**1a**) reacts *trans*-β-nitrostryrene (**2a**) to give a [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 dienolate from α,γ-diphenyl-substituted enals reported by Xu and coworkers.[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 a very low yield (Scheme 2, lower equation). Following control experiments revealed that the reaction was not catalyzed by the MDO, instead, **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** (2 molecules of **2a** are involved) via a domino[9] 1,3- and 1,5-dialkylation of the dienolate intermediates by the nitroalkenes followed by an intramolecular Henry reaction. Herein we wish to report a highly diastereo- and enantioselective three-component reaction between γ-aryl-substituted α,β-unsaturated aldehydes and nitroalkenes by using cinchona alkaloid-derived (thio)ureas and squaramides as the catalyst.

Scheme 1. Formation of dienamine and dienolate intermediates of an enolizable α,β-unsaturated aldehyde



While catalyst **5a** led to the formation of **4a**, the yield, dr, and ee value 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 of some representative catalysts (Figure 1) are collected in Table 1 (for more details, please see Table S-1 of the Supporting Information). 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, please see Supporting Information). On the other hand, the 6'-thiourea catalyst **5c** failed to catalyze the desired reaction completely (entry 3). An improved diastereoselectivity (79:21) and a much improved ee value (95% ee) were obtained when the quinidine-derived squaramide catalyst **5d** was employed (entry 4). These results indicate that a squaramide moiety at the C9 position is more effective in stereocontrol

Scheme 2. Comparison of dienamine- and dienolate-mediated reactions of 1a and 2a [Ar = 3,5-$(CF_3)_2C_6H_3$-]



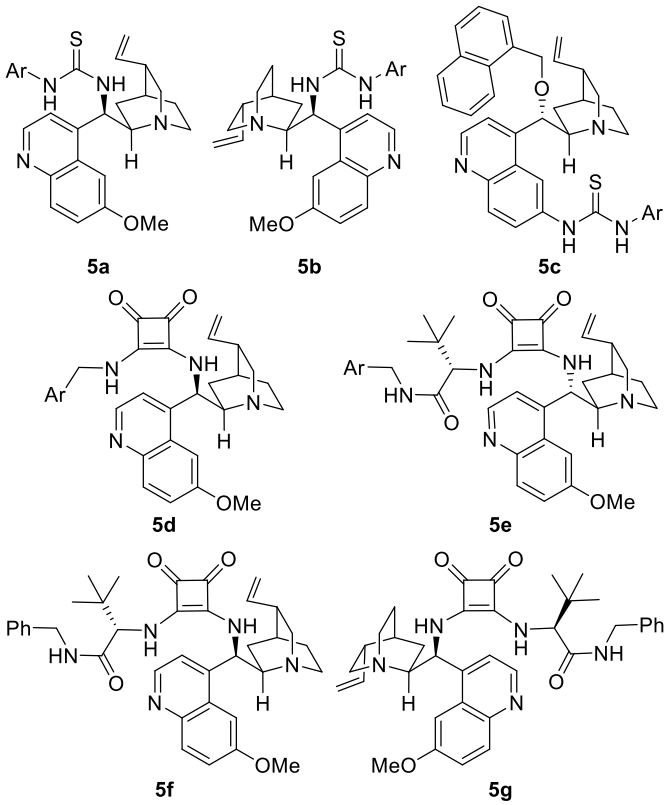
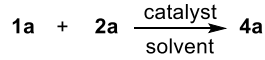


Figure 1. Structure of selected catalysts employed in this study [Ar = 3,5-$(CF_3)_2C_6H_3$-].

than a thiourea moiety at the same location. Previously, Jacobsen and coworkers have shown 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 ee value was slightly increased to 97% ee, but the product yield was much lower than that of **5d**, and 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%, and a dr of 88:12 and an ee value of 99% of the product were obtained (entry 6). In addition, when the quinine-derived **5g** was applied, the opposite enantiomer of **4a** was obtained in a good yield and similarly high ee value (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.

