A novel chiral oxazolidine organocatalyst for the synthesis of an oseltamivir intermediate using a highly enantioselective Diels-Alder reaction of 1,2-dihydropyridine

著者	NAKANO Hiroto, OSONE Kenichi, TAKESHITA Mitsuhiro, KWON Eunsang, SEKI Chigusa, MATSUYAMA Haruo, TAKANO Nobuhiro, KOHARI Yoshihito
journal or publication title	Chemical communications
volume	46
number	26
page range	4827-4829
year	2010-07-14
URL	http://hdl.handle.net/10258/660

doi: info:doi/10.1039/c0cc00110d

A novel chiral oxazolidine organocatalyst for the synthesis of an oseltamivir intermediate using a highly enantioselective Diels-Alder reaction of 1,2-dihydropyridine

著者	NAKANO Hiroto, OSONE Kenichi, TAKESHITA Mitsuhiro, KWON Eunsang, SEKI Chigusa, MATSUYAMA Haruo, TAKANO Nobuhiro, KOHARI Yoshihito
journal or publication title	Chemical communications
volume	46
number	26
page range	4827-4829
year	2010-07-14
URL	http://hdl.handle.net/10258/660

doi: info:doi/10.1039/c0cc00110d

A novel chiral oxazolidine organocatalyst for a synthesis of oseltamivir intermediate using a highly enantioselective Diels-Alder reaction of 1,2-dihydropyridine

Hiroto Nakano,^{*a} Kenichi Osone,^b Mitsuhiro Takeshita,^{*b} Eunsang Kwon,^c Chigusa Seki,^a Haruo Matsuyama,^a Nobuhiro Takano,^a Yoshihito Kohari^b

Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X

First published on the web Xth XXXXXXXXX 200X

DOI: 10.1039/b000000x

Enantioselective Diels-Alder reactions of 1,2-dihydropyridines with acroleins using a novel chiral oxazolidine organocatalyst afforded chiral isoquinuclidines that is efficient synthetic intermediate of oseltamivir, with fairly good chemical yield and excellent enantioselectivity (90%, up to >99% ee).

The 2-azabicyclo[2.2.2]octanes (isoquinuclidines) are found widely in natural products such as iboga-type indole alkaloids, which have varied and interesting biological properties.¹

Scheme 1. Utility of isoquinuclidines

In particular, as shown in Scheme 1, there are pharmacologically important vinca alkaloids such as vinblastine and vincristine, which possesses isoquinuclidines, with the aspidosperma portion.² It has recently been indicated that ibogaine reduces cravings for alcohol and other drugs by means of its ability to boost the levels of a growth factor known as glial cell line-derived neurotrophic factor (GDNF).³ In addition, most recently it was also showed that the isoquinuclidines can be used as the synthetic intermediate for the synthesis of oseltamivir phosphate (Tamiflu) which is an important *anti*-influenza drug.⁴ Tamiflu is a potent inhibitory of neuraminidase, and is used worldwide as a drug for type A or B influenza. Furthermore, isoquinuclidines are

also valuable intermediates in the synthesis of other alkaloids⁵ and in medicinal chemistry.⁶ It is therefore meaningful to establish an effective asymmetric synthetic methodology for chiral isoquinuclidines. A well-established route to the chiral ring system is through the asymmetric Diels-Alder (DA) reaction of 1,2-dihydropyridines with dienophiles. However, only a little example of employing organometal catalyst or organocatalyst has been reported by our group and others.⁷ Despite the obvious advantages of the catalytic enantioselective version using an organocatalyst, to the best of our knowledge, only one example employing MacMillan catalyst has been reported for the organocatalytic asymmetric version of this reaction that was used as the key reaction for the efficient practical total synthesis of Tamiflu by Fukuyama and co-workers.⁴ Nevertheless, this reaction afforded low chemical yield (26%), but excellent enantioselectivity (99% ee).

In the present study, we planned to develop a novel organocatalyst that afford chiral isoquinuclidines at a practical level with regard to both chemical yield and enantioselectivity.

