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# Asymmetric Vinylogous Aldol Reaction of Silyloxy Furans with a Chiral Organic Salt

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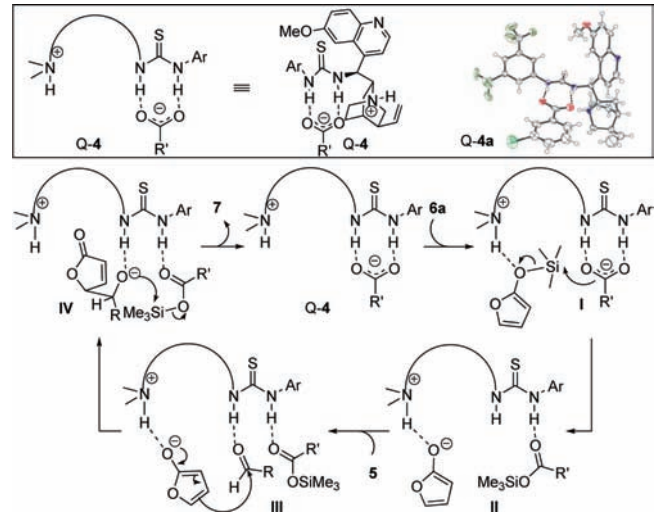
***Abstract:*** Despite their synthetic significance there is a general lack of asymmetric vinylogous aldol reactions that tolerate variations of both the silyloxy furans and aldehydes. We have developed a new chiral organic catalyst based on a carboxylate-ammonium salt prepared from a thiourea-amine and a carboxylic acid. This new catalyst enabled us to develop an efficient asymmetric vinylogous aldol reaction of unprecedented scope with respect to both 2-trimethylsilyloxy furans and aldehydes.

Chiral butenolides are a common structural subunit in natural products[1] and provide valuable chiral building blocks for the asymmetric synthesis of biologically active compounds.[2] Owing to their synthetic significance, the development of efficient catalytic methods for the generation of optically active butenolides has attracted considerable attention.[3] In particular asymmetric vinylogous aldol reactions of 2-silyloxy furan and prochiral carbonyl compounds have been investigated with both chiral metal and organic catalysts.[4] Significant progress has also been made in the promotion of catalytic asymmetric vinylogous aldol reactions between dihydrofuranone and aldehydes.[5] Nonetheless, the development of such asymmetric vinylogous aldol reactions that afford useful levels of enantioselectivity and diastereoselectivity with both aryl and alkyl aldehydes still represents a challenging task. Moreover there is a general lack of catalytic methods that tolerate variations of both the silyloxy furans and aldehydes. For example, there are only two examples of *anti*-selective, highly enantioselective vinylogous aldol reactions of silyloxy furans and aliphatic aldehydes, which are achieved with a chiral Cu-bisoxazoline complex and chiral phase transfer catalyst, respectively.[4b,g] However, the former affords useful enantioselectivity and diastereoselectivity for only benzyloxyacetaldehyde while the latter for only the 4-methyl-2-trimethylsilyloxy furan. Herein, we report the design and development of a chiral organic catalyst system that effectively promotes *anti*-selective asymmetric vinylogous aldol reactions of various 2-trimethylsilyloxyfurans with aryl, alkenyl, and alkyl aldehydes.

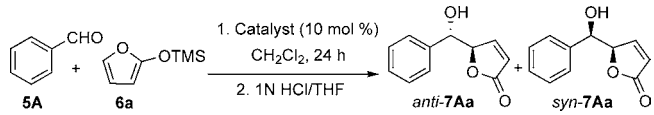
***Scheme 1.*** Plausible Catalytic Cycle for Vinylogous Aldol Reaction




Earlier we reported a highly enantioselective addition of TMSCN to α-acetal ketones with cinchona alkaloids as monofunctional chiral Lewis base catalysts.[6] Recently, modified cinchona alkaloids bearing various hydrogen bond donors have been shown by us and others to be efficient bifunctional chiral organic catalysts with a broad range of asymmetric reactions, including 1,2-additions to carbonyls.[7] These precedents prompted us to explore 6′-OH, 6′- and 9-thiourea cinchona alkaloids as bifunctional catalysts for the vinylogous aldol reactions of 2-trimethylsilyloxyfuran (**6a**) and benzaldehyde (**5A**). As summarized in Table 1 quinine and 6′-OH cinchona alkaloids Q-**1** gave very poor conversion (entries 1 and 2). On the other hand, the thiourea catalysts Q-**2** and Q-**3** were found to be more active. However, even the better catalyst Q-**3** provided only modest enantioselectivity.

