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

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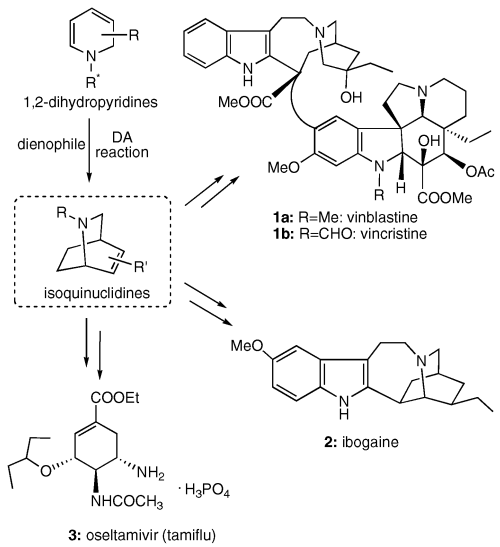
Enantioselective Diels–Alder reactions of 1,2-dihydropyridines with acroleins using a novel chiral oxazolidine organocatalyst afforded chiral isoquinuclidines that is an efficient synthetic intermediate of oseltamivir, with fairly good chemical yield and excellent enantioselectivity (90%, up to >99%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

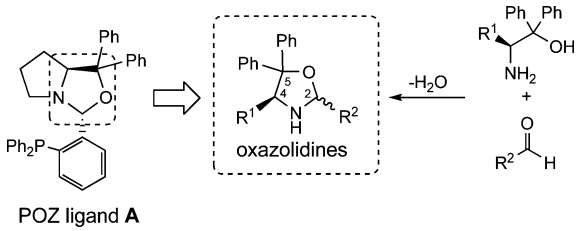
In particular, as shown in Scheme 1, there are pharmacologically important vinca alkaloids such as vinblastine and vincristin, which possess isoquinuclidines, with the aspidosperma portion.[2] It has recently been indicated that ibogaine reduces cravings for alcohol and other drugs by means of its ability 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 shown 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 inhibitor 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 alkaloids[5] 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 few examples of employing organometal catalysts or organocatalysts have 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 a 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).



Scheme 1 Utility of isoquinuclidines.

In the present study, we planned to develop a novel organocatalyst that afforded 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 phosphinooxazolidine (POZ) ligand **A** (Scheme 2).[7] The Pd-POZ organometalic catalyst showed an excellent catalytic property in the DA reaction with 1,2-dihydropyridines as a diene.[7b,c] In the reaction, the substituted



Scheme 2 Concept of organocatalyst.

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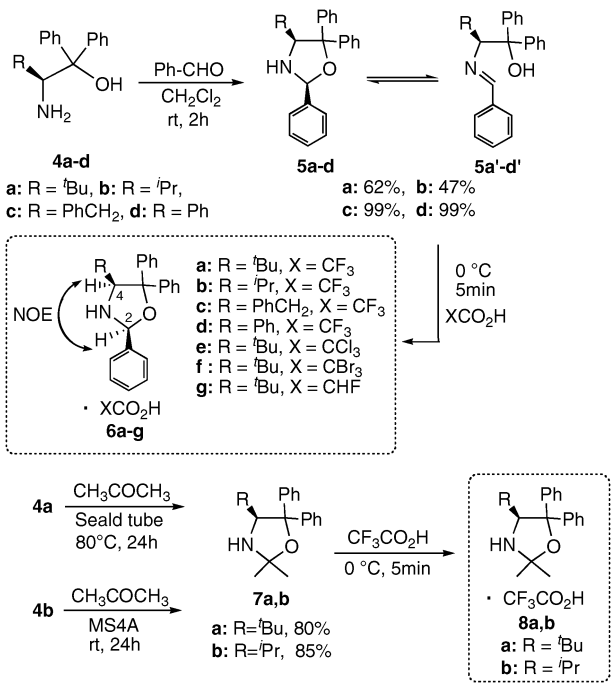
† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectral data for compounds **5a**, **6a**, **11a,b**, and **12a,b**; The absolute stereochemistry assignment for the new DA adducts **11a**, **16**, **20**, **21**. See DOI: 10.1039/c0cc00110d

oxazolidine structure of the catalyst worked 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. The oxazolidine catalyst was easily prepared by the reaction of an amino alcohol with a carbonyl compound. The resulting compound contained one covalent site, and the stability of the oxazolidine ring system could be maintained by the diphenyl groups at the 5-position.

