

Highly Z-Selective Asymmetric 1,4-Addition Reaction of 5*H*-Oxazol-4-ones with Alkynyl Carbonyl Compounds Catalyzed by Chiral Guanidines

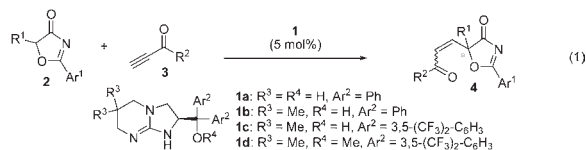
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S Supporting Information

ABSTRACT: An asymmetric 1,4-addition reaction of 5*H*-oxazol-4-ones with alkynyl carbonyl compounds was developed, and, for the first time, high enantiomeric and geometric control was achieved to afford the thermodynamically unstable *Z*-isomer predominantly using chiral guanidine catalysts bearing a hydroxy group at the appropriate position. The method provides synthetically useful γ -butenolide ester bearing a chiral quaternary stereogenic center.

Catalytic asymmetric 1,4-addition of carbon nucleophiles to α,β -unsaturated carbonyl compounds is a well-established enantioselective carbon–carbon bond-forming reaction. Various types of 1,4-additions to conjugated alkenyl carbonyl compounds have been developed¹ and applied to the syntheses of many biologically active natural products.² In contrast, catalytic asymmetric 1,4-additions to the corresponding alkynyl carbonyl compounds are few.³ In the 1,4-additions of this type, the geometric control of newly formed olefin is greatly important for further stereoselective transformation of the obtained products as well as the enantiomeric control. However, the high geometric control has not been achieved yet.⁴ The reported catalytic asymmetric 1,4-additions have preferably led to thermodynamically stable *E*-isomers in insufficient selectivity.³ Jørgensen et al.^{3a} and Shibasaki et al.^{3c} prepared only the *E*-isomer by the isomerization of the *Z/E* mixed products after the 1,4-additions, but the isomerization could not produce the thermodynamically unstable *Z*-isomers.⁵ Here, we report a highly *Z*-selective asymmetric 1,4-addition of 5*H*-oxazol-4-ones to alkynyl carbonyl compounds catalyzed by chiral guanidines **1** (eq 1). This 1,4-addition can also form an oxygen-atom-substituted chiral quaternary stereogenic center at the α -carbon atom.



Previously, we successfully developed a direct asymmetric aldol reaction of 5*H*-oxazol-4-ones **2** as pronucleophiles with aldehydes catalyzed by bicyclic chiral guanidines **1** bearing a hydroxy group.⁶ We disclosed that the combination of 5*H*-oxazol-4-one **2** and guanidine **1** as a Brønsted base catalyst⁷

Table 1. Screening of Reaction Conditions for the 1,4-Addition of 5*H*-Oxazol-4-one **2a** (R¹ = CH₃, Ar¹ = Ph) to Alkynyl Carbonyl Compound **3a** (R² = OCH₃) Using **1a–d** To Obtain Adduct **4a**^a

entry	catalyst 1	solvent	temp (°C)	time (h)	yield ^b (%)	Z/E ratio ^c	ee ^d (%)
1	1a	THF	0	1	50	87/13	43 (<i>R</i>)
2	1b	THF	0	3	55	92/8	53 (<i>R</i>)
3	1c	THF	0	1	47	87/13	84 (<i>R</i>)
4	1c	toluene	0	1	53	96/4	90 (<i>R</i>)
5	1c	CPME	0	1	47	93/7	92 (<i>R</i>)
6	1c	CPME	−40	24	59	97/3	92 (<i>R</i>)
7	1c	^t BuOMe	−40	16	52	97/3	93 (<i>R</i>)
8	1c	toluene	−40	11	56	98/2	94 (<i>R</i>)
9	1d	toluene	0	28	54	90/10	36 (<i>S</i>)

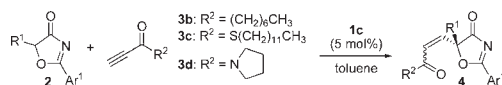
^a Reactions were performed on a 0.3 mmol scale in 1.0 mL of anhydrous solvent using 1.5 equiv of alkynyl carbonyl compound **3** and 5 mol % of catalyst **1**. ^b Combined isolated yield of *Z/E*-**4**. ^c Determined by 600 MHz ¹H NMR analysis of the crude mixture. ^d Enantiomeric excess of the *Z* isomer, determined by chiral HPLC analysis.

effectively induced a highly enantioselective carbon–carbon bond formation, producing α -oxygen-atom-substituted carboxylates bound to a chiral quaternary α -carbon atom. Thus, instead of using aldehydes, we selected alkynyl carbonyl compounds as the electrophiles to prove the high stereocontrolability of the bicyclic chiral guanidines **1** by achieving, for the first time, high enantiomeric and geometric control during the catalytic 1,4-addition.

