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Organocatalytic 1,4-Addition Reaction of 2-Formyl(thio)esters to Vinylketones: An Efficient Access to Acyclic Chiral Building Blocks with a Quaternary Carbon Stereocenter

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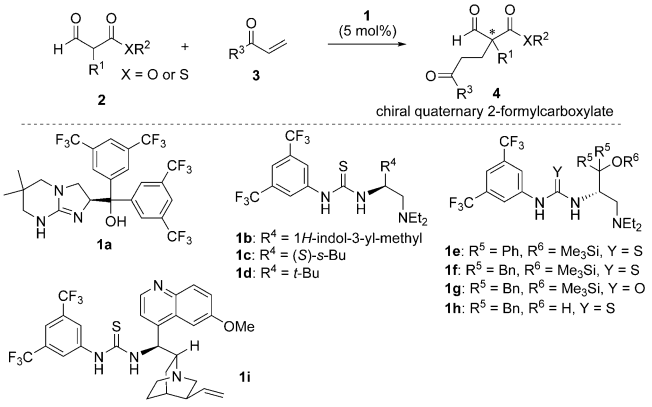
Abstract: 2-Formyl(thio)esters were utilized as pronucleophiles to obtain less-accessible acyclic chiral building blocks bearing versatile functional groups on a quaternary carbon atom for enantioselective 1,4-addition to vinylketones. To achieve high enantioselectivity in the present 1,4-addition reaction, thiourea-tertiary amines containing a bulky chiral backbone were developed as catalysts, and several derivatizations of the products were performed to demonstrate the synthetic utility of the products.

Quaternary carbon stereocenters[1] are often found as partial structures in many pharmaceuticals and biologically active natural products. However, enantioselective construction of such stereogenic centers by efficient catalytic C–C bond-forming reactions is one of the great challenges in modern organic synthesis,[1d,l,2] because such construction usually involves the difficult tasks of steric recognition and/or effective activation of sterically hindered substrates; this difficulty is especially pronounced in acyclic systems.[1j,2h,i] Catalytic enantioselective C–C bond-forming reactions with α-substituted 1,3-dicarbonyl compounds acting as pronucleophiles are regarded as an important approach for the construction of chiral quaternary stereogenic centers. Among these reactions, conjugate addition reactions have been widely used for C–C bond formation, and many types of conjugate addition reactions have been reported.[3–6] Transition-metal catalyst-mediated asymmetric allylic alkylations[7] and phase-transfer-catalyzed asymmetric alkylations[8] have also been developed and are another powerful potential approach for C–C bond formation. Although cyclic 1,3-dicarbonyl compounds are mainly employed as pronucleophiles in most of these reports, some excellent C–C bond-forming reactions of acyclic 1,3-dicarbonyl compounds have also been developed in recent years.[4,7g,8i,j] However, 2-formylcarboxylic acid derivatives, which are a type of 1,3-dicarbonyl compounds, have not yet been employed as pronucleophiles for catalytic enantioselective C–C bond-forming reactions in the construction of chiral quaternary carbon atoms.[9] The C–C bond-forming reaction products bearing versatile functional groups on a quaternary carbon atom would be useful as chiral building blocks, especially for the preparation of a variety of less-accessible acyclic carbon frameworks containing a chiral quaternary carbon atom at the center of the structure. Despite their high possibility as useful chiral building blocks in synthetic chemistry,[10] direct catalytic asymmetric preparation methods are currently limited to only one example of the insertion reaction of diazoesters to aromatic aldehydes, yielding 2-formylcarboxylates bearing an aromatic ring on a chiral quaternary α-carbon atom.[11] To the best of our knowledge, a direct preparation method of 2-formylcarboxylic acid derivatives bearing α,α-dialkyl substituents on a chiral quaternary α-carbon atom has not yet been reported.[12] Here, we report an enantioselective 1,4-addition reaction of 2-formyl(thio)esters to vinylketones involving a quaternary carbon stereocenter construction catalyzed by thiourea-tertiary amine containing a bulky chiral backbone (Scheme 1).



Scheme 1. Asymmetric 1,4-addition reaction of 2-formylcarboxylic acid derivatives.