We recently determined the structure by X-ray crystallography of a carboxylate ammonium salt Q-**4a**, which was derived from a solution of Q-**3** and *m*-chlorobenzoic acid in methanol (Scheme 1). As expected the quinuclidine nitrogen was protonated. Interest-

***Table 1.*** Vinylogous Aldol Reaction with Cinchona Alkaloids




| entry | Catalyst | *T* (°C) | % Conv[b] | dr[b] (*anti*/*syn*) | % ee (*anti*)[c] | entry | Catalyst | *T* (°C) | % Conv[b] | dr[b] (*anti*/*syn*) | % ee (*anti*)[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Quinine | 23 | ∼8 | ND | − | 5 | Q-**4a** | 23 | 64 | 74:26 | 79 |
| 2 | Q-**1** | 23 | ∼5 | ND | − | 6 | Q-**4b** | 23 | 68 | 69:31 | 70 |
| 3 | Q-**2** | 23 | 86 | 59:41 | −26 | 7 | Q-**4c** | 23 | 77 | 81:19 | 88 |
| 4 | Q-**3** | 23 | 54 | 63:37 | 73 | 8[d] | Q-**4c** | −20 | 96 | 95:5 | 95 |

[a] Unless noted, reactions were performed with 0.1 mmol of **5A** and 0.15 mmol of **6a** in 0.2 mL of $CH_2Cl_2$ with 10 mol % of catalyst. [b] Determined by $^1$H NMR analysis. [c] Determined by HPLC analysis. [d] Reaction was performed in 0.1 mL of $Et_2O/CH_2Cl_2$ (1/1) for 96 h.



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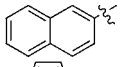
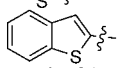
***Table 2.*** Reactions of **5** and **6a** with Q-**4c** (QD-**4c**)

| entry[a] | 5 | R | *T*(°C) | yield/%[b] | dr[c] (*anti*:*syn*) | % ee (*anti*)[d] |
|---|---|---|---|---|---|---|
| 1 | **5A** | Ph | -20 | 94 (91) | 95:5 (91:9) | 95 (91)[e] |
| 2 | **5B** | 4-F-$C_6H_4$ | -20 | 95 | 96:4 | 95 |
| 3 | **5C** | 4-$CF_3$-$C_6H_4$ | -20 | 96 | 96:4 | 93 |
| 4 | **5D** | 4-Cl-$C_6H_4$ | -20 | 93 | 94:6 | 93 |
| 5[f] | **5E** | 4-Br-$C_6H_4$ | -20 | 97 (98) | 96:4 (94:6) | 94 (92)[e] |
| 6 | **5F** | 4-Me-$C_6H_4$ | -10 | 75 | 94:6 | 90 |
| 7 | **5G** | 3-MeO-$C_6H_4$ | -50 | 96 | 95:5 | 95 |
| 8 | **5H** |  | -20 | 98 (92) | 95:5 (91:9) | 95 (92)[e] |
| 9 | **5I** |  | -20 | 71 | 84:16 | 93 |
| 10 | **5J** |  | -10 | 78 | 92:8 | 91 |
| 11 | **5K** |  | -30 | 98 | 90:10 | 93 |
| 12 | **5L** | Ph | -20 | 74(60)[g] | 81:19 | 86 |
| 13[h] | **5M** | $CH_3$ | -50 | 76 | 72:28 | 93 |
| 14 | **5N** | Ph | -10 | 51 | 73:27 | 88 |
| 15[h] | **5O** | $CH_3(CH_2)_5CH_2$ | 23 | 64 | 82:18 | 80 |
| 16[i] | **5P** | *c*-$C_6H_{11}$ | 0 | 47(37)[g] | 78:22 | 84 |

[a] Unless noted, reactions were performed with 0.25 mmol of **5**, 0.37 mmol of **6a**, and 10 mol % of Q-**4c** in 0.25 mL of solvent. [b] Unless noted, isolated yield of vinylogous aldol adduct **7** with ratio of *anti*/*syn* diastereomers indicated. [c] Determined by $^1$H NMR analysis of crude reaction mixture. [d] Determined by HPLC analysis. [e] The results in parentheses were obtained with QD-**4c**; see Supporting Information (SI) for details. [f] The absolute configuration of the aldol adduct *anti*-**7Ea** was established by X-ray crystallographic analysis (see SI). [g] Isolated yield of pure *anti*-**7**. [h] Reaction was run with 1.25 mmol of **5M** and 0.25 mmol of **6a** and 10 mol % of Q-**4c** in 0.25 mL of solvent. [i] Reaction was performed with 20 mol % of Q-**4c**.

ingly, the carboxylate was found to bind to the thiourea moiety through hydrogen-bonding interactions[8] instead of forming a tight ion pair with the quinuclidinium cation. We envisaged a catalytic cycle for a Q-**4a**-promoted vinylogous aldol reaction (Scheme 1). Presumably, the hydrogen-bonded carboxylate could react with silyloxy furan **6a** to form the corresponding trimethylsilylester and the 2-furoxy anion while releasing a thiourea-NH that could serve as a hydrogen bond donor to activate aldehyde **5A** (Intermediates I and II). With the 2-furoxy anion and aldehyde **5A** interacting with the protonated quinuclidine and thiourea-NH, respectively, the reaction between the two reactants might proceed in a highly diastereoselective and enantioselective fashion (Intermediate III). Importantly, the silyl transfer step should be facile in light of the proximity of the trimethylsilylester and the aldolate in intermediate

