doi:10.1246/cl.2012.1675
Published on the web December 8, 2012

Chiral Guanidine-catalyzed 1,4-Addition Reaction of 5*H*-Oxazol-4-ones to Alkynones

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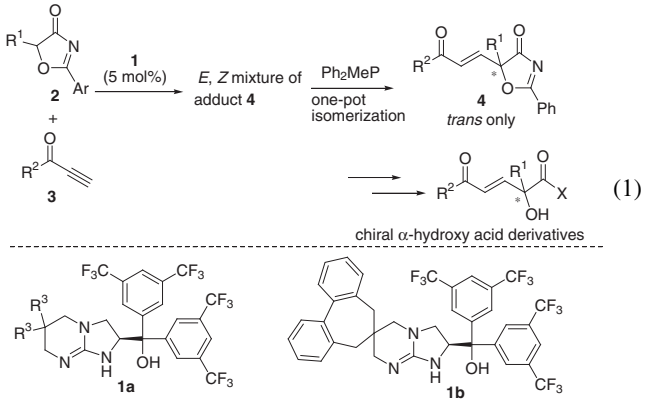
An asymmetric 1,4-addition reaction of 5*H*-oxazol-4-ones to alkynones using chiral guanidine catalysts bearing a hydroxy group at the appropriate position was developed, and applied to several substrates. The method provides a synthetically useful enone-substituted α-hydroxy acid derivatives with a chiral quaternary α-carbon atom.

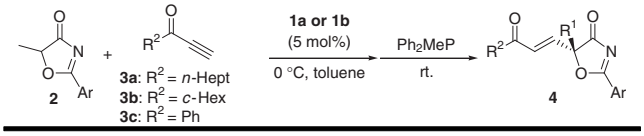
Since the report on 1,4-additions of 1,3-diketones to alkynones by Jørgensen et al.[1] in 2004, a few successful catalytic asymmetric 1,4-additions of carbon nucleophiles to alkynyl carbonyl compounds have been reported.[2] Later on, we also developed a 1,4-addition of 5*H*-oxazol-4-ones to propiolic acid derivatives and, for the first time, achieved high enantiomeric and geometric control of a newly formed olefin using chiral guanidines[3] as Brønsted base catalysts.[4] The method provides a synthetically useful γ-butenolide ester bearing a chiral quaternary stereogenic center. From the viewpoint of synthetic chemistry, the development of a highly general 1,4-addition of 5*H*-oxazol-4-ones to alkynones,[5] which provides various chiral α-hydroxy acid derivatives bearing an enone, is as important as the 1,4-addition to propiolates. Here, we report an asymmetric 1,4-addition of 5*H*-oxazol-4-ones to alkynones, catalyzed by chiral guanidines **1** (eq 1). The chiral guanidines **1**, originally developed as Brønsted base catalysts by our research group, have high stereocontrollability in several addition reactions of 5*H*-oxazol-4-ones to electrophiles.[4,6] Since catalytic enantioselective carbon–carbon bond formation producing α-oxygen-atom-substituted carboxylates bound to a chiral quaternary α-carbon atom[7] is limited by the difficulty of effective enolate generation of glycolate derivatives, we developed the present 1,4-addition as following research of our continuing work.



(1)

In the previous research, the 1,4-addition to an alkynone **3a** (R^2 = *n*-Hept) instead of propiolates, using catalyst **1a**, also showed high enantioselectivity, as shown in Table 1, Entry 1. Although low *E*/*Z* selectivity (*E*/*Z* = 56/44, *E*: 91% ee, *Z*: 91% ee) of the newly formed olefin was observed, isomerization of the *E*/*Z* mixed adduct using Ph_2MeP[2c] only afforded the *E*-isomer in 91% ee.[4] However, insufficient enantioselectivities were observed in the 1,4-addition with other alkynones **3b** (R^2 = *c*-Hex) and **3c** (R^2 = Ph) in the following research (Entries 2 and 3). Thus, we attempted to improve the generality of the alkynone in the 1,4-addition by examining the effect of the aromatic substituent (Ar) on 5*H*-oxazol-4-one **2** with catalysts **1a** or **1b**, which have previously been developed as Brønsted base catalysts for the asymmetric aldol reaction of 5*H*-oxazol-4-ones.[6] As shown in Entry 4, the use of bulky catalyst **1b** was not effective for the enhancement of the enantioselectivity in the 1,4-addition to alkynone **3a**. However, in the 1,4-addition to alkynone **3c**, the enantioselectivity was improved with catalyst **1b** (Entry 5). The use of 5*H*-oxazol-4-ones **2b**–**2d**, which contain a substituted aromatic ring, was not effective (Entries 6–8). However, some improvement in the enantio-

