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β-AMINO ALCOHOL ORGANOCATALYSTS FOR ASYMMETRIC ADDITIONS

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Abstract – A design of a chiral organocatalyst is very important for obtaining of a chiral product with a high optical purity in a catalytic asymmetric reaction. Recently, we developed a series of chiral β-amino alcohol organocatalysts **A** that showed high level of catalytic activity in some asymmetric reactions. These β-amino alcohols are stable in air, and have two advantageous features, easy preparation and exhibiting high stereoselectivity in an enantioselective reaction. This review summarizes our recent works involving the Diels-Alder (DA) reactions of 1,2-dihydropyridines, anthrones or 3-hydroxy-2-pyridones as dienes with dienophiles, the asymmetric 1,3-dipolar cycloaddition of nitrones with α,β-unsaturated aldehydes and the crossed aldol reaction of isatins with acetaldehyde, by the use of the simple primary β-amino alcohols as efficient chiral organocatalysts for the asymmetric reactions.

CONTENTS

Dedicated to Dr. Kiyoshi Tomioka on the occasion of his 70th birthday

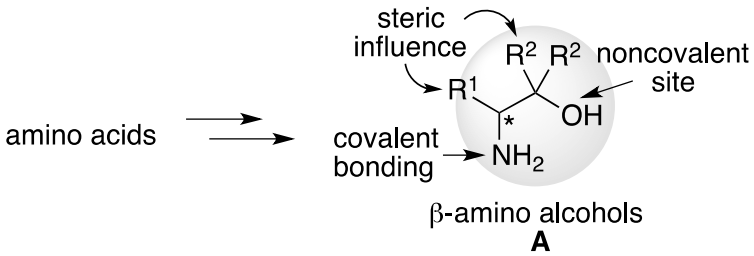
1. INTRODUCTION

Most of the bioactive compounds, including medicines, are optically active substances. It is well known that a pair of enantiomers exhibit different biological activities, hence one of enantiomers is usually required for certain purposes. In medicines particularly, the differences in the absolute configuration are often related not only to the presence or absence of a pharmacological action, but also to the expression of toxicity that causes serious harmful side effects. Therefore, an asymmetric synthesis for bioactive compounds, which affords a desired optically active substance in a highly selective manner, must be developed. A catalytic asymmetric synthesis, in which a trace amount of chiral molecules catalyzes a reaction and produces many chiral products, has been actively studied from energy-saving and environmentally friendly viewpoints.[1,2] The asymmetric catalysts used for catalytic asymmetric synthesis are classified into organometallic and organocatalysts that do not contain metals. Although organometallic catalysts have advantages of being highly active and they afford the desired optically active substances in a high optical yield, they also suffer from several disadvantages, for example, they are sensitive to air and moisture; they are made of metals that are expensive, toxic, and difficult to dispose; and they are not environmentally friendly. In contrast, organocatalysts have been receiving much attention as next-generation environment-friendly catalysts and are being actively studied and developed because they are stable in air, easy to handle and inexpensive.

The mechanisms of the action of organocatalysts are broadly divided into two types: noncovalent and covalent.[3] While a noncovalent asymmetric organocatalyst fixes a substrate by hydrogen bonding and activates a reaction site by the same mechanism with Lewis acids, a covalent asymmetric organocatalyst with an amine moiety forms imine, iminium or enamine to firmly fix the substrate to the catalyst and activate a reaction site of the substrate. We conducted research to fabricate general, versatile, and highly active asymmetric organocatalysts with multiple recognition sites, with the functionality of both noncovalent- and covalent-type catalysts. We have also been focusing particularly on amino alcohol **A** to

develop novel organocatalysts that can be synthesized in a single-step process from easily available substrates (Scheme 1).[4]

β-Amino alcohol **A** can be easily synthesized from various amino acid derivatives,[4d] and it has high stability. β-Amino alcohols can form imines (iminiums) and enamines, and have a nitrogen atom, which acts as a base, and a hydroxy group, which can form a hydrogen bond with a substrate. Hence, they are expected to work as multiple-recognition catalysts that use their different functionalities for different substrates. However, systematic studies focusing on the functionality of such organocatalysts have not yet been conducted. Our review will discuss the detailed applications of β-amino alcohol-based organocatalysts for asymmetric additions, and development of various strategies to synthesis of bioactive compounds.

