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A highly enantioselective Diels–Alder reaction of 1,2-dihydropyridine using a simple β-amino alcohol organocatalyst for a practical synthetic methodology of oseltamivir intermediate

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ABSTRACT

An easily prepared chiral amino alcohol catalyst was found to provide an efficient synthetic intermediate of oseltamivir with excellent chemical yield and enantioselectivity (up to 98% yield and up to 98% ee) in enantioselective Diels–Alder reactions of 1,2-dihydropylidines with acroleins.

The development of the new chiral organocatalysts for use in asymmetric catalytic reactions has drawn considerable interest in the last 10 years. Excellent covalent and non-covalent organocatalysts have been developed for use in a wide range of reactions.[1] Quite recently, we also developed an oxazolidine organocatalyst[2] that works as an efficient catalyst much with MacMillan's imidazolidone-based catalyst[3] in the asymmetric Diels–Alder (DA) reaction of 1,2-dihydropyridines[4] **1**, which is an important reaction for the construction of chiral isoquinuclidines (2-azabicyclo[2.2.2]octanes) **2**. The isoquinuclidines **2** are valuable synthetic intermediates of biologically active iboga-type alkaloids[5] such as ibogaine **3**[6] and pharmacologically important oseltamivir phosphate (Tamiflu)[4,7] **4** (Scheme 1). As an example, Tamiflu is a potent inhibitory of neuraminidase that is used worldwide as a drug for type A or B influenza. However, most recently, a microbe resistant to Tamiflu was confirmed. Therefore, the development of effective Tamiflu-based drugs is needed as soon as possible to overcome this Tamiflu-resistant bacterium, and thus it is meaningful to establish an effective asymmetric synthetic methodology for chiral isoquinuclidines that might be converted into new Tamiflu-based influenza drugs based on the organocatalyzed DA reaction with 1,2-dihydropyridines **1** using an organocatalyst.

In designing the planned catalyst, we paid attention to simple α-amino alcohol **A**, which is easily converted from the corresponding β-amino acid ester, as the precursor of our developed oxazolidine catalyst (Fig. 1). To the best of our knowledge, the catalytic effectiveness of primary β-amino alcohol as an organocatalyst in an asymmetric reaction has not yet been shown.

The formation of the iminium ion intermediate from the reaction of **A** with acroleins might be able to control the attack of a diene that was fixed by the hydrogen bonding interactions between the hydrogen on the iminium ion intermediate and the carbonyl group on 1,2-dihydropyridines to afford high enantioselectivity in the reaction (pathway **X**), although oxazolidine catalyst **B** and MacMillan catalyst control the attack of the diene only by the steric interactions of substituents at both sides of the amino covalent site (pathway **Y**) (Scheme 2).

We report herein that the new β-amino alcohol with CF_3CO_2H is an efficient organocatalyst for the DA reaction of 1,2-dihydropyridines with acroleins, affording chiral isoquinuclidines at an excellent chemical yield (up to 98%) and an excellent enantioselectivity (up to 98% ee). This is the first organocatalyst that affords the corresponding chiral isoquinuclidines at a practical level with regard to both chemical yield and enantioselectivity.

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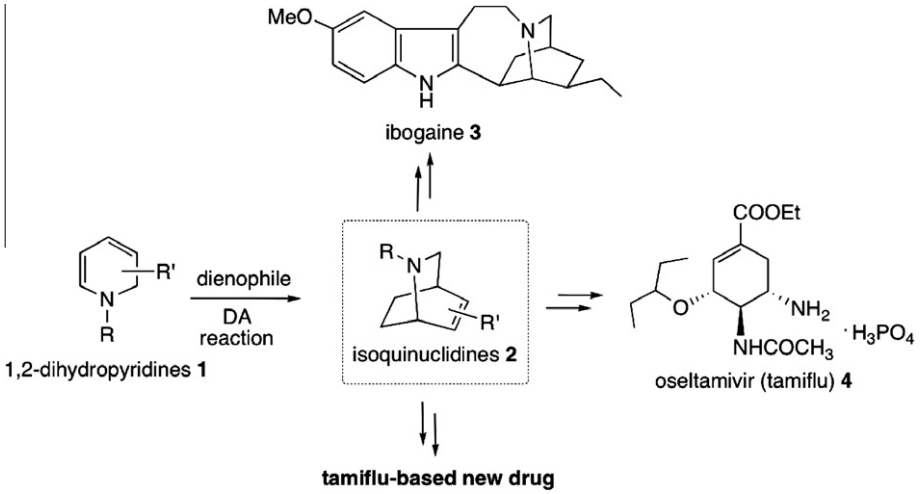


