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Editor's Choice

1,4-Addition Reaction of 5*H*-Oxazol-4-ones to Allenic Esters and Ketones Catalyzed by Chiral Guanidines

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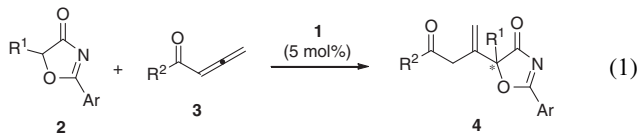
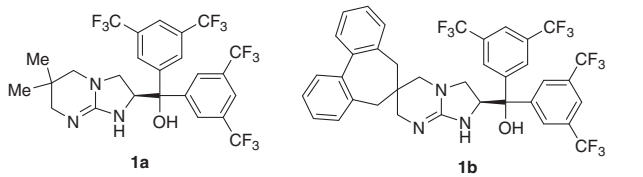
In this paper, a chiral guanidine-catalyzed 1,4-addition reaction of 5*H*-oxazol-4-ones to allenic esters and ketones is described. 5*H*-Oxazol-4-ones substituted with a 2-chlorophenyl group were suitable pronucleophiles that gave high enantioselectivities. Subsequent hydrolysis of the obtained adduct gave the corresponding γ-butenolide ester without loss of enantiopurity and was transformed into (+)-crobarbatic acid in a few steps.

Recently, electron-deficient allene compounds have been used as reactive electrophilic reactants in several organic reactions[1] including catalytic asymmetric carbon–carbon bond-forming reactions.[2] Some conjugate 1,4-addition reactions of carbon nucleophiles to allenyl carbonyl compounds have also been developed.[3] However, Jørgensen et al. reported the only successful example of catalytic asymmetric 1,4-addition of carbon nucleophiles to allenyl carbonyl compounds in 2008.[2c] We have successfully developed addition reactions of 5*H*-oxazol-4-ones as pronucleophiles catalyzed by bicyclic chiral guanidines[4] bearing a hydroxy group,[5] and disclosed that the combination of 5*H*-oxazol-4-one and the guanidine is quite effective for the highly enantioselective carbon–carbon bond formation producing a less-accessible chiral building block, α-oxygen atom-substituted carboxylates bound to a chiral quaternary α-carbon atom.[6] Because the catalytic enantioselective carbon–carbon bond formation producing synthetically useful α-hydroxy carboxylates is limited because of the difficulty in the effective enolate generation of glycolate derivatives,[7] we here developed a method for the asymmetric 1,4-addition of 5*H*-oxazol-4-ones to allenic esters and ketones catalyzed by chiral guanidines as part of our continuous study (eq 1).

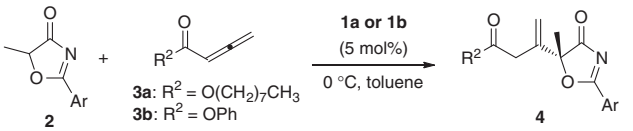


(1)



We selected octyl allenic ester **3a** as an electrophile for the development of the new 1,4-addition method, and the initial attempt at reacting α-methyl group-substituted 5*H*-oxazol-4-one (**2a**: Ar = Ph) to **3a** using guanidine **1a** revealed that the 1,4-addition proceeded with appreciable enantioselectivity, as shown in Table 1, Entry 1. Note that, the migration of the β,γ

Table 1. Optimization of the 1,4-addition of 5*H*-oxazol-4-ones **2** to allenic esters **3** using catalyst **1a** or **1b**[a]