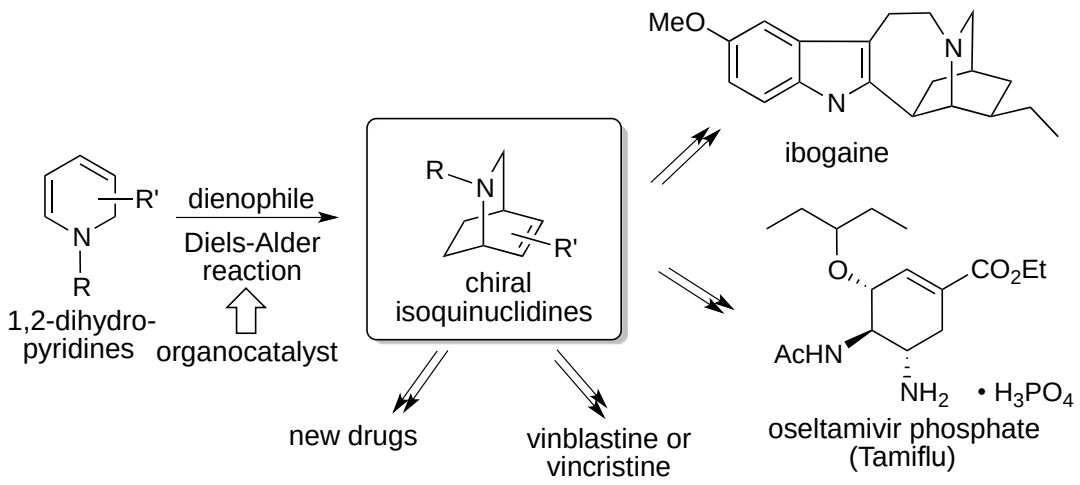


Scheme 1. Functionality of β-amino alcohols

2. ASYMMETRIC CYCLOADDITIONS USING β-AMINO ALCOHOL-BASED ORGANOCATALYSTS

2-1. Asymmetric Diels-Alder reaction of 1,2-dihydropyridines

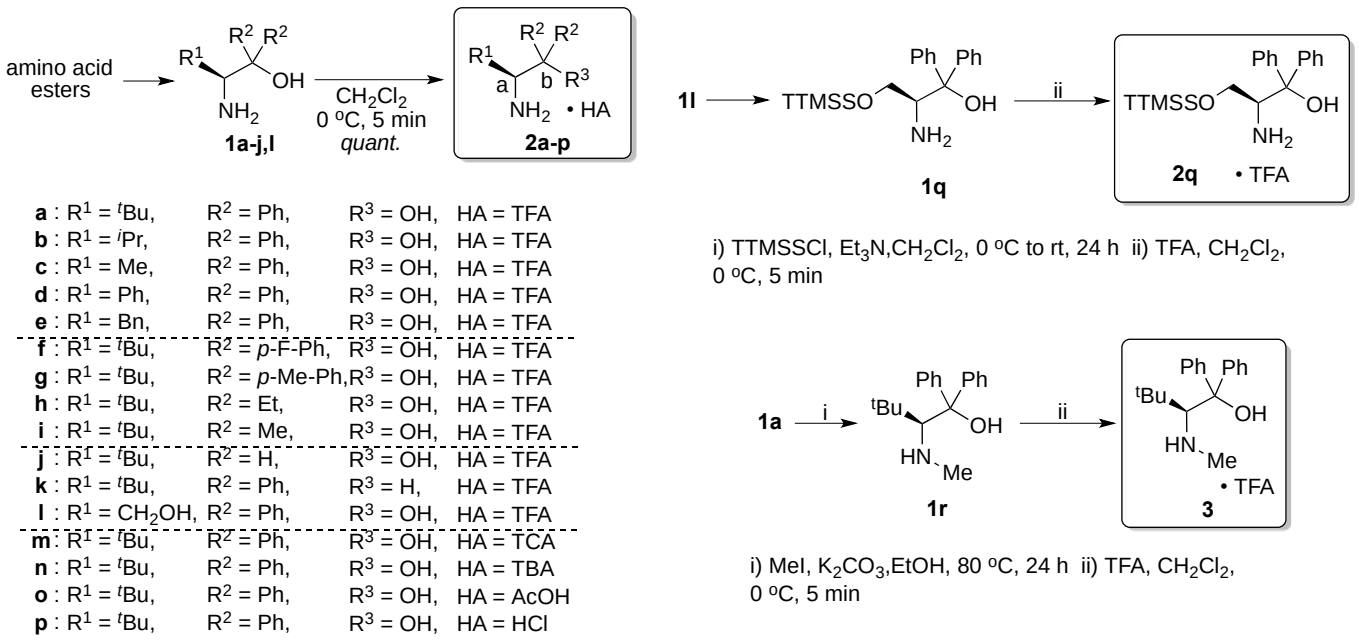
Isoquinuclidine derivatives obtained by the catalytic asymmetric Diels-Alder (DA) reaction using 1,2-dihydropyridines[4d-f] as diene are useful synthetic intermediates for various bioactive compounds,



Scheme 2. Utility of isoquinuclidines

including the anti-influenza drug Tamiflu and the anticancer drug vinblastine (Scheme 2).[5] Although Tamiflu has been widely used as an anti-influenza drug, a virus resistant to Tamiflu has been detected, which may make Tamiflu ineffective. Therefore, it is necessary to develop new drugs that are effective against the Tamiflu-resistant virus.[5d] We studied the synthesis of optically active isoquinuclidine derivatives by the catalytic asymmetric DA reaction of 1,2-dihydropyridines using β-amino alcohol salts as organocatalysts.

We examined the asymmetric catalytic activity of β-amino alcohol-based organocatalysts (Scheme 3) in the DA reaction of 1,2-dihydropyridines (diene) **4a-c** with various substituents on their rings with acrolein (dienophile) **5** (Scheme 4). Trifluoroacetate catalyst **2a** with a bulky *tert*-butyl group at the β-position afforded the desired *endo*-DA adducts (7*S*)-**6a**,**c** in good chemical yield and an almost complete enantioselectivity (**6a**: 98%, 96% ee, respectively; **6c**: 75%, 96% ee, respectively).