In designing the planned catalyst, we paid attention to our previously developed phosphino-oxazolidine (POZ) ligand A (Scheme 2).⁷ The Pd-POZ organometallic catalyst shows an excellent catalytic property in the DA reaction with 1,2-dihydropyridines as a diene.^{7b,c} In the reaction, the substituted oxazolidine structure of the catalyst works effectively to give high enantioselectivity. Given the above, we designed a series of oxazolidines, 2,4-substituted 5,5-diphenyloxazolidines, as a novel organocatalyst for the DA reaction of 1,2-dihydropyridines. Oxazolidine catalyst is easily prepared by the reaction of an amino alcohol with a carbonyl compound. The resulting compound contains one covalent site, and the stability of the oxazolidine ring system can be maintained by the diphenyl groups at the 5-position.

Scheme 2 Concept of organocatalyst

We report herein that 2-phenyl-4-*tert*-butyl-5,5-diphenyloxazolidine with CF₃CO₂H exhibits a high degree of enantioselectivity (up to >99% ee) and good chemical yield (up to 90%) in the DA reaction of 1,2-dihydropyridines with acroleins. Although a high chemical yield is not obtained in this reaction using the MacMillan catalyst, this is the first organocatalyst that affords the corresponding chiral isoquinuclidines at a practical level with regard to both high chemical yield and enantioselectivity.

The catalysts, respectively, were prepared by the condensation of the corresponding β -amino alcohol with an aldehyde or a ketone, followed by treatment with an organic acid (Scheme 3). Thus, the reactions of β -amino alcohols **4a-d** with benzaldehyde, respectively, afforded the precursor oxazolidine **5** in good chemical yields, but the ¹H-NMR analysis of the obtained crystallized products showed a tautomeric mixture of oxazolidines **5a-d** and imines **5a'-d'**. However, the treatments of **5** with XCO₂H (X = CF₃, CHF₂, CCl₃, CBr₃) afforded the desired chiral oxazolidine salts **6a-g**. Thus, the reactions of the compounds **5a,b** with XCO₂H (X = CF₃, CCl₃, CBr₃, CHF₂), respectively, gave the desired catalysts **6a,b,e-g** as a single structure in quantitative yields. However, the reactions of the compounds **5c,d** with CF₃COOH afforded compound **6c,d** as a single structure with decomposed product. Furthermore, catalysts **8a** and **8b**⁸ were also obtained from the condensations of **4a,b** with acetone in the presence of MS 4A followed by the treatment with CF₃CO₂H, respectively. In the four compounds **6a-g**, the assigned stereochemistry at the 2-position of the oxazolidine ring was determined by NOE difference spectra. NOE enhancement was observed between the hydrogen at the 2-position and the hydrogen at the 4-position when the 2- and 4-positions were irradiated, respectively.⁶

Scheme 3 Synthesis of oxazolidine catalysts

We first examined the DA reaction of common 1-

phenoxycarbonyl-1,2-dihydropyridine **9** with acrolein **10**. The reaction was carried out at 0 °C in CH₃CN-H₂O in the presence of 10mol% of catalysts **6a,b,e-g** to give the DA adduct **11**, and its chemical and optical yields were determined by converting to the alcohol **12**. The results are summarized in Table 1. The reaction catalyzed by 5-*tert*-butyl-**6a** with CF₃CO₂H gave the *endo*-DA adduct **11a**[†] in good chemical yield (71%) and excellent enantioselectivity (>99% ee) (entry 1). The use of 5-isopropyl-**6b** with CF₃CO₂H brought about a slight decrease in enantioselectivity (97% ee), but the DA adduct was obtained in 77% (entry 2). In contrast, 2-dimethylated catalysts **8a,b** with *tert*-butyl or *iso*-propyl groups at the 5-position afforded both the *endo* and *exo* DA adducts as a mixture in only low chemical yields and enantioselectivity (entries 3, 4). These above results indicate that the stereochemistry of the substituent group at the 2-position of the oxazolidine ring is important for obtaining an satisfactory enantioselectivity. Catalysts **6e-g** with other organic acids (XCO₂H: X = Cl₃C, Br₃C, F₂CH) also did not give satisfactory results for either chemical yield or enantioselectivity (entries 5-7). Based on the above, 2-monosubstituted **6a,b** might be better than the corresponding 2-disubstituted **8a,b** in the reaction. Thus, the substituents at 2- and 4-positions having *cis*-configuration on the oxazolidine ring might act to control the equilibrium between iminium conformers blocking one iminium face from attacking of diene to afford high enantioselectivity.