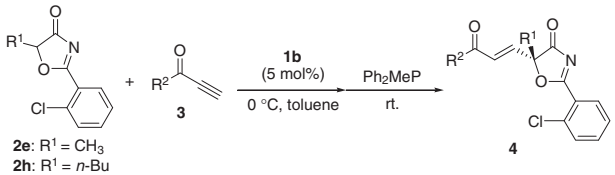
Table 1. Screening of the aromatic substituent (Ar) on 5*H*-oxazol-4-one **2** for the 1,4-addition using catalysts **1a** or **1b**[a]



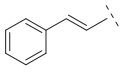
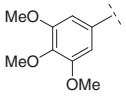
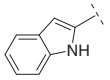
Entry	Substrates		Cat.	Time[b]	Product	Yield	ee[c]
	2: Ar	**3**	**1**	/h	**4**	/%	/%
1	**2a**: Ph	**3a**	**1a**	47	**4a**	68	91
2	**2a**: Ph	**3b**	**1a**	4	**4b**	66	89
3	**2a**: Ph	**3c**	**1a**	24	**4c**	76	74
4	**2a**: Ph	**3a**	**1b**	20	**4a**	66	90
5	**2a**: Ph	**3c**	**1b**	12	**4c**	71	88
6	**2b**: 4-CH_3O-C_6H_4	**3a**	**1b**	48	**4d**	60	90
7	**2c**: 4-Cl-C_6H_4	**3a**	**1b**	2.5	**4e**	74	64
8	**2d**: 3-Cl-C_6H_4	**3a**	**1b**	4	**4f**	67	87
9[d]	**2e**: 2-Cl-C_6H_4	**3a**	**1b**	2	**4g**	72	93
10	**2e**: 2-Cl-C_6H_4	**3a**	**1a**	22	**4g**	70	86
11[d]	**2e**: 2-Cl-C_6H_4	**3c**	**1b**	0.5	**4h**	74	92
12[e]	**2e**: 2-Cl-C_6H_4	**3a**	**1b**	48	**4g**	68	90
13	**2f**: 2,3-Cl_2-C_6H_3	**3a**	**1b**	21	**4i**	63	85
14	**2g**: 2-CH_3-C_6H_4	**3a**	**1b**	38	**4j**	64	90

[a]Reactions were performed on a 0.3 mmol scale in 1.0 mL of toluene using 1.5 equiv of alkynone **3** and 5 mol % of catalyst **1a** or **1b**. [b]Reaction time for the 1,4-addition. After completion of the 1,4-addition, Ph_2MeP (0.3 equiv) was added for the isomerization. [c]Determined by chiral HPLC analysis. [d]Reactions were also attempted without Ph_2MeP-mediated isomerization. The results were as follows: for adduct **4g**: *E*/*Z* = 61/39, *E*: 95% ee, *Z*: 93% ee, for adduct **4h**: *E*/*Z* = 57/43, *E*: 92% ee, *Z*: 92% ee. [e]Reaction was carried out at −20 °C.

Table 2. Catalytic 1,4-addition of 5*H*-oxazol-4-ones **2** to various alkynones **3**, catalyzed by **1b**[a]



2e: $R^1 = CH_3$
2h: $R^1 = n$-Bu
2i: $R^1 = BnO(CH_2)_4$
2j: $R^1 = i$-Pr

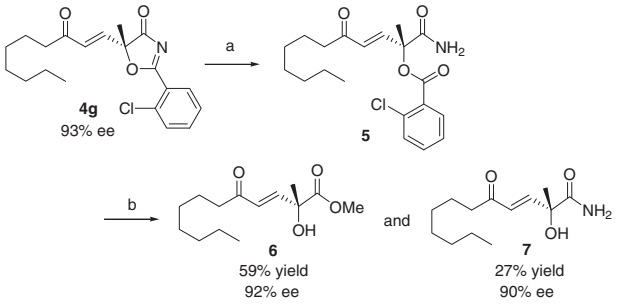
Entry	Substrates		Time[b]	Product	Yield	ee[c]
	2	**3**: R^2	/h	**4**	/%	/%
1	**2e**	**3a**: *n*-Hept	2	**4g**	75	93
2	**2e**	**3b**: *c*-Hex	2.5	**4k**	73	93
3	**2e**	**3c**: Ph	0.5	**4h**	74	92
4	**2h**	**3b**: *c*-Hex	40	**4l**	64	92
5	**2i**	**3b**: *c*-Hex	6	**4m**	63	91
6[d]	**2j**	**3a**: *n*-Hept	96	**4n**	45	79
7	**2e**	**3d**: $Cl(CH_2)_3$	0.5	**4o**	74	94
8	**2e**	**3e**: 	0.5	**4p**	53	84
9	**2e**	**3f**: 	2.5	**4q**	62	91
10	**2e**	**3g**: 	0.5	**4r**	55	94