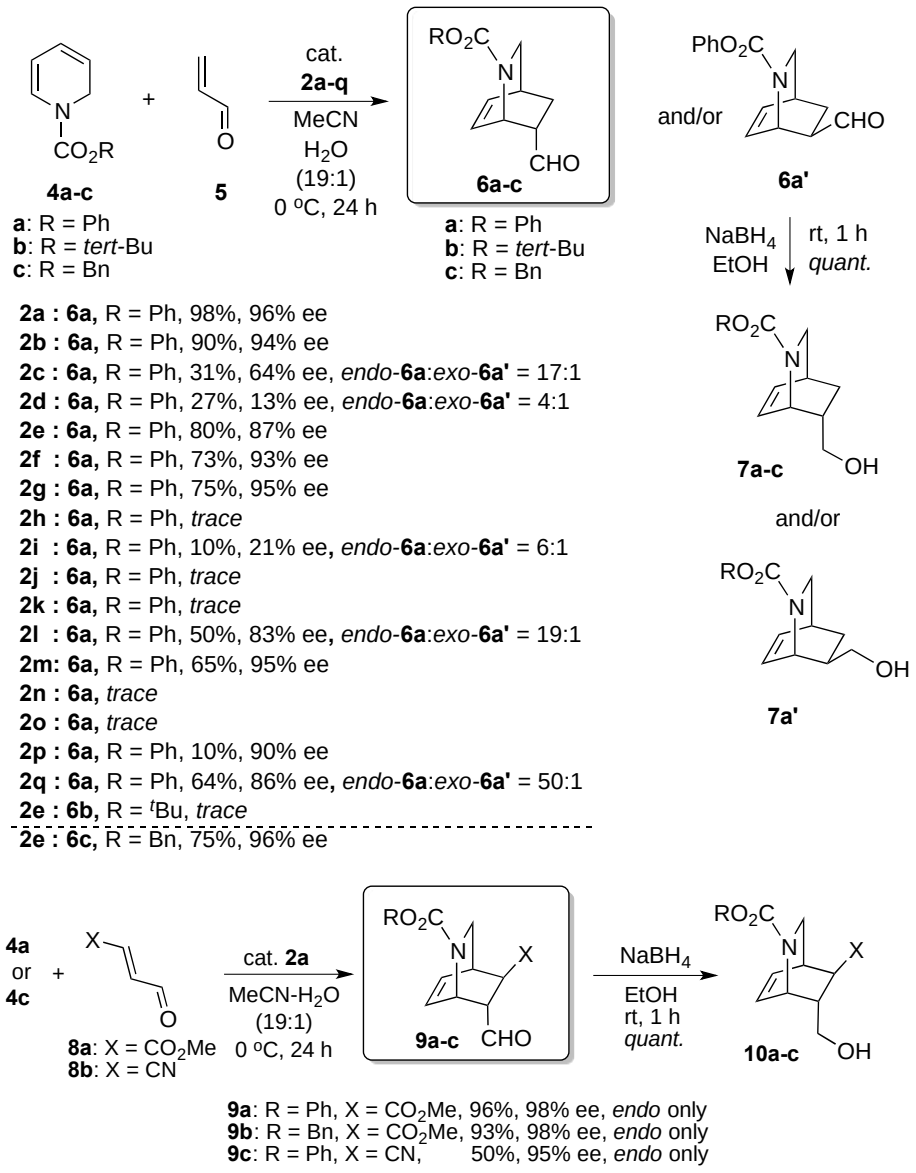


Scheme 3. Synthesis of β-amino alcohol organocatalysts

To expand the substrate applicability of the β-amino alcohol organocatalysts with good results, we examined the asymmetric DA reaction between 1,2-dihydropyridine derivatives **4a,c** and two dienals (methyl fumaraldehydate **8a** and 4-oxo-2-butenenitrile **8b**) used as dienophiles in the presence of **2a** (Scheme 4). First, the DA reaction between diene **4a** and dienophile **8a** was carried out. As a result, the desired DA adduct **9a** was obtained in an excellent chemical yield (96%) and almost complete enantioselectivity (98%). A similar reaction between diene **4c** and dienophile **8a** also successfully afforded the DA adduct **9b** in an excellent chemical yield (93%) and almost complete enantioselectivity

(98%). Furthermore, the reaction between diene **4a** and dienophile **8b** provided the desired DA adduct **9c** in a fair chemical yield (50%) and an excellent enantioselectivity (95%).

These results strongly suggest that the β-amino alcohol-based organocatalysts can be applied to various kinds of dienophiles in the arymmetric DA reaction, and this DA reaction can be used for the synthesis of optically active isoquinuclidine derivatives with several substituents on their rings, which are synthetic intermediates observed during the synthesis of Tamiflu analogs.