Table 1 Enantioselective DA reaction of **9** with **10** using catalysts **6,8**

Entry	Catalyst	Product	Yield (%) ^a	<i>endo</i> : <i>exo</i> ^b (11a : 11b)	<i>endo</i> -11a ee (%) ^c	<i>exo</i> -11b ee (%)
1	6a	11a	71	<i>endo</i> only	>99 (S)	
2	6b	11a	70	"	97 (S)	
3	8a	11a,b	19	12 : 1	27 (S)	29
4	8b	11a,b	19	51 : 1	85 (S)	39
5	6e	11a,b	73	75 : 1	39 (S)	18
6	6f	11a	16	<i>endo</i> only	33 (S)	
7	6g	11a	53	"	42 (S)	

^aIsolated yields. ^bThe *endo/exo* ratio was determined by ¹H NMR. ^cThe ee of the *endo* and *exo* isomers were determined by chiral HPLC using a Daicel AD-H column (hexane/2-propanol : 85/15) of **12a,b**.

The activity of most effective catalyst **6a** was then evaluated in the reaction consisting of 10 mol% catalyst with 1-benzyloxycarbonyl or 1-*tert*-butoxycarbonyl-1,2-dihydropyridines (**13** and **14**) and acrolein **10**. The chemical and optical yields of the DA adducts **15**, **16**[†] were determined by converting to the alcohols **17**, **18**. The results are shown in Table 2. The use of 1-benzyloxycarbonyl-diene **13** further increased efficacy of catalyst **6a** (entry 1). In this reaction, fairly good chemical yield (90%) was observed together with excellent enantioselectivity (>99% ee). Furthermore, the effect of reducing

the molar ratio of catalyst **6a** were examined. At low catalytic loading to 5 mol % of **6a**, equally satisfactory results (67%, 97% ee, entry 2) were obtained, but 2.5 mol % greatly decreased both the chemical yield and enantioselectivity (44%, 85% ee, entry 4). Similarly, **6a** was also effective in the DA reaction using 1-*tert*-butoxycarbonyl-diene **14** and the desired DA adduct **16** was obtained with almost complete enantioselectivity (>99% ee) with a moderate chemical yield (entry 5).

Table 2 Enantioselective DA reaction of **13** or **14** with acrolein using catalysts **6a**

Entry	Catalyst (mol%)	Time (h)	Substrate	Product	15,16 yield (%) ^a	<i>endo</i> - 15a,16 ee (%) ^b	<i>exo</i> - 15b ee (%) ^b
1	6a (10)	24	13	15a	90	>99 (S)	
2	6a (5)	24	13	15a	61	97 (S)	
3	6a (5)	48	13	15a	67	97 (S)	
4	6a (2.5)	24	13	15a,b	44 ^c	85 (S)	73
5	6a (10)	24	14	16a	51	>99 (S)	

^aIsolated yields. ^bThe ee of the *endo* and *exo* isomers were determined by chiral HPLC using a Daicel chiral column of **17a,b, 18**. ^cThe *endo/exo* ratio was 67:33, which was determined by ¹H NMR.

We examined the effectiveness of acrolein derivative **19** using superior catalyst **6a** (Scheme 3). The reactions of dienes, **9, 13** with dienophile **19**, respectively, were carried out at 0 °C in the presence of 10 mol% of superior catalyst **6a** to give the DA adducts **20**, **21**,[†] and those chemical and optical yields were determined by converting to the alcohol **22**, **23**, respectively. The desired DA adducts, **20, 21** were obtained in good chemical yields and almost complete enantioselectivity (**20**: 68%, >99% ee, **21**: 83%, >99% ee) in the both reactions. This is the first example of an enantioselective DA reaction of 1,2-dihydropyridine with substituted dienophile using an organocatalyst.

Scheme 4 Enantioselective DA reactions of **9** or **13** with **19** using catalyst **6a**

In conclusion, we have succeeded in carrying out a highly enantioselective Diels-Alder reaction of 1,2-dihydropyridines that provides an efficient methodology for obtaining

pharmacologically important compound such as Tamiflu and its derivative, using a novel oxazolidine organocatalyst **6**. The developed oxazolidine catalyst **6** was easily prepared in two steps and showed dramatic reactivity and excellent enantioselectivity for the tried all reactions of three kinds of 1,2-dihydropyridines **9, 13, 14** with two kinds of acroleins **10, 19**, comparable to the results of the report of Fukuyama group.⁴ Further studies to examine the scope and limitations of this organocatalyst for the catalytic asymmetric version of the DA reactions of 1,2-dihydropyridines are now in progress.