We report herein that 2-phenyl-4-*tert*-butyl-5,5-diphenyloxazolidine with CF_3CO_2H 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 ^{1}H-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 XCO_2H (X = CF_3, CHF_2, CCl_3, CBr_3) afforded the desired chiral oxazolidine salts **6a–g**. Thus, the reactions of the compounds **5a,b** with XCO_2H (X = CF_3, CCl_3, CBr_3, CHF_2), 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 CF_3COOH afforded compound **6c,d** as a single structure with a decomposed product. Furthermore,

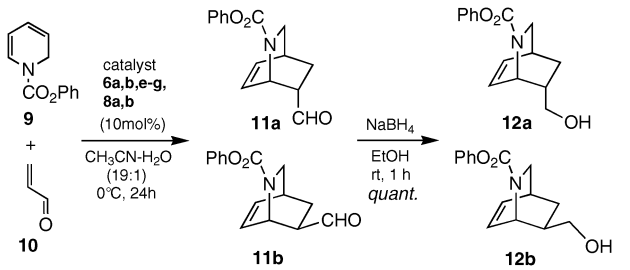


Scheme 3 Synthesis of oxazolidine catalysts.

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 CF_3CO_2H, respectively. In the seven 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]

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 CH_3CN–H_2O in the presence of 10 mol% 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 CF_3CO_2H 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 CF_3CO_2H brought about a slight decrease in enantioselectivity (97% ee), but the DA adduct was obtained in 70% (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 a satisfactory enantioselectivity. Catalysts **6e–g** with other organic acids (XCO_2H: X = Cl_3C, Br_3C, F_2CH) 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 a *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.

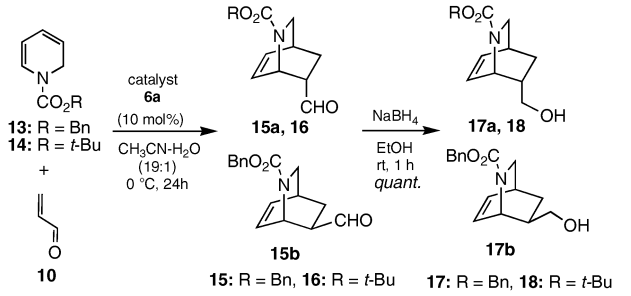
Table 1 Enantioselective DA reaction of **9** with **10** using catalyst **6,8**



Entry	Catalyst	Product	Yield (%)[a]	*endo* : *exo*[b] (**11a**:**11b**)	*endo*-**11a** ee(%)[c]	*exo*-**11b** ee(%)
1	**6a**	**11a**	71	*endo only*	>99(S)	
2	**6b**	**11a**	70	*endo only*	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	*endo only*	33(S)	
7	**6g**	**11a**	53	*endo only*	42(S)	

[a] Isolated yields. [b] The *endo*/*exo* ratio was determined by ^{1}H NMR. [c] The 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**.

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



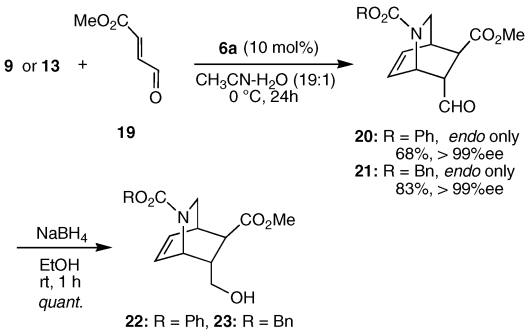
Entry	Catalyst (mol%)	Time/h	Substrate	Product	**15**,**16** yield (%)[a]	*endo*-**15a**,**16** ee(%)[b]	*exo*-**15b** ee(%)[b]
1	**6a**(10)	24	13	**15a**	90		>99(S)
2	**6a**(5)	24	13	**15a**	61	97(S)	
3	**6a**(5)	48	13	**15a**	67	97(S)	
4	**6a**(2.5)	24	13	**15a**,**b**	44[c]	85(S)	73
5	**6a**(10)	24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

[a] Isolated yields. [b] The ee of the *endo* and *exo* isomers were determined by chiral HPLC using a Daicel chiral column of **17a**,**b**,**18**. [c] The *endo*/*exo* ratio was 67 : 33, which was determined by ^{1}H NMR.

The activity of the 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** was examined. At low catalytic loading to 5 mol% of **6a**, equally satisfactory results (61%, 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).

We examined the effectiveness of acrolein derivative **19** using superior catalyst **6a** (Scheme 4). 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.

In conclusion, we have succeeded in carrying out a highly enantioselective Diels–Alder reaction of 1,2-dihydropyridines



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

that provides an efficient methodology for obtaining a 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 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 the 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.

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