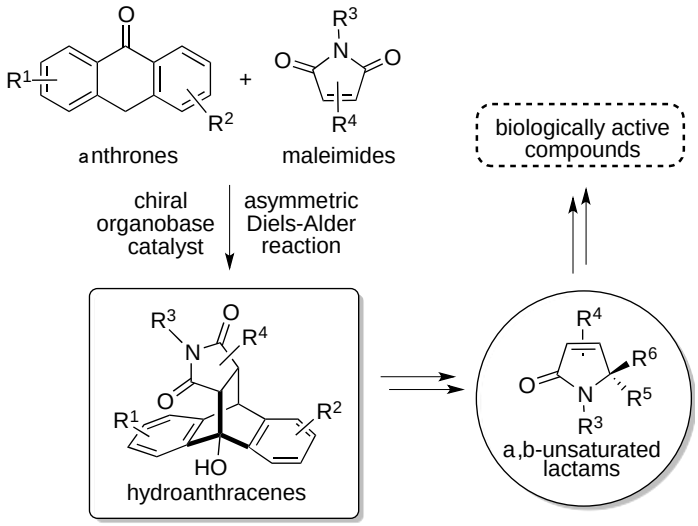


Scheme 4. Asymmetric DA reaction between 1,2-dihydropyridines with acrolein using β-amino alcohols

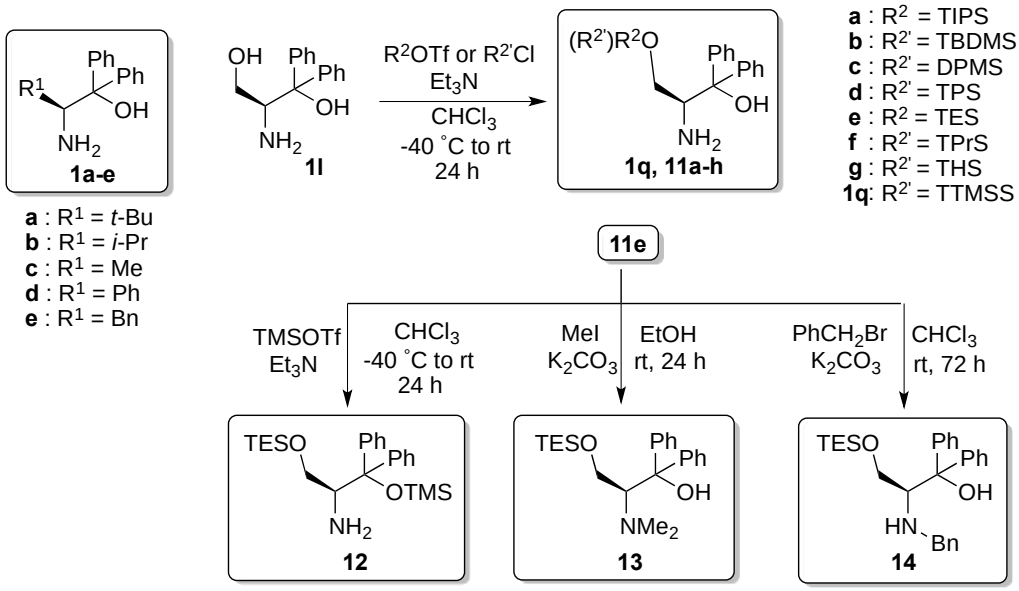
2-2. Asymmetric Diels-Alder reaction of anthrones

Research on organocatalysts acting as Brønsted bases (organic base catalysts) has been actively conducted in recent years. We focused herein on the use of β-amino alcohols as organic base catalysts and examined the asymmetric DA reaction[6] between anthrones (diene)[4c] and maleimides (dienophile) in

the presence of β-amino alcohols (Scheme 5). The hydroanthracenes obtained from the reaction were used as precursors for the synthesis of α,β-unsaturated lactams,[7] which are useful synthetic intermediates of various bioactive compounds, including medicines. Hence, it is very important to develop a DA reaction using organic base catalysts, which will afford hydroanthracenes in high optical purity.