An initial attempt at reacting 5*H*-oxazol-4-one (**2a**: R¹ = CH₃, Ar¹ = Ph) with methyl propiolate (**3a**) using guanidine **1a** revealed that the 1,4-addition proceeded with appreciable enantioselectivity (Table 1, entry 1). Interestingly, the *Z*-isomer was the major product. This result prompted us to enhance the stereoselectivity by screening the reaction conditions and, more specifically, tuning the steric and electronic properties of the guanidines **1**. As shown in Table 1, the use of electron-deficient aromatic substituents (Ar²) on guanidine **1**, such as 3,5-bis-(trifluoromethyl)phenyl groups, remarkably improved the enantioselectivity without enhancing the *Z/E* selectivity (entry 3). Further investigation of the reaction conditions using **1c** revealed

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Table 2. Catalytic 1,4-Addition of Various *SH*-Oxazol-4-ones **2** to Alkynyl Carbonyl Compounds **3**, Catalyzed by **1c**^a

entry	substrate		conditions (°C, h)	product 4	yield ^b (%)	<i>Z/E</i> ratio ^c	ee ^d (%)
	2 : R ¹ , Ar ¹	3					
1	2b : CH ₃ (CH ₂) ₃ , Ph	3a	-40, 16	4b	73	99/1	93
2 ^e	2c : (CH ₃) ₂ CH, Ph	3a	-40, 22	4c	66	98/2	86
3	2d : PhCH ₂ , Ph	3a	-40, 39	4d	74	96/4	84
4	2e : CH ₂ =CHCH ₂ , Ph	3a	-40, 41	4e	67	98/2	91
5 ^e	2f : BnO(CH ₂) ₄ , Ph	3a	-40, 19	4f	77	97/3	90
6	2a : CH ₃ , Ph	3b	0, 47	4g	77	44/56	91(91 ^f)
7 ^{g,h}	2a : CH ₃ , Ph	3b	0, 47	4g	68	1/>99	91 ^f
8 ⁱ	2a : CH ₃ , Ph	3c	0, 26	4h	88	76/24	88(72 ^f)
9 ^j	2a : CH ₃ , Ph	3d	0, 22	4i	50	>99/1	97
10 ^j	2b : CH ₃ (CH ₂) ₃ , Ph	3d	0, 48	4j	40	>99/1	98
11 ^j	2c : (CH ₃) ₂ CH, Ph	3d	0, 71	4k	55	>99/1	99
12 ^j	2d : PhCH ₂ , Ph	3d	0, 40	4l	49	>99/1	94
13 ^j	2e : CH ₂ =CHCH ₂ , Ph	3d	0, 40	4m	43	>99/1	98
14 ^j	2f : BnO(CH ₂) ₄ , Ph	3d	0, 43	4n	58	>99/1	96
15	2g : CH ₃ , 4-CF ₃ -C ₆ H ₄	3a	-40, 38	4o	15	99/1	89
16 ^k	2h : CH ₃ , 4- ⁱ PrO-C ₆ H ₄	3a	-40, 42	4p	26	93/7	83
17	2i : CH ₃ , 2-CH ₃ -C ₆ H ₄	3a	-40, 5	4q	70	94/6	94
18	2g : CH ₃ , 4-CF ₃ -C ₆ H ₄	3c	0, 7	4r	33	83/17	91(70 ^f)
19	2h : CH ₃ , 4- ⁱ PrO-C ₆ H ₄	3c	0, 45	4s	61	70/30	38(20 ^f)

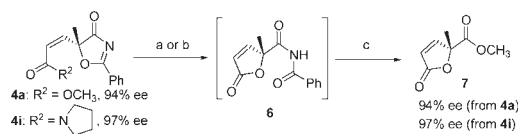
^{a-d} See corresponding footnote in Table 1. ^e CH₂Cl₂ was used as solvent instead of toluene. ^f Enantiomeric excess of the *E* isomer. ^g After completion of the 1,4-addition, Ph₂MeP (0.3 equiv) was added for the isomerization. ^h The absolute configuration of *E*-**4g** was determined by X-ray analysis of the corresponding compound having a bromo substituent at the 4-position of the phenyl group.¹² ⁱ The absolute configuration of *Z*-**4h** was determined by conversion into compound **7**.¹² ^j 100 mg of 3 Å molecular sieves/0.3 mmol of **2** was added.¹³ ^k Low conversion yield (35%) caused the low isolated yield.

that toluene was the best of the investigated solvents, especially at -40 °C (entries 3–8). It is noteworthy that the reaction with **1d**, which contains a methyl ether-protected hydroxy group, proceeded significantly more slowly and afforded the opposite enantiomer in low selectivity (entry 9).