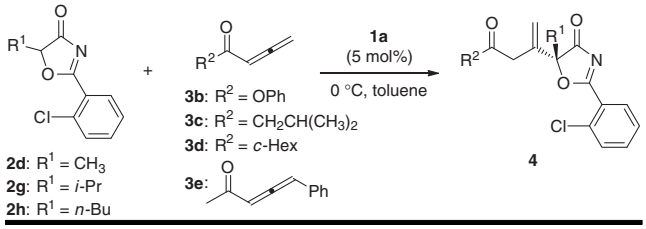
Entry	Substrates 2: Ar	3	Cat. 1	Time /h	Product 4	Yield /%	ee[b] /%
1	**2a**: Ph	**3a**	**1a**	12	**4a**	66	75
2	**2a**: Ph	**3a**	**1b**	19	**4a**	65	62
3	**2a**: Ph	**3b**	**1a**	3.5	**4b**	76	86
4	**2b**: 4-Cl-C_6H_4	**3b**	**1a**	0.5	**4c**	68	3
5	**2c**: 3-Cl-C_6H_4	**3b**	**1a**	4	**4d**	68	53
6	**2d**: 2-Cl-C_6H_4	**3b**	**1a**	1	**4e**	85	94
7	**2e**: 2-F-C_6H_4	**3b**	**1a**	1	**4f**	81	93
8	**2f**: 2-Br-C_6H_4	**3b**	**1a**	1	**4g**	83	93
9[c]	**2d**: 2-Cl-C_6H_4	**3b**	**1a**	1	**4e**	88	97
10[c]	**2d**: 2-Cl-C_6H_4	**3b**	**1b**	2	**4e**	84	93

[a]Reactions were performed on a 0.3 mmol scale in 1.0 mL of toluene using 1.2 equiv of allenyl carbonyl compound **3** and 5 mol % of catalyst **1a** or **1b**. [b]Determined by chiral HPLC analysis. [c]Reaction was performed at −20 °C.

carbon–carbon double bond on adduct **4** was not observed during the 1,4-addition. The use of guanidine **1b** did not enhance the enantioselectivity in the 1,4-addition to **3a** (Entry 2), whereas guanidine **1b** was a suitable catalyst for the 1,4-addition to alkynones, as shown in our previous report.[5c] The use of phenyl allenic ester **3b** instead of **3a** enhanced the reaction rate and enantioselectivity (Entry 3). Thus, by using **3b** as an electrophile and **1a** as a catalyst, we investigated the effect of the aromatic substituent (Ar) on 5*H*-oxazol-4-one **2** to further improve enantioselectivity (Entries 4–8). The 1,4-additions of 5*H*-oxazol-4-ones **2b** and **2c** showed low enantioselectivity (Entries 4 and 5). When the 2-chlorophenyl group-substituted 5*H*-oxazol-4-one **2d** was used as a pronucleophile, the enantioselectivity of the 1,4-addition was improved to 94% ee (Entry 6). The 1,4-additions of the 2-fluoro and 2-bromo analogues **2e** and **2f**, respectively, also showed high chemical yields and enantioselectivities (Entries 7 and 8). The enantioselectivity was improved to 97% ee by lowering the reaction temperature (Entry 9).

Next, we applied the optimized conditions to the 1,4-addition of some 5*H*-oxazol-4-ones **2d**, **2g**, and **2h** (Ar = 2-Cl-C_6H_4) to phenyl allenic ester **3b** using catalyst **1a** (Table 2, Entries 1–3). As a result, adducts **4**[8,9] were obtained in high chemical yields with high enantioselectivities, even in the case of bulky pronucleophile **2g**. We also performed the 1,4-addition with allenic ketones **3c** and **3d** as electrophiles, and the

Table 2. Catalytic 1,4-addition of 5*H*-oxazol-4-ones **2** (Ar = 2-Cl-C_6H_4) to allenic esters and ketones **3**, catalyzed by **1a**[a]



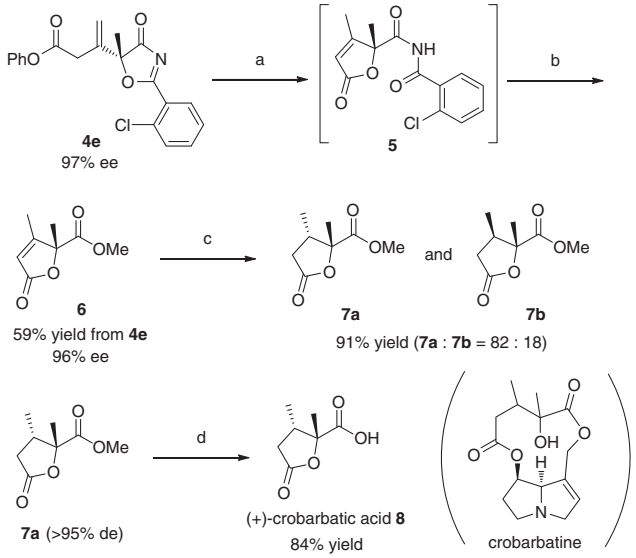
Entry	Substrates		Time	Product	Yield	ee[b]
	2	**3**	/h	**4**	/%	/%
1[c]	**2d**	**3b**	1	**4e**	88	97
2[c]	**2g**	**3b**	2	**4h**	81	96
3	**2h**	**3b**	0.5	**4i**	77	93
4	**2d**	**3c**	1	**4j**	83	98
5	**2d**	**3d**	1	**4k**	81	96
6	**2d**	**3e**	24[d]	—	<40[e]	—