[a–c]See corresponding footnote in Table 1. [d]Low conversion yield (62%) caused the low isolated yield.

selectivity was found when **2e** bearing a 2-chlorophenyl group and catalyst **1b** were employed (Entry 9). In particular, in the 1,4-additions to alkynone **3c**, the enantioselectivity was remarkably improved, from 74% ee to 92% ee, by using **2e** and **1b** instead of **2a** and **1a**, as shown in Entries 3 and 11. The significant effects of the aromatic substituent (Ar) on **2f**, **2g** were not observed in further investigations (Entries 13 and 14).

We next investigated the substrate scope of the 1,4-addition of the 2-chlorophenyl-substituted 5*H*-oxazol-4-ones to several types of alkynones, using catalyst **1b** (Table 2). As a result, adducts **4**[8,9] were obtained with high enantioselectivity, except for the 1,4-addition of 5*H*-oxazol-4-one **2j**. Several functionalities in **2** or **3** had almost no influence on the high enantioselectivity (Entries 5 and 7–10). A chlorine-substituted alkynone **3d**, with the possibility of 5-membered ring formation,[10] and indole-substituted alkynone **3g**, without a protective group on the nitrogen atom, were also applicable to the 1,4-addition (Entries 7 and 10). In the case of bulky **2j**, the 1,4-addition proceeded remarkably slowly and with somewhat low enantioselectivity (Entry 6).

Adducts **4** can be easily converted into the corresponding chiral α-hydroxy methyl esters and α-hydroxy amides without loss of the enantiopurities.[9] As illustrated in Scheme 1, the ring-opening reaction of 5*H*-oxazol-4-one through treatment of adduct **4g** with aqueous NaOH in THF readily afforded the corresponding amide **5**, which was converted to methyl ester **6** in 59% yield by CH_3ONa-mediated methanolysis, along with amide **7**[4] in 27% yield as the minor product. The enantiopurities of **6** and **7** were confirmed by HPLC analysis, and the absolute configuration of amide **7** was assigned as (*R*) after comparison



Scheme 1. Derivatization of adduct **4g** to **6** and **7**. (a) 1.0 M NaOH(aq), THF, 0 °C, 10 min; (b) cat. CH_3ONa, mixture of CH_3OH and THF (1:1), 0 °C, 3 h, then rt, 10 h (**6**: 59%, **7**: 27% from **4g**).

between the optical rotation value of the obtained **7** and our previously reported value.[4]

In conclusion, we developed a highly enantioselective 1,4-addition of 5*H*-oxazol-4-ones **2** to alkynones **3** using chiral guanidine **1b**. By examining the effect of the aromatic substituent (Ar) on **2** using catalyst **1a** or **1b**, we disclosed that 2-chlorophenyl-substituted 5*H*-oxazol-4-ones as pronucleophiles are suitable for 1,4-additions to various alkynones **3** with catalyst **1b**.

References and Notes

1 M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672.

2 a) X. Wang, M. Kitamura, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 1038. b) Q. Lan, X. Wang, K. Maruoka, *Tetrahedron Lett.* **2007**, *48*, 4675. c) Z. Chen, M. Furutachi, Y. Kato, S. Matsunaga, M. Shibasaki, *Angew. Chem., Int. Ed.* **2009**, *48*, 2218. d) Q. Lan, X. Wang, S. Shirakawa, K. Maruoka, *Org. Process Res. Dev.* **2010**, *14*, 684. e) Z. Wang, Z. Chen, S. Bai, W. Li, X. Liu, L. Lin, X. Feng, *Angew. Chem., Int. Ed.* **2012**, *51*, 2776.