Next, we investigated the substrate scope of the 1,4-addition using **1c** (Table 2). The 1,4-addition to methyl propiolate (**3a**) proceeded highly *Z*-selectively with good to excellent enantioselectivities (entries 1–5). Although the 1,4-additions to alkyne **3b** and thioester **3c** showed low *Z/E* selectivities, their enantioselectivities were high (entries 6, 8). Isomerization of *Z/E* mixed adduct **4g** using Ph₂MeP afforded only the *E*-isomer, as described by Shibasaki^{3c} (entry 7). Uniformly high *Z/E* selectivities and excellent enantioselectivities were observed when amide **3d** was used as an electrophile (entries 9–14). It should be noted that the 1,4-addition of bulky pronucleophile **2c**, the *Z*-adduct of which was thermodynamically more disadvantageous, also resulted in excellent *Z/E* selectivities (entries 2, 11). We also performed the 1,4-addition with **2g–i**, which contain a substituted aromatic ring. The 1,4-addition with **2g** bearing an electron-withdrawing group showed higher *Z/E* selectivity (entries 15, 18), and **2h** bearing an electron-donating group showed lower *Z/E* selectivity (entries 16, 19). *Ortho*-substituted **2i** also gave low *Z/E* selectivity (entry 17). In all cases, the remarkable side reactions were not observed by the ¹H NMR analysis of the crude mixture, but relatively low chemical yields were observed in some cases. The ring-opening reaction of the

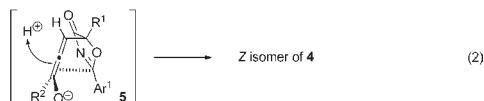
SH-oxazole ring of adduct **4** derived from **2g** or **3d** was observed during the purification by silica gel column chromatography (entries 9–15, 18).

Among reported 1,4-additions of carbon nucleophiles to propiolates under simple basic conditions, 1,4-additions of 4*H*-oxazol-5-ones (azlactones),⁸ which are structurally similar to *SH*-oxazol-4-ones **2**, or glycine Schiff base derivatives^{9,10} show *Z*-selectivity. The present 1,4-addition of **2a** to **3a** also proceeds *Z*-selectively, even in the presence of DBU (*Z/E* = 85/15) or K₂CO₃ (*Z/E* = 72/28) instead of **1c**. These results indicate that the *Z/E* selectivity depends on the nature of the pronucleophile and that this dependence suggests the existence of some interaction. As shown in eq 2, it is likely that one face of the enolate anion in the intermediate **5** is shielded by the *SH*-oxazole ring because the electron-enriched π orbital of the enolate interacts with the electron-deficient carbon atom at the 2-position of the *SH*-oxazole ring.^{10,11} Therefore, intermediate **5** most likely undergoes protonation from the other face to afford the thermodynamically unstable *Z*-isomer. The electron donation effect of the R² group on electrophile **3** and an electron-deficient aromatic substituent at the 2-position of the *SH*-oxazole ring should enhance the shielding effect arising from this intramolecular interaction. Accordingly, the *Z/E* selectivity of the present 1,4-addition was enhanced in proportion to the electron donation ability of the R² group (alkyne **3b**, *Z/E* = 44/56; thioester **3c**, *Z/E* = 76/24; ester **3a**, *Z/E* = 96/4–99/1; amide **3d**, *Z/E* > 99/1).

Scheme 1. Derivatization of Adducts Z-4a and Z-4i to 7^a

^a Conditions: (a) for 4a, 1.0 M NaOH (aq), THF, 0 °C, 1.5 h; (b) for 4i, CF₃CO₂H, THF, H₂O, 0 °C, 1 h, then rt, 15 h; (c) CH₃OLi, CH₃OH, 0 °C, 1 h, then rt, 65 h (63% from 4a, 54% from 4i).

The *Z/E* selectivity order 2g > 2a > 2h was also in agreement with the proposed mechanism.



Adducts Z-4 derived from 3a or 3d can be easily converted into synthetically useful γ -butenolide without loss of enantiopurity. As illustrated in Scheme 1, the γ -butenolide ring formation subsequent to the hydrolysis of 5*H*-oxazol-4-one through treatment of Z-4a with aqueous NaOH in THF readily afforded the corresponding imide 6, which was converted into methyl ester 7¹² by the CH₃OLi-mediated methanolysis. The CF₃-CO₂H-mediated acidic hydrolysis also converted adduct Z-4i into 6. The enantiopurity of 7 was confirmed by HPLC analysis.

In conclusion, we developed a highly *Z*-selective asymmetric 1,4-addition of 5*H*-oxazol-4-ones 2 to alkynyl carbonyl compounds 3 and, for the first time, achieved high enantiomeric and geometric control using chiral guanidine 1c.

■ ASSOCIATED CONTENT

Supporting Information. Representative experimental procedures and spectral data for pronucleophiles 2g–i, electrophile 3c, adducts 4, and derivatized product 7; X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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