Scheme 1. Utility of isoquinuclidines.

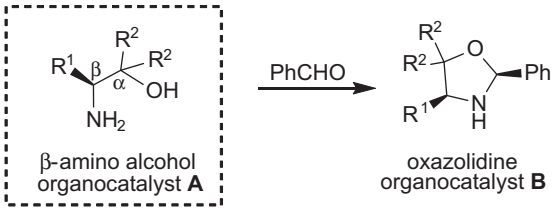
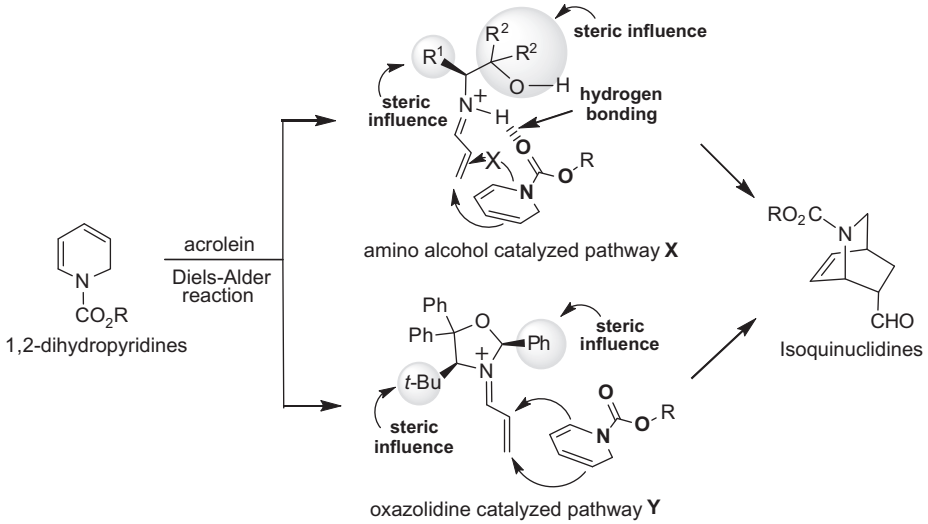


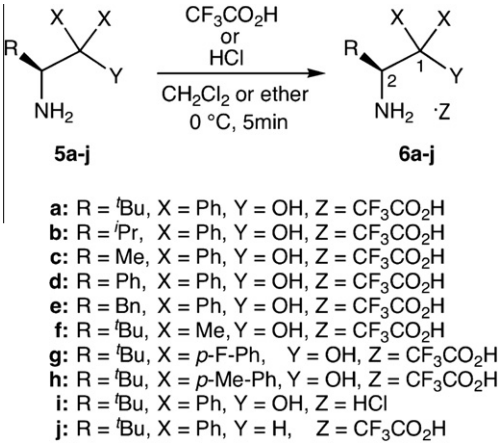
Figure 1. Design of amino alcohol organocatalyst.

The catalysts **6a**–**j** were easily prepared by the well-known synthetic methods (Scheme 3), and the Grignard reactions of amino acid esters afforded the corresponding amino alcohols **5a**–**i**, respectively. The treatments of both the obtained **5a**–**i** and the compound **5j** linking no hydroxyl group with CF_3CO_2H or HCl afforded the desired chiral β-amino alcohol salts **6a**–**j**, respectively, in quantitative yield.