Table 1: Catalyst screening and condition optimizations for the three-component reaction[a]



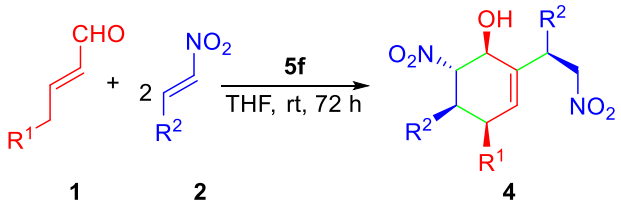
Entry	Catalyst	Solvent	Yield (%)[b]	dr[c]	ee (%)[d]
1	**5a**	THF	41	60:40	53
2	**5b**	THF	53	65:35	64[e]
3	**5c**	THF	0	---	---
4	**5d**	THF	51	79:21	95
5	**5e**	THF	34	70:30	97
6	**5f**	THF	80	88:12	99
7	**5g**	THF	75	81:19	97[e]
8	**5f**	1,4-Dioxane	62	78:22	98
9	**5f**	Ether	46	81:19	97
10	**5f**	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 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]Yield of the isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [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]Carried out at 0 °C. [i]The catalyst loading was 10 mol %.

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, including polar and protic solvents, were used (entries 8-15). However, the product yield and diastereoselectivities were more susceptible to the solvent used (entries 8-15), with methanol gave the lowest yield and the 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 the product yield was very sensitive towards the concentration of the starting materials. The latter also affected the stereoselectivities, albeit to a much lesser extent (entries 16-17). The optimal loading of THF is 0.7 mL for 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 16-17 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.

Table 2. Substrate scope of the three-component reaction[a]



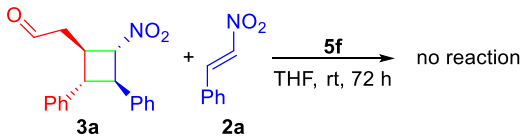
Entry	R^1	R^2	**4**/ Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	Ph	**4a**/80	88:12	99
2	Ph	4-MeC_6H_4	**4b**/73	84:16	99
3	Ph	4-FC_6H_4	**4c**/70	80:20	98
4	Ph	4-ClC_6H_4	**4d**/70	78:22	99
5	Ph	4-BrC_6H_4	**4e**/75	85:15	99
6	Ph	2-BrC_6H_4	**4f**/65	76:24	98
7	Ph	3-BrC_6H_4	**4g**/68	80:20	98
8	Ph	2-Thiophenyl	**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 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]Yield of the isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis. [e]Carried out with 1.0 mmol of **1a**, 3.0 mmol of **2a**, and 0.20 mmol (20 mol %) of **5f** in THF (3.5 mL).

Once the reaction conditions were optimized, the scope of this three-component reaction were evaluated (Table 2). As the results in Table 2 show, besides *trans*-β-nitrostyrene (**2a**, entry 1), substituted *trans*-β-nitrostryrenes are also good substrates for this reaction and the desired products (**4b**-**4g**) were obtained in good yields and diastereoselectivities, and excellent ee values (entries 2-7). The electronic nature of the substituent and its location on the phenyl ring have only minimal influence on the stereoselectivities of this reaction. A heteroaryl-substituted (2-thiothenyl) nitroalkene also led to the formation of the expected product **4h** in 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**-**4m**) in good yields and diastereoselectivities and excellent ee values (entries 10-14). Again, the electronic nature of the substituent on the phenyl ring of the enals has 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 in 1.0 mmol scale of the enal **1a** yielded the desired product **4a** in similar stereoselectivities and yield (entry 16).

The absolute stereochemistry of the major product was determined by the X-ray crystallographic analysis of compound **4a** (For details, please see the Supporting Information).[11]