Scheme 5. Utility of hydroxyanthracenes

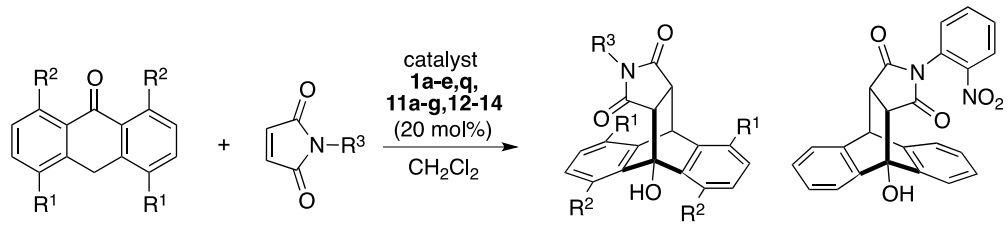


Scheme 6. Synthesis of β-amino alcohol organocatalysts

We designed and synthesized amino alcohol-based organic base catalysts by introducing bulky trialkylsilyl groups onto the oxygen atom at γ-position of amino alcohols (Scheme 6). We then examined the DA reaction using these organic bases.

The asymmetric catalytic activity of the synthesized β-amino alcohol-based organic base catalysts **1a-e**, **11a-g**, **1q**, **12-14**, was investigated in the DA reaction between anthrones **15**, **16a**,**b** (diene) and *N*-phenyl-maleimide **17** (dienophile) (Table 1). The reaction using catalyst **11e** with a triethylsilyl (TES) group on the γ-oxygen atom provided the best chemical yield and enantiomeric excess (92%, 42% ee, respectively, entry 1). The asymmetric DA reaction between anthrones **15**, **16a**,**b** and maleimides **17**, **18a-f** using catalyst **11e** was also examined (Table 1). The reaction, in which *N*-(2-nitrophenyl)maleimide **18d** was used as a dienophile, afforded the corresponding DA adduct **20d** in the best enantioselectivity (94% ee, entry 6). Interestingly, the configuration of **20d** was opposite to that of the products of other substrates, which suggested that the products with the desired configuration can be selectively synthesized by considering the characteristics of the β-amino alcohol-based organocatalysts and substrates and by changing the combination of the reactants to change their interaction.

Table 1. Asymmetric Diels-Alder reaction between anthrones and maleimides using β-amino alcohol organocatalysts



15, 16a,b **17, 18a-f** **19, 20a-c,e-h** **20d**

15 : $R^1 = R^2 = H$
16a : $R^1 = Cl$, $R^2 = H$
16b : $R^1 = H$, $R^2 = Cl$

17 : R^3 = Ph
18a : R^3 = Me
18b : R^3 = 4-Me-Ph
18c : R^3 = Bn
18d : R^3 = 2-NO_2-Ph
18e : R^3 = 3-NO_2-Ph
18f : R^3 = 4-NO_2-Ph