We first examined the DA reaction of common 1-phenoxycarbonyl-1,2-dihydropyridine **7** with acrolein **8**. The reaction of **7** (1 equiv) with **8** (3 equiv) was carried out at 0 °C in CH_3CN–H_2O (19:1) in the presence of 10 mol % of catalysts **6a**–**j** to give the DA adduct **9**, and its chemical and optical yields were determined by converting into alcohol **10**. The results are summarized in Table 1. The reaction in the absence of a catalyst hardly proceeded (entry 1). The reaction catalyzed by **6a** bearing 2-*tert*-butyl moiety gave the *endo*-DA adduct **9a** in good chemical yield (82%) and with excellent enantioselectivity (96% ee) (entry 2). Although the use of **6b** bearing 2-isopropyl moiety brought about an increase in chemical yield (90% ee), the enantioselectivity slightly decreased to 94% (entry 3). In contrast, the catalytic activity of both **6c** bearing 2-methyl moiety and **6d** bearing 2-phenyl moiety was low and those reactions proceeded slightly with *exo*-DA adduct **9b**, although the reasons are unclear (entries 4 and 5). On the other hand, **6e** bearing 2-benzyl moiety showed a high catalytic activity to afford the *endo*-DA adduct **9a** at 80% yield and 87% ee (entry 6). Furthermore, the catalytic activity of 2-*tert*-butyl catalyst **6f** with an aliphatic dimethyl group at the 1-position was also examined, but satisfactory results were not obtained for either chemical yield or enantioselectivity (entry 7). We next examined the efficiencies of the catalysts **6g** and **h** having *p*-fluoro electron-withdrawing or *p*-methyl electron-donating groups on the phenyl groups at the 1-position on the catalyst in this reaction. Although both catalysts **6g** and **h** brought about fairly good asymmetric inductions with good



Scheme 2. Function of β-amino alcohol organocatalyst.

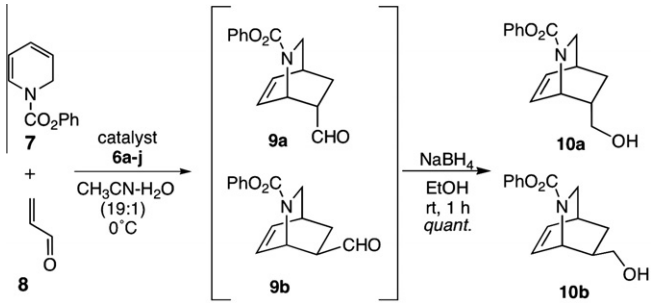


Scheme 3. Preparation of β-amino alcohol catalysts **6a–j**.

chemical yields (**6g**: 73% yield, 93% ee, **6h**: 75% yield, 95% ee) (entries 8 and 9), those catalysts did not afford better results than those of **6a**. The reaction using catalyst **6i** with strong HCl as an acid hardly proceeded, although high enantioselectivity was obtained (8% yield, 90% ee) (entry 10). In addition, we tested the reaction using catalyst **6j** with no substitution for the hydroxyl group, but the catalyst did not show effective catalytic activity (entry 11). Furthermore, the same reaction using β-amino alcohol **5a** as a catalyst and CF_3CO_2H as a co-catalyst also did not afford better results than those of a catalyst with CF_3CO_2H salt **6a** in the chemical yield and enantioselectivity (entry 12). From the above results, we see that β-amino alcohol–CF_3CO_2H salt **6a** was the most efficient catalyst to give *endo*-DA adduct **9a** in this DA reaction. These results indicated that the existence of both the diphenyl and the hydroxyl groups at the 1-position on β-amino alcohol is important for obtaining a satisfactory enantioselectivity and chemical yield. To optimize the reaction conditions using superior catalysts **6a**, we next examined the effect of reducing the molar ratio of **6a**. Although the reaction mixtures containing 5 mol % of **6a** afforded almost equal enantioselectivity to that of the reaction containing 10 mol % of **6a**, the chemical yield decreased to 72% (entry 13). Lower catalytic loading to 2.5 mol % greatly decreased the chemical yield (35%), but enantioselectivity was only slightly decreased to 93% ee (entry 14). A dramatic increase in chemical yield to 98% was accomplished with excellent enantioselectivity (96% ee) when the reaction time was changed from 24 to 36 h (entry 15).

