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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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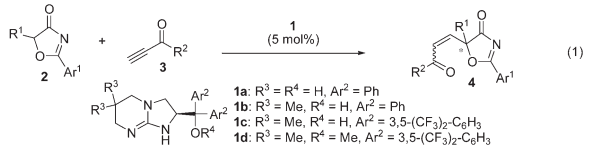
Supporting Information

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 developed[1] 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.



(1)

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 catalyst[7] 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.

Table 1. Screening of Reaction Conditions for the 1,4-Addition of 5*H*-Oxazol-4-one 2a (R^1 = CH_3, Ar^1 = Ph) to Alkynyl Carbonyl Compound 3a (R^2 = OCH_3) 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 (*R*)
2	**1b**	THF	0	3	55	92/8	53 (*R*)
3	**1c**	THF	0	1	47	87/13	84 (*R*)
4	**1c**	toluene	0	1	53	96/4	90 (*R*)
5	**1c**	CPME	0	1	47	93/7	92 (*R*)
6	**1c**	CPME	−40	24	59	97/3	92 (*R*)
7	**1c**	^{t}BuOMe	−40	16	52	97/3	93 (*R*)
8	**1c**	toluene	−40	11	56	98/2	94 (*R*)
9	**1d**	toluene	0	28	54	90/10	36 (*S*)

[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 ^{1}H NMR analysis of the crude mixture. [d] Enantiomeric excess of the *Z* isomer, determined by chiral HPLC analysis.

An initial attempt at reacting 5*H*-oxazol-4-one (**2a**: R^1 = CH_3, Ar^1 = 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 (Ar^2) 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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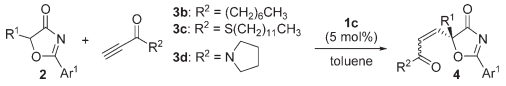
Table 2. Catalytic 1,4-Addition of Various 5*H*-Oxazol-4-ones 2 to Alkynyl Carbonyl Compounds 3, Catalyzed by 1c[a]



	substrate						
entry	**2**: R^1, Ar^1	**3**	conditions (°C, h)	product **4**	yield[b] (%)	*Z*/*E* ratio[c]	ee[d] (%)
1	**2b**: $CH_3(CH_2)_3$, Ph	**3a**	−40, 16	**4b**	73	99/1	93
2[e]	**2c**: $(CH_3)_2CH$, 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**: $(CH_3)_2CH$, 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_6H_4	**3a**	−40, 38	**4o**	15	99/1	89
16[k]	**2h**: CH_3, 4-^{i}PrO-C_6H_4	**3a**	−40, 42	**4p**	26	93/7	83
17	**2i**: CH_3, 2-CH_3-C_6H_4	**3a**	−40, 5	**4q**	70	94/6	94
18	**2g**: CH_3, 4-CF_3-C_6H_4	**3c**	0, 7	**4r**	33	83/17	91(70[f])
19	**2h**: CH_3, 4-^{i}PrO-C_6H_4	**3c**	0, 45	**4s**	61	70/30	38(20[f])

[a–d] See corresponding footnote in Table 1. [e] CH_2Cl_2 was used as solvent instead of toluene. [f] Enantiomeric excess of the *E* isomer. [g] After completion of the 1,4-addition, Ph_2MeP (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 alkynone **3b** and thioester **3c** showed low *Z*/*E* selectivities, their enantioselectivities were high (entries 6, 8). Isomerization of *Z*/*E* mixed adduct **4g** using Ph_2MeP 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 ^{1}H NMR analysis of the crude mixture, but relatively low chemical yields were observed in some cases. The ring-opening reaction of the 5*H*-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 5*H*-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 K_2CO_3 (*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 5*H*-oxazole ring because the electron-enriched π orbital of the enolate interacts with the electron-deficient carbon atom at the 2-position of the 5*H*-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 R^2 group on electrophile **3** and an electron-deficient aromatic substituent at the 2-position of the 5*H*-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 R^2 group (alkynone **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).