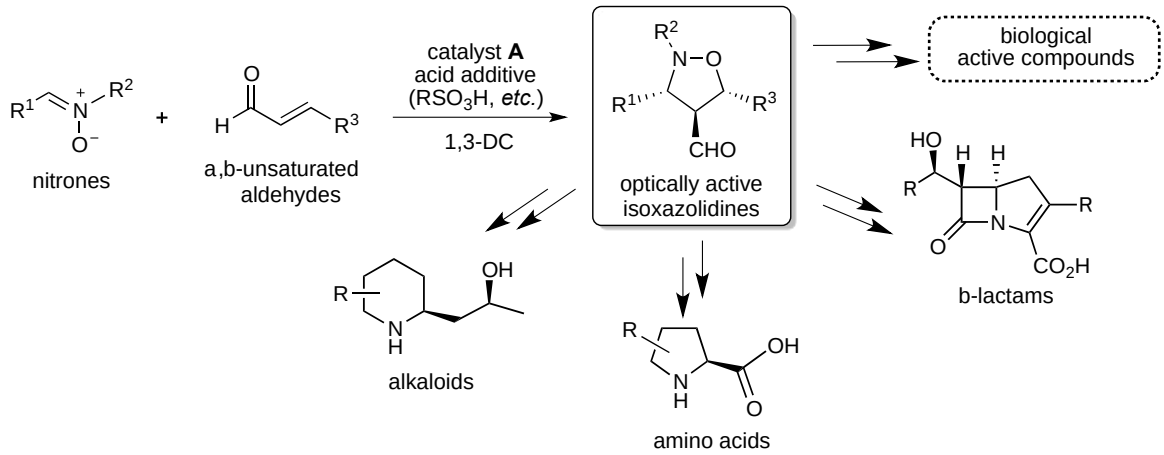
19 : $R^1 = R^2 = H$, R^3 = Ph
20a : $R^1 = R^2 = H$, R^3 = Me
20b : $R^1 = R^2 = H$, R^3 = 4-Me-Ph
20c : $R^1 = R^2 = H$, R^3 = Bn
20d : $R^1 = R^2 = H$, R^3 = 2-NO_2-Ph
20e : $R^1 = R^2 = H$, R^3 = 3-NO_2-Ph
20f : $R^1 = R^2 = H$, R^3 = 4-NO_2-Ph
20g : R^1 = Cl, R^2 = H, R^3 = Ph
20h : R^1 = H, R^2 = Cl, R^3 = Ph

entry	diene	dienophile	time (h)	temp. (°C)	DA adduct	yield (%)	ee (%) **19, 20a-c,e-h**	ee (%) **20d**
1	**15**	**17**	48	rt	**19**	92	42	
2	**15**	**18a**	48	rt	**20a**	97	39	
3	**15**	**18b**	48	rt	**20b**	91	32	