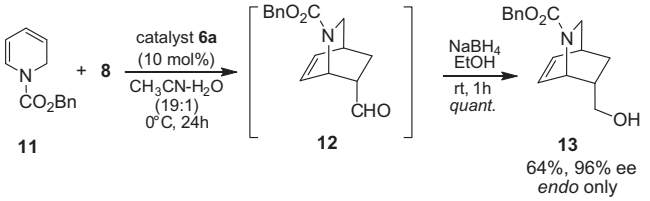
Synthetically useful 1,2-dihydropyridine **11** was also examined using superior catalyst **6a** and dienophile **8** (Scheme 4). The reaction was carried out at 0 °C for 24 h in the presence of 10 mol % of the best catalyst **6a** to give the corresponding *endo*-DA adduct **12**. The chemical and optical yields of the DA adduct **12** were determined by converting into the alcohol **13**. Catalyst **6a** showed high catalytic activity affording good chemical yield and excellent enantioselectivity (64% yield, 96% ee) in this reaction using diene **11**.

Table 1
Enantioselective DA reaction of 1,2-dihydropyridine **7** with acrolein **8** using catalysts **6a–j**

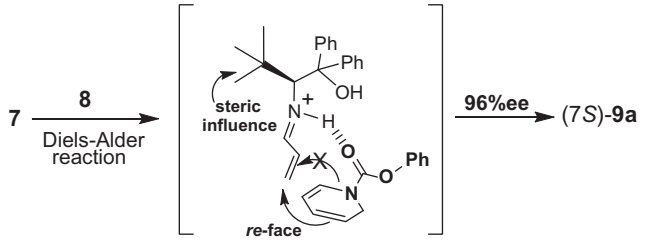


Entry	Catalyst (mol %)	Time (h)	Yield[a] (%)	*endo*/*exo*[b] (**9a**: **9b**)	*endo*-(*S*)-**10a**[c] ee (%)	*exo*-**10b** ee (%)
1	—	24	Trace		—	
2	**6a** (10)	24	82	*endo* only	96	
3	**6b** (10)	24	90	*endo* only	94	
4	**6c** (10)	24	31	17:1	64	38
5	**6d** (10)	24	27	4:1	13	68
6	**6e** (10)	24	80	*endo* only	87	
7	**6f** (10)	24	30	*endo* only	65	
8	**6g** (10)	24	73	*endo* only	93	
9	**6h** (10)	24	75	*endo* only	95	
10	**6i** (10)	24	8	*endo* only	90	
11	**6j** (10)	24	5	6:1	54	
12	**5a** (10)	24	66	*endo* only	95	
13	**6a** (5)	24	72	*endo* only	94	
14	**6a** (2.5)	24	35	*endo* only	93	
15	**6a** (10)	36	98	*endo* only	96	

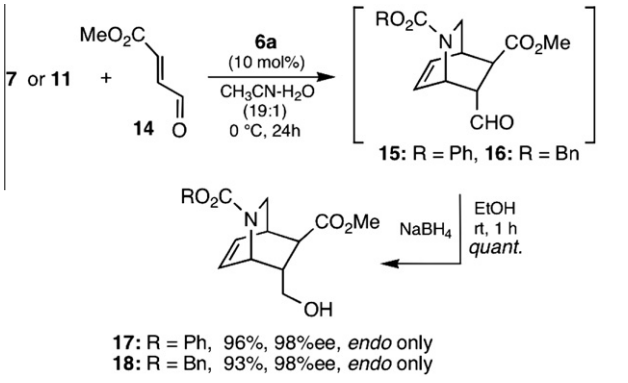
[a] Isolated yield.
[b] Thc *endo*/*exo* ratio was determined by ^{1}H NMR.
[c] The ee of the *endo* isomer was determined by chiral HPLC using a Daicel AD-H column (hexane/2-propanol: 85:15).



Scheme 4. Enantioselective Diels–Alder reaction of **11** with **8** using catalyst **6a**.