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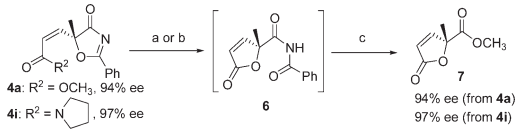
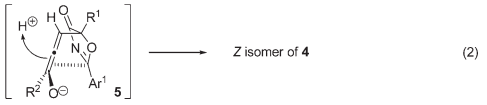
Scheme 1. Derivatization of Adducts *Z*-4a and *Z*-4i to 7[a]



[a] Conditions: (a) for **4a**, 1.0 M NaOH (aq), THF, 0 °C, 1.5 h; (b) for **4i**, CF_3CO_2H, THF, H_2O, 0 °C, 1 h, then rt, 15 h; (c) CH_3OLi, CH_3OH, 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.



(2)

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 **7**[12] by the CH_3OLi-mediated methanolysis. The CF_3CO_2H-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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■ ACKNOWLEDGMENT

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■ REFERENCES

(1) For organocatalysis, see: (a) Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. In *Asymmetric Organocatalysis*; List, B., Ed.; Springer: Berlin and Heidelberg, 2010; pp 145—200. For metal catalysis, see: (b) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279.

(2) Examples of natural products, see the following. For spiculisporic acid: (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. For (+)-tanikolide: (b) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301. For (+)-cylindricine C:(c) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635. Also see ref 1b.

(3) (a) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672. (b) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038. (c) Chen, Z.; Furutachi, M.; Kato, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2218. For related work, see: (d) Poulsen, T. B.; Bernardi, L.; Bell, M; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551.

(4) For *Z*-selective racemic 1,4-addition, see: (a) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252. (b) Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871. (c) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669. (d) Mueller, A. J.; Jennings, M. P. *Org. Lett.* **2007**, *9*, 5327. See also refs 8—10 for *Z*-selective 1,4-addition.

(5) Jørgensen also isolated the *Z*-isomer from the *Z*/*E* mixed product by the selective decomposition of the *E*-isomer.[3a]

(6) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286.

(7) For the chiral guanidine catalysis, see: (a) Ishikawa, T. In *Superbases for Organic Synthesis*; Ishikawa, T., Ed.; John Wiley & Sons: Chippenham, 2009; pp 93—143. For a review, see: (b) Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, *4*, 488 and references therein.

(8) (a) Steglich, W.; Gruber, P.; Höfle, G.; König, W. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 653. (b) Wegmann, H.; Schulz, G.; Steglich, W. *Liebigs Ann. Chem.* **1980**, 1736.

(9) (a) López, A.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1996**, *52*, 8365. (b) Guillena, G.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 7310. For an exceptionally *E*-selective 1,4-addition of the Schiff base substrate, see: (c) Rubio, A.; Ezquerra, J. *Tetrahedron Lett.* **1995**, *36*, 5823.

(10) An intramolecular interaction of intermediates had been proposed for the explanation about *Z*-selectivity in a 1,4-addition of Schiff base substrates: Freeman, F.; Kim, D. S. H. L. *J. Org. Chem.* **1993**, *58*, 6474.

(11) For a [3+2] cycloaddition via a related intermediate, see: Obrecht, D.; Zumbrunn, C.; Müller, K. *J. Org. Chem.* **1999**, *64*, 6891.

(12) The absolute configurations of *Z*-**4a**, -**4h**, and -**4i** and *E*-**4g** were assigned as (*R*). Except for that of *E*-**4g**, they were determined by the conversion of **7** into the known γ-lactonecarboxylic acid: Partridge, J. J.; Shiuey, S.-J.; Chadha, N. K.; Baggiolini, E. G.; Blount, J. F.; Uskoković, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1253. See the Supporting Information for details.

(13) The ring-opening reaction via hydrolysis of the 5*H*-oxazole ring of adduct **4** derived from **3d** was observed during the 1,4-addition without MS 3 Å.