3 For the chiral guanidine catalysis, see: a) T. Ishikawa, *Guanidines in Organic Synthesis* in *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*, ed. by T. Ishikawa, John Wiley & Sons, Chippenham, **2009**, pp. 93–143. doi:10.1002/9780470740859.ch4. For a review, see: b) D. Leow, C.-H. Tan, *Chem.—Asian J.* **2009**, *4*, 488, and references therein.

4 T. Misaki, K. Kawano, T. Sugimura, *J. Am. Chem. Soc.* **2011**, *133*, 5695.

5 Examples of racemic 1,4-additions to alkynones, see: a) F. Bohlmann, D. Rahtz, *Chem. Ber.* **1957**, *90*, 2265. b) G. Schulz, P. Gruber, W. Steglich, *Chem. Ber.* **1979**, *112*, 3221. c) J.-F. Lavallée, G. Berthiaume, P. Deslongchamps, F. Grein, *Tetrahedron Lett.* **1986**, *27*, 5455. d) S.-I. Murahashi, T. Naota, H. Taki, M. Mizuno, H. Takaya, S. Komiya, Y. Mizuho, N. Oyasato, M. Hiraoka, M. Hirano, A. Fukuoka, *J. Am. Chem. Soc.* **1995**, *117*, 12436. e) M. Miesch, G. Mislin, M. Franck-Neumann, *Tetrahedron Lett.* **1998**, *39*, 6873. f) P. H. Lee, J. Park, K. Lee, H.-C. Kim, *Tetrahedron Lett.* **1999**, *40*, 7109. g) R. B. Grossman, S. Comesse, R. M. Rasne, K. Hattori, M. N. Delong, *J. Org. Chem.* **2003**, *68*, 871. h) B. Yao, Y. Zhang, Y. Li, *J. Org. Chem.* **2010**, *75*, 4554. For diastereoselective 1,4-addition, see: i) H. Monti,

G. Audran, J.-P. Monti, G. Leandri, *J. Org. Chem.* **1996**, *61*, 6021.
6 T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286.
7 Examples of catalytic chiral quaternary α-carbon atom constructions, see: a) B. M. Trost, K. Dogra, M. Franzini, *J. Am. Chem. Soc.* **2004**, *126*, 1944. b) T. Ooi, K. Fukumoto, K. Maruoka, *Angew. Chem., Int. Ed.* **2006**, *45*, 3839. c) P. S. Hynes, D. Stranges, P. A. Stupple, A. Guarna, D. J. Dixon, *Org. Lett.* **2007**, *9*, 2107. d) K. Zhang, Q. Peng, X.-L. Hou, Y.-D. Wu, *Angew. Chem., Int. Ed.* **2008**, *47*, 1741. e) T. Hashimoto, K. Fukumoto, N. Abe, K. Sakata, K. Maruoka, *Chem. Commun.* **2010**, *46*, 7593. f) H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye, *Chem. Commun.* **2012**, *48*, 461. g) B. M. Trost, K. Hirano, *Angew. Chem., Int. Ed.* **2012**, *51*, 6480.
8 General procedure: To a stirred solution of 5*H*-oxazol-4-one **2** (0.30 mmol) and alkynone **3** (0.45 mmol) in toluene (1.0 mL) was added chiral guanidine **1** (15 µmol) at 0 °C. After stirring at same temperature for indicated time in Table 1 or 2 under a N_2 atmosphere, methyldiphenylphosphine (18 mg, 0.09 mmol) was added to the reaction mixture, followed by being stirred at room temperature until the *Z*-isomer became undetectable by silica gel TLC analysis (for 3–27 h). The resulting reaction mixture was concentrated to give a crude mixture, which was purified by SiO_2-column chromatography to give the adduct **4**.
9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
10 Examples of 5-membered ring (tetrahydrofuran ring) formation via enolate anion of 3-chloropropylketones, see: a) A. Svendsen, P. M. Boll, *Acta Chem. Scand., Ser. B* **1975**, *29*, 197. b) H. H. Zoorob, M. A. Ismail, L. Strekowski, *J. Heterocycl. Chem.* **2001**, *38*, 359. c) S. Calvet, O. David, C. Vanucci-Bacqué, M.-C. Fargeau-Bellassoued, G. Lhommet, *Tetrahedron* **2003**, *59*, 6333. d) O. V. Khilya, T. A. Volovnenko, A. V. Turov, R. I. Zubatyuk, O. V. Shishkin, Y. M. Volovenko, *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2011**, *47*, 1141.