4	**15**	**18c**	48	rt	**20c**	93	46	
5	**15**	**18d**	48	rt	**20d**	97		66
6	**15**	**18d**	72	0	**20d**	83		94
7	**15**	**18e**	48	rt	**20e**	97	32	
8	**15**	**18f**	48	rt	**20f**	95	35	
9	**16a**	**17**	48	rt	**20g**	98	25	
10	**16b**	**17**	48	rt	**20h**	98	38	

2-3. Asymmetric 1,3-dipolar cycloaddition of nitrones

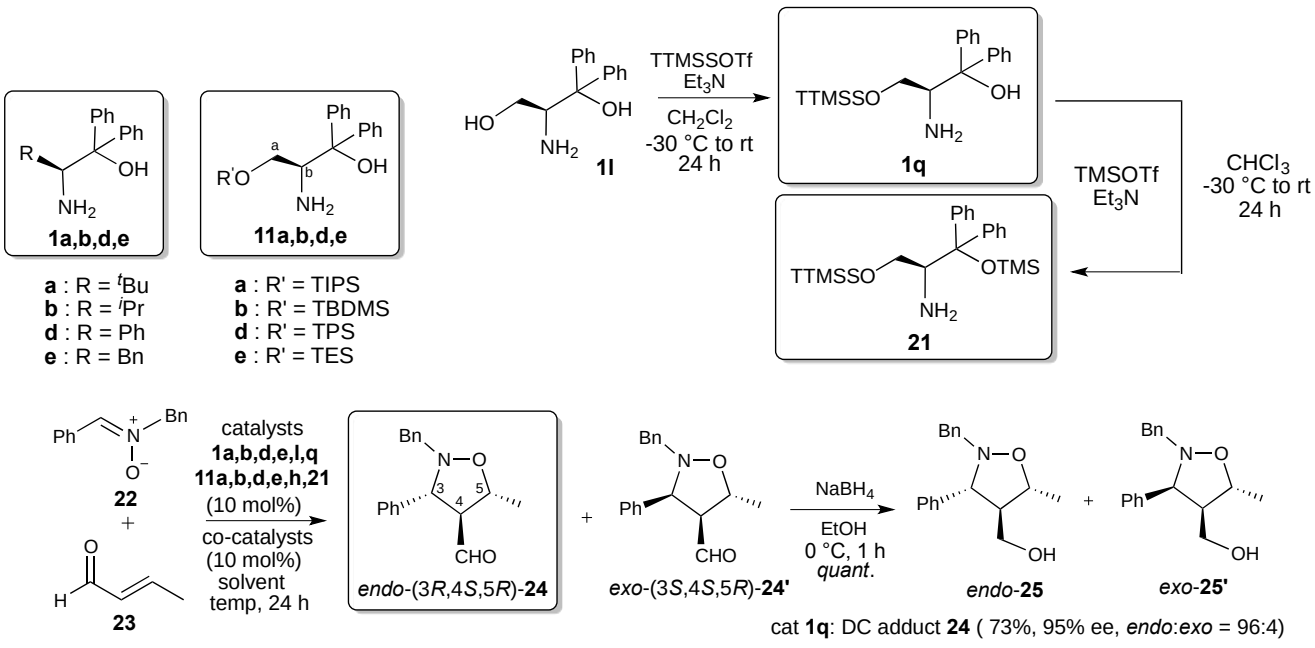
1,3-Dipolar cycloaddition (1,3-DC) is a useful reaction to synthesize optically active isoxazolidine derivatives.[4b] Isoxazolidines are useful chiral building blocks that lead to γ-amino alcohols, β-amino acids,