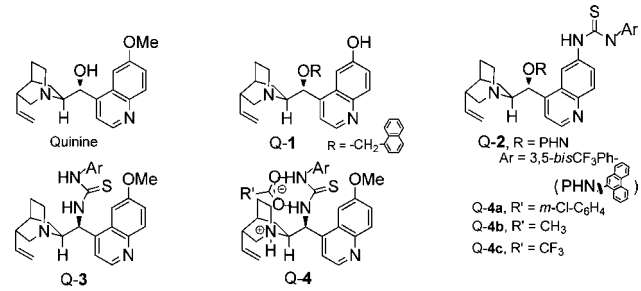



***Figure 1.*** Structure of cinchona alkaloid catalysts.

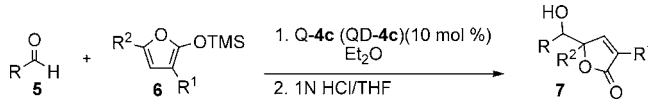
IV. In this proposed catalytic cycle the carboxylate is postulated to serve a dual role: activating the silyloxy furan **6a** and facilitating the silyl transfer from **6a** to the aldolate product. It should be noted that the second function was also speculated to be responsible for the beneficial effect of the carboxylate ligand on asymmetric aldol[9] and vinylogous aldol reactions[10] mediated by metal-based chiral Lewis acids.

We were pleased to find that the salt Q-**4a**, prepared by simply mixing Q-**3** and *m*-chlorobenzoic acid in a 1:1 ratio, furnished improved activity and selectivity over those by Q-**3** under identical conditions (entry 4 vs 5, Table 1). Upon investigation of various carboxylic acids we found the reaction occurred in a highly diastereo- and enantioselective fashion with the trifluoroacetic acid derived salt Q-**4c** (Table 1, entry 7). A further improved reaction was achieved at −20 °C in $Et_2O/CH_2Cl_2$ (1:1), affording the *anti*-adduct **7Aa** in 95/5 dr and 95% ee.

Under the optimized conditions the Q-**4c** catalyzed reactions of **6a** and various aldehydes (**5A**−**P**) were investigated. Aryl and heteroaryl aldehydes (**5A**−**K**) were converted into the corresponding *anti*-adduct **7** in 84/16 to 95/5 dr, 91−95% ee, and 71−94% yield (Table 2). Useful diastereoselectivity and enantioselectivity could be attained with alkenyl (**5L**) and, most significantly, alkyl aldehydes (**5M**−**P**). These results constitute significant progress for asymmetric vinylogous aldol reactions of silyloxy furans and this class of synthetically useful but highly challenging aldehydes. We also investigated the reaction with various substituted 2-trimethylsilyloxy furans (**6b**−**e**) (Table 3). Remarkably, the catalyst **4c** even afforded useful selectivity for reactions of sterically hindered 5-substituted-2-trimethylsilyloxy furans **6c**−**e**, which generate chiral adducts bearing adjacent tertiary-quaternary centers.

In summary, we have developed a readily accessible and efficient organic catalyst based on a carboxylate ammonium salt prepared by mixing a thiourea-amine and a carboxylic acid. This new catalyst enabled us to develop an efficient asymmetric vinylogous aldol reaction of 2-trimethylsilyloxy furans and aldehydes of unprec-

***Table 3.*** Reaction with Substituted 2-Silyloxy Furan




| entry[a] | 5 | R | 6 | $R^1$ | $R^2$ | *T*(°C) | yield[b] (%) | dr[c] | % ee[d] (major) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **5A** | Ph | **6b** | Me | H | 0 | 75 | 93:7[e] | 94 |
| 2 | **5N** | $PhCH_2CH_2$ | **6b** | Me | H | 0 | 62 | 80:20[e] | 87 |
| 3[f] | **5A** | Ph | **6c** | Me | Me | rt | 77 | 95:5[g] | 85 |
| 4 | **5A** | Ph | **6d** | H | $CH_3CH_2$ | −10 | 65 | 95:5[g] | 81 |
| 5 | **5A** | Ph | **6e** | H | $CH_2CH{=}CH_2$ | −10 | 70 | 96:4[g] | 84 |

[a] Unless noted, reactions were run with 0.1 mmol of aldehyde, 0.15 mmol of **6**, and 10 mol % of Q-**4c** in 0.1 mL of $Et_2O$. [b] Isolated yield of vinylogous aldol adduct **7** with ratio of *anti*/*syn* diastereomers indicated in the SI. [c] Determined by $^1$H NMR analysis of crude reaction mixture. [d] ee of major diastereomer as determined by HPLC analysis. [e] Ratio of *anti*/*syn* diasteromers. [f] Reaction was run with 10 mol % of QD-**4c** (see SI). [g] *Anti*/*syn* diastereomers not determined.

edented scope with respect to both reactants.[11] As a broad range of both chiral amine-ureas and carboxylic acids are readily available, such chiral salts provide a new class of easily tunable chiral catalysts. Finally, the cooperative and multifunctional catalysis by these chiral salts designed for the promotion of the asymmetric vinylogous aldol reactions should in principle be applicable to a range of other asymmetric reactions.

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**Supporting Information Available:** Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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