To realize the C–C bond forming reaction that provides various 2-formylcarboxylic acid derivatives including a quaternary carbon atom, we selected vinylketones as electrophiles bearing a changeable carbon substituent (R^3) according to application. Initially, we attempted to realize the 1,4-addition with methyl 2-formylbutanoate (**2a**)[13] and methyl vinyl ketone (**3a**) using a catalytic amount of chiral guanidine **1a**. Though the 1,4-addition proceeded smoothly, the enantioselectivity was low, as shown in Table 1, entry 1, whereas the use of guanidine **1a** as

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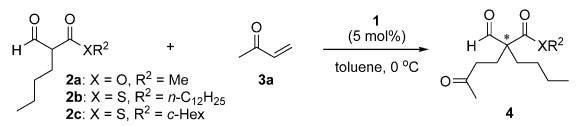
Table 1. Evaluation of catalysts **1a–i** in the 1,4-addition of **2** to **3a**.[a]



Entry	2[b]	cat. 1	Time	product 4	Yield [%]	ee [%][c]
1	**2a**	**1a**	45 min	**4a**	52	33
2	**2b**	**1a**	30 min	**4b**	70	33
3	**2b**	**1b**	5 h	**4b**	67	74
4	**2b**	**1c**	3.5 h	**4b**	49	78
5	**2a**	**1c**	48 h	**4a**	70	76
6	**2b**	**1d**	3.5 h	**4b**	68	79
7	**2b**	**1e**	18 h	**4b**	64	91[d]
8	**2b**	**1f**	8 h	**4b**	59	93[d]
9	**2b**	**1g**	5.5 h	**4b**	75	73[d]
10	**2b**	**1h**	144 h	**4b**	37[e]	40[d]
11	**2b**	**1i**	6.5 h	**4b**	70	66
12	**2c**	**1f**	6 h	**4c**	84	94[d]

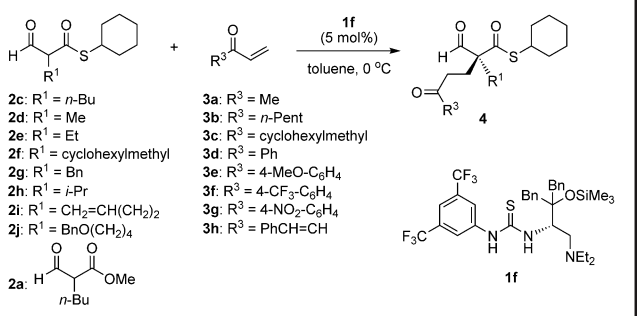
[a] Reactions were performed on a 0.3 mmol scale in 1.0 mL of toluene using 2.0 equiv of **3a** and 5 mol% of catalyst **1**. [b] See the Supporting Information for the keto enol composition. [c] Determined by chiral HPLC analysis. [d] Opposite enantiomer was formed. [e] Low conversion yield (56%) caused the low isolated yield.

a catalyst resulted in high enantioselectivity for several addition reactions of 5*H*-oxazol-4-ones.[14] The use of 2-formylthioester **2b** as a pronucleophile was not effective for enhancing the enantioselectivity (entry 2). Although the enantioselectivity of the 1,4-addition catalyzed by guanidine **1a** was low, the reaction rate was sufficiently high. Therefore, we then attempted to perform the 1,4-addition using thiourea-tertiary amines[15] as catalysts of relatively low base strength instead of guanidine **1a**. We first examined the 1,4-addition using a known tryptophan-based thiourea-tertiary amine catalyst **1b**,[15h] and obtained the product with a significant enantioselectivity (entry 3). This result prompted us to enhance the enantioselectivity by steric tuning of thiourea-tertiary amine catalysts. The employment of isoleucine-based catalyst **1c** bearing a branched side chain or *tert*-leucine-based catalyst **1d** bearing a bulky *tert*-butyl group showed a slight improvement in the enantioselectivity (entries 4 and 6). Additionally, the 1,4-addition of methyl ester **2a** with catalyst **1c** took a long time to complete (entry 5). Thus, we examined the 1,4-addition using 2-formylthioester **2b**with newly prepared catalysts **1e**–**h** bearing a bulky side chain (entries 7–10). Consequently, the introduction of a bulky side chain into the catalyst was effective in enhancing the enantioselectivity, and we found that catalyst **1f** (R^5 = Bn) showed a somewhat higher catalytic activity and a slightly higher enantioselectivity than catalyst **1e** (R^5 = Ph) (entries 7, 8). The urea catalyst **1g** showed a relatively high catalytic activity, but the enantioselectivity was decreased (entry 9). The presence of a free hydroxy group on the side chain of the catalyst significantly reduced the catalytic activity and enantioselectivity (entry 10). We also examined the 1,4-addition using a bifunctional cinchona alkaloid derivative **1i** as a catalyst,[3k,8f,15b,c,e,f,h–j] but the enantioselectivity was lower than that of amino acid-based catalysts **1b**–**d** (entry 11). As shown in entry 12, catalyst **1f**-mediated 1,4-addition using 2-formylthioester **2c** (R^2 = *c*-Hex) instead of **2b** obtained a higher chemical yield and a slightly enhanced enantioselectivity.