[a,b]See corresponding footnote in Table 1. [c]Reaction was performed at −20 °C. [d]Reaction was performed at 0 °C for 10 h then at rt for 14 h. [e]Conversion yield.

corresponding adducts **4j** and **4k** were obtained in high chemical yields with excellent enantioselectivities (Entries 4 and 5). Unfortunately, the 1,4-addition to γ-phenyl allenic ketone **3e** slowly proceeded under the optimized conditions, and a low conversion yield (<40%) was observed after prolonged stirring at room temperature (Entry 6).

Adduct **4e** formed by the 1,4-addition of **2d** to **3b** can be easily converted into the corresponding γ-butenolide **6** without loss of enantiopurity.[9] As illustrated in Scheme 1, the γ-butenolide ring formation, after the ring-opening hydrolysis of 5*H*-oxazol-4-one through the treatment of **4e** with aqueous NaOH in THF, readily afforded the corresponding imide **5**, which was converted into γ-butenolide **6** by CH_3OLi-mediated methanolysis. The enantiopurity of **6** was confirmed by HPLC analysis. To assign the absolute configuration of adduct **4e** and also to demonstrate the utility of the present 1,4-addition, we converted γ-butenolide **6** into (+)-crobarbatic acid **8**,[10,11] which is a hydrolysis product of a pyrrolizidine alkaloid crobarbatine.[11] The Pd–C-catalyzed hydrogenation of γ-butenolide **6** afforded a mixture of diastereoisomers **7a** and **7b** (**7a**:**7b** = 82:18), and the major isomer **7a** was isolable through purification by simple column chromatography. Finally, the hydrolysis of isomer **7a** (>95% de) gave (+)-crobarbatic acid (**8**) in 84% yield. The absolute configuration of obtained **8** was assigned as (2*R*, 3*S*) by comparing its optical rotation value with the reported value;[10] hence, the absolute configuration of adduct **4e** was *R*. All spectral data for obtained **8** were also consistent with the reported data.[10]

In conclusion, we developed a highly enantioselective 1,4-addition of 5*H*-oxazol-4-ones **2** (Ar = 2-Cl-C_6H_4) to allenic esters and ketones **3** using chiral guanidine **1a**. By examining the effect of Ar on **2**, we found that the 2-chlorophenyl group was suitable for the 1,4-addition and gave high enantioselectivities. An obtained adduct **4e** of the 1,4-addition was derived into (+)-crobarbatic acid in a few steps.



Scheme 1. Derivatization of adduct **4e** to **6** and (+)-crobarbatic acid (**8**). (a) 1.0 M NaOH (aq), THF, 0 °C, 1 h. (b) 1.0 M CH_3OLi, CH_3OH, 0 °C, 2.5 h. (c) 10% Pd–C, H_2, MeOH, rt, 24 h. (d) 4.0 M NaOH (aq), THF, 100 °C, 4 h, then 2 M HCl (aq), 100 °C, 1 h. Optical rotation value of **8**: $[\alpha]_D^{20} = +3.76$ (*c* 0.66, H_2O) [lit.[10] $[\alpha]_D^{25} = +3.56$ (*c* 1.4, H_2O) (2*R*, 3*S*)].

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8 General procedure: To a stirred solution of 5*H*-oxazol-4-one **2** (0.30 mmol) and allenyl carbonyl compound **3** (0.36 mmol) in toluene (1.0 mL) was added chiral guanidine **1** (15 µmol) at −20 or 0 °C. After stirring at same temperature for indicated time in Table 1 or 2 under a N_2 atmosphere. The resulting reaction mixture was concentrated to give a crude mixture, which was purified by SiO_2-column chromatography to give the adduct **4**.

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