Scheme 3. Control reaction conducted with compound 3a

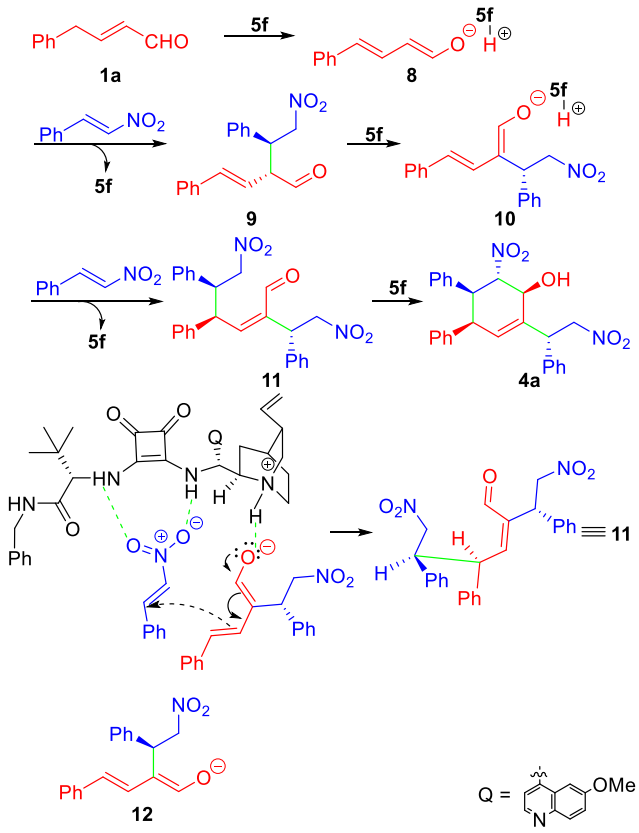


In order to understand the reaction mechanism, we synthesized the cyclobutane derivative **3a** by using the reported method[6d] and attempted the reaction of **3a** with *trans*-β-nitrostryrene (**2a**), using **5f** as the catalyst under the optimized conditions. Nonetheless, no reaction between **3a** and **2a** was observed (Scheme 3). This negative result rules out the possible involvement of **3a** as an intermediate of this reaction. We previously have demonstrated that cinchona alkaloid (thio)ureas can be used as organocatalysts to deprotonate weakly acidic substrates,[12] such as α-styrylacetate.[12f] Xu and coworkers also demonstrated that cinchona alkaloid derivatives can deprotonate α,γ-diphenyl-substituted enals.[7] Based on these results, we believe the reaction proceeds through the enolate mechanism via consecutive α- (i.e., 1,3-reaction) and γ-functionalizations (i.e., 1,5-reaction). As shown in Scheme 4, the enal **1a** is enolized by catalyst **5f** to form the dienolate **8**, which is associated with the catalyst via ionic interactions. The reaction of **8** with **2a** yields the intermediate **9**, which is an α-functionalization (i.e., 1,3-reaction) product, via a transition state similar to the one proposed for formation of the intermediate **11** (Scheme 4, bottom). Intermediate **9** is again enolized to form the 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 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, please see the Supporting Information). According to this mechanism, the failure of the 4-isopropyl-substituted enal (Table 2, entry 15) to participate in this reaction is most likely because this substrate can't be enolized by **5f**.

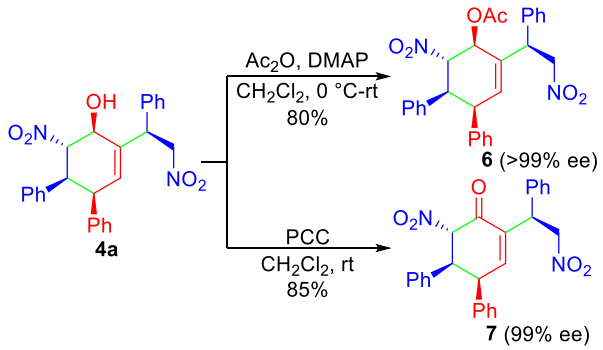
The obtained cyclohexenol product **4a** can be readily converted to the corresponding *O*-acetyl derivative **6** and the enone derivative **7** in high yields with complete retention of the stereochemistry (Scheme 5).

In summary, we have discovered a distinct reactivity of the dienolates of γ-aryl-substituted enals catalyzed by cinchona alkaloid thioureas and squaramides, which participate in three-component reactions with nitroalkenes via an α,γ-dialkylation and ensuing intramolecular Henry reaction. Using the squaramide **5f** as the catalyst, the reaction yields the cyclohexanol products with five stereogenic centers in good yields and diastereoselectivities and high enantioselectivities.

Scheme 4. Proposed reaction mechanism



Scheme 5. Synthetic transformations of the reaction product 4a



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Detailed experimental procedures, ORTEP drawing of compound **4a**, compound characterization data, and copy of NMR spectra and HPLC chromatograms of the reaction products.

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1883852 contains the supplementary crystallographic data for **4a**. These data can be obtained free of charge from the Cambridge Crystallographic Data center via http://www.ccdc.cam.ac.uk/data_request/cif.

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