Next, we investigated the substrate scope of the 1,4-addition using the newly developed thiourea-tertiary amine catalyst **1f** (Table 2). Various vinylketones **3** (R^3 = alkyl, aryl, and alkenyl) were used for the enantioselective 1,4-addition (Table 2, entries 1–7). The electronic properties of the substituents on the aromatic ring of arylvinylketones **3d**–**g** has only a limited effect on the enantioselectivities (entries 3–6). A variety of alkyl substituents can be introduced as R^1 into the 2-formylthioesters **2** to obtain the desired products with equally high enantioselectivities (entries 8–14). The 1,4-addition of bulky **2h** (R^1 = *i*Pr) was also found to show high enantioselectivity (entry 12), and the benzyloxy group in **2j** did not affect the high enantioselectivity during the 1,4-addition (entry 14). It should be noted that 1,4-addition of methyl ester **2a** also showed high enantioselectivity (entry 15).

In this 1,4-addition reaction, in addition to the face control of the enolate anion of 2-formyl(thio)esters at the C–C bond forming step, the high level of geometric control at the enolate anion generating step is essential for achieving high enan-

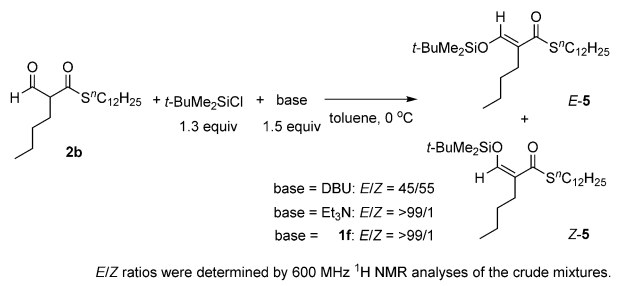
Table 2. 1,4-Addition of various 2-formyl(thio)esters **2** to vinylketones **3** catalyzed by **1f**.[a]



Entry	2[b]	3	Time	product 4	Yield [%]	ee [%][c]
1	**2c**	**3b**	23 h	**4d**	86	92
2[d]	**2c**	**3c**	18 h	**4e**	67	90
3	**2c**	**3d**	2 h	**4f**	82	95
4	**2c**	**3e**	3 h	**4g**	81	96
5[d]	**2c**	**3f**	3.5 h	**4h**	74	92
6[d]	**2c**	**3g**	1 h	**4i**	76	85
7	**2c**	**3h**	1 h	**4j**	84	92
8	**2d**	**3a**	4 h	**4k**	73	90
9	**2e**	**3a**	4 h	**4l**	82	91
10	**2f**	**3a**	15 h	**4m**	88	94
11	**2g**	**3a**	7 h	**4n**	72	91
12[e]	**2h**	**3d**	26 h	**4o**	72	94
13	**2i**	**3a**	4.5 h	**4p**	71	92
14	**2j**	**3a**	7 h	**4q**	82	90
15	**2a**	**3a**	97 h	**4a**	57	90

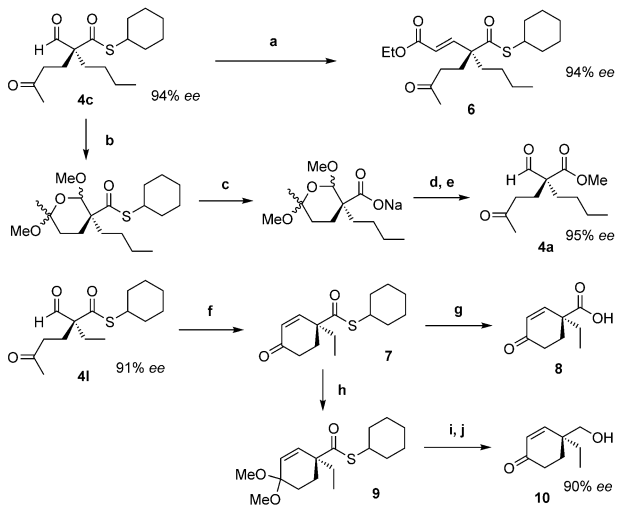
[a] Reactions were performed on a 0.3 mmol scale in 1.0 mL of toluene using 1.5 equiv of **3** (2.0 equiv for **3a**) and 5 mol% of catalyst **1f**. [b] See Supporting Information for the keto enol composition. [c] Determined by chiral HPLC analysis. [d] Reactions were carried out at −40 °C. [e] The reaction was carried out at room temperature with 10 mol% of catalyst **1f**.