Notes and references

- ^a Division of Applied Science and Engineering, College of Environmental Technology, Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto, Muroran, Hokkaido 050-8585, Japan, Fax: 81 14 346 5727; Tel: 81 14 346 5727; E-mail: catanaka@mmm.muroran-it.ac
- ^b Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan, Fax: 81 22 727 0146; Tel: 81 22 727 0147; E-mail: catanaka@tohoku-pharm.ac.jp
- ^c Research and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, sendai 980-8578, Japan, Fax: 81 22 795 6752; Tel: 81 22 795 6752; E-mail: ekwon@m.tains.tohoku.ac.jp
- [†] Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectral data for compounds **5a, 6a, 11a,b**, and **12a,b**; The absolute stereochemistry assignment for the new DA adducts **11a, 16, 20, 21**. See DOI: 10.1039/b000000x/
- (a) M. E. Kuehne, I. Marko, in *Syntheses of Vinblastine-type Alkaloids. The Alkaloids. Antitumor Bisindole Alkaloids from Catharanthus roseus (L.)*, eds. A. Brossi, M. Suffness, Academic: San Diego, 1990, Vol. 37, 77-131. (b) P. Popik, P. Skolnick, in *Pharmacology of Ibogaine and Ibogaine-related Alkaloids. The alkaloids. Chemistry and Biology*, ed. G. A. Cordell, Academic: San Diego, 1999, Vol. 52, 197-231. (c) S. D. Glick, I. M. Maisonneuve, K. K. Szumlinski, in *Mechanisms of Action of Ibogaine: Relevance to Putative Therapeutic Effects and Development of a Safer Iboga Alkaloid Congener. The Alkaloids*, eds. K. R. Alper, S. D. Glick, G. A. Cordell, Academic: San Diego, 2001, Vol. 56, 39-53.
- (a) G. Buchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, F. E. Ziegler, *J. Am. Chem. Soc.*, **1996**, 88, 3099-3109. (b) C. Marazano, M. LeGoff, J. Fourrey, B. C. Das, *J. Chem. Soc., Chem. Commun.*, **1981**, 389-391. (c) S. Raucher, B. L. Bray, *J. Org. Chem.*, **1987**, 109, 442-446. (d) M. T. Reding, T. Fukuyama, *Org. Lett.*, **1999**, 1, 973-976.
- D. Y. He, N. N. McGough, A. Ravindranathan, J. Jeanblanc, M. L. Logrip, K. Phamluong, P. H. Janak, D. Pon, *J. Neurosci.*, **2005**, 25, 619-28.
- (a) N. Satoh, T. Akiba, S. Yokoshima, T. Fukuyama, *Angew. Chem. Int. Ed.*, **2007**, 46, 5734-5736. (b) N. Satoh, T. Akiba, S. Yokoshima, T. Fukuyama, *Tetrahedron*, **2009**, 65, 3239-3245.
- S. F. Martin, H. Rueger, S. A. Williamson, S. Grzeszczak, *J. Am. Chem. Soc.*, **1987**, 109, 6124-6134.
- (a) C. H. Mitch, U. S. Patent 5,834,458, 1998; *Chem. Abstr.* **1999**, 129, 343498. (b) C. H. Mitch, U. S. Patent 5,889,019, 1999; *Chem. Abstr.* **1999**, 130, 252363. (c) G. R. Krow, O. H. Cheung, Z. Hu, Q. Huang, J. Hutchinson, N. Liu, K. T. Nguyen, S. Ulrich, J. Yuan, Y. Xiao, D. M. Wypij, F. Zuo, P. J. Carroll, *Tetrahedron*, **1999**, 5, 7747-7756.
- (a) N. Takenaka, Y. Huang, V. H. Rawal, *Tetrahedron*, **2002**, 58, 8299-8305. (b) H. Nakano, N. Tsugawa, R. Fujita, *Tetrahedron Lett.*, **2005**, 46, 5677-5681. (c) H. Nakano, N. Tsugawa, K. Takahashi, Y. Okuyama, R. Fujita, *Tetrahedron*, **2006**, 62, 10879-10887.
- A. D. Gupta, B. Singh, V. K. Singh, *Indian J. C.*, **1994**, 3B, 981-983.