Scheme 5. Plausible reaction course for DA reaction of **7** with **8** using catalyst **6a**.



Scheme 6. DA reactions of **7** or **11** with **14** using catalyst **6a**.

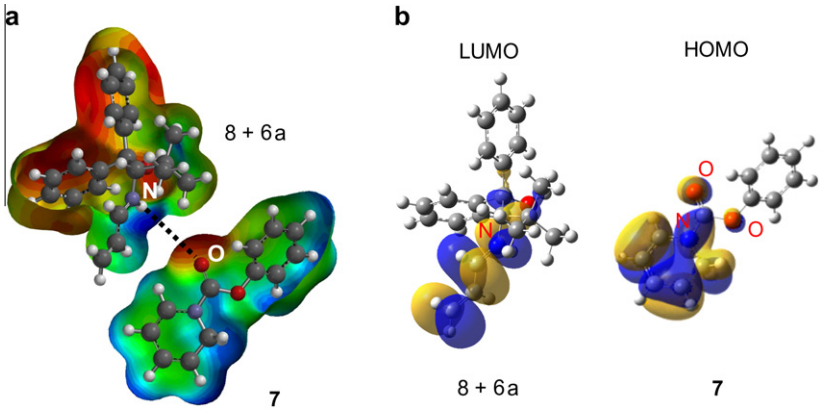


Figure 2. (a) B3LYP/6-311++g(d,p) 0.002 au isodensity surface with superimposed electrostatic potential using the optimized structure at the B3LYP/6-311++g(d,p) level of theory. (b) Frontier orbitals calculated at the B3LYP/6-311++g(d,p) level of theory for the iminium ion (left) and **7** (right).

The origin of the enantioselectivity in our catalytic system would be affected by the structural and electronic features of the amino alcohol catalysts. As shown in Scheme 5, for the highly enantioselective DA reaction of (7*S*)-**9a** (96% ee), **7** approaches from the sterically less hindered bottom face of the iminium ion intermediate to generate a hydrogen bond between the N–H hydrogen atom of the iminium and the carbonyl oxygen atom of **7**, as well as an electrostatic interaction between those two molecules. Thus the electrostatic potential analysis shows that there exists an effective intermolecular interaction between the iminium and **7** [Fig. 2 (**a**)]. Simultaneously, *si*-face of the olefin moiety on the iminium was attacked by the diene **7**, which would enable a more favorable frontier orbital overlap [Fig. 2 (**b**)] and thus enhance the enantioselectivity.

We next evaluated the effectiveness of superior catalyst **6a** in the DA reaction using acrolein derivative **14** (Scheme 6). The reactions of dienes, **7** or **11** with dienophile **14** were carried out at 0 °C in the presence of 10 mol % of superior catalyst **6a** to give the DA adducts **15** or **16** and the chemical and optical yields were determined by converting to the alcohols **17** or **18**, respectively. Both reactions showed satisfactory asymmetric catalytic activity and the desired DA adducts **17** or **18** were obtained in excellent chemical yields and excellent enantioselectivities (**17**: 96% yield, 98% ee, **18**: 93% yield, 98% ee).

In conclusion, new chiral β-amino alcohol organocatalysts **6a–j** were prepared easily in two steps, and they showed dramatic reactivity, excellent chemical yield, and excellent enantioselectivity (up to 98% yield, up to 98% ee) in the Diels–Alder reactions of 1,2-dihydropyridines 7 or 11 with acroleins 10 or 14. In particular, **6a** bearing 2-*tert*-butyl moiety gave the chiral isoquinuclidines **9a** in almost complete chemical yields and excellent enantioselectivities when the catalyst was used in the DA reactions of **7** or **11** with **10** or **14**, respectively. One advantage is that the developed catalysts are very stable in air and might be superior for practical use compared with the results of the same reactions of oxazolidine (**9a**: 82%, 99% ee) and MacMillan catalysts (**9a**: 26% yield, 99% ee). Further studies to examine the scope and limitations of this β-amino alcohol organocatalyst for the catalytic asymmetric version of the DA reactions of 1,2-dihydropyridines with acroleins are now in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.109.

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