tioselectivity. Thus, to gain preliminary insights into the enantiodiscriminating step in 1,4-addition, we confirmed geometric controllability of catalyst **1 f** at the enolate anion-generating step by trapping the enolate anion of 2-formylthioester **2 b** in the corresponding enol silyl ether **5** (Scheme 2). As a result, **1 f** mediated silylation only obtained the *E* isomer. Because the use of triethylamine also obtained only the *E* isomer,[16] the tertiary amine moiety of catalyst **1 f** most likely functions as a base to generate the *E*-enolate anion selectively in the present 1,4-addition, and the high enantioselectivity is achieved by the protonated **1 f**-mediated face-selective addition of the *E*-enolate anion to the vinylketone.



Scheme 2. Geometric controllability in the silylation of 2-formylthioester **2 b**.

The utility of the products **4** bearing a chiral quaternary stereogenic center was demonstrated using several transformations. As illustrated in Scheme 3, the product **4 c** can be converted into the corresponding α,β-unsaturated ester **6** without loss of enantiopurity by the Horner–Wadsworth–Emmons reaction.[17] The ester exchange reaction of product **4 c** was also possible through the use of an acetal stereomixture to obtain **4 a** without any loss of the enantiopurity. Incidentally, the absolute configuration of the methyl ester **4 a** derived from **4 c** was the same as that of **4 a** formed by the 1,4-addition of **2 a** to **3 a** shown in Table 2, entry 15. The intramolecular aldol condensation of **4 l** readily obtained cyclohexenone **7** in high yield, and the corresponding carboxylic acid **8** was easily obtained from **7** in high yield. Compound **7** can be also converted into the known alcohol **10** without loss of the enantiopurity by the reduction of thioester moiety of acetal **9** derived from **7**, followed by deprotection. The absolute configuration of obtained **10** was assigned as *S* by comparing its optical rotation value with the reported value;[18] hence, the absolute configuration of **4 l** was *S*.



Scheme 3. Transformation of products **4** and assignment of absolute configuration of **4 l**. Reaction conditions: a) $EtO_2CCH_2PO(OEt)_2$, NaH, THF, −78 °C to −40 °C, 10.5 h, yield 76%; b) $CH(OMe)_3$, cat. Pyr·TsOH, MeOH, RT, 1 h; c) NaOH (solid), MeOH, 60 °C, 72 h, then concentrated; d) MeI, DMF, RT, 19 h; e) cat. Pyr·TsOH, acetone, RT, 10.5 h, yield 66% from **4 c**; f) cat. TsOH·H_2O, cyclohexane, reflux, 2 h, yield 98%; g) 8 M NaOH (aq), MeOH, RT, 16 h, yield 95%; h) $CH(OMe)_3$, cat. Pyr·TsOH, MeOH, RT, 3 h; i) $LiAlH_4$, Et_2O, 0 °C, 0.5 h; j) cat. Pyr·TsOH, acetone, RT, 24 h, yield 69% from **7**. Optical rotation value of **10**: $[\alpha]_D^{20}$ −30.0 (*c* 1.67, $CHCl_3$) {ref. [18], $[\alpha]_D^{20}$ −26.9 (*c* 0.658, $CHCl_3$, 88% *ee*), absolute configuration: *S*}.

In conclusion, we have developed an asymmetric 1,4-addition reaction of 2-formyl(thio)esters **2** to vinylketones **3** using the newly developed thiourea-tertiary amine catalyst **1 f** involving a quaternary carbon stereocenter construction in an acyclic system. This reaction is the first catalytic asymmetric C–C bond-forming reaction of 2-formylcarboxylic acid derivatives. The facile transformations of the products **4** demonstrate the high potential of **4** as new synthetically useful acyclic chiral building blocks bearing versatile functional groups on a quaternary carbon atom.

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