and β-lactams. Isoxazolidines are also known as the synthetic intermediates of various bioactive compounds, including medicines.[8] Therefore, we used amino alcohol-based organocatalysts for the asymmetric 1,3-DC reaction between nitrones and α,β-unsaturated aldehydes. We used β-amino alcohols as amino alcohol-based organocatalysts with a primary amino group and a bulky substituent at the γ-position (Scheme 7).



Scheme 7. Utility of isoxazolidine intermediates

We planned to examine this reaction using the following catalysts: amino alcohol catalysts with aliphatic or aromatic substituents at the β-position (**1a**,**b**,**d**,**e**); amino alcohol catalysts with bulky silyl groups at the γ-oxygen atom (**11a**,**b**,**d**,**e**); dihydroxy amino alcohol (**1l**), which is a precursor of the silylated catalysts;



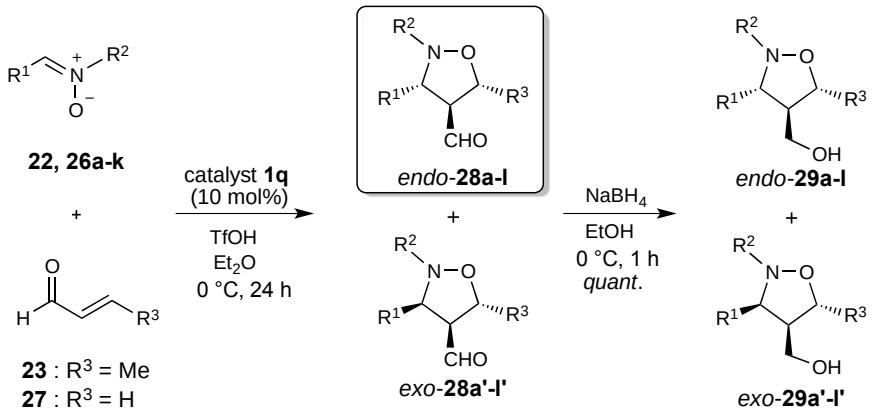
Scheme 8. 1,3-Dipolar cycloaddition of nitrones with α,β-unsaturated aldehydes using β-amino alcohol organocatalysts

amino alcohol with the most bulky supersilyl group [tris(trimethylsilyl) group (TTMSS group)] (**1q**); and the α-hydroxy group of **1q** masked with the TMS group (**21**) (Scheme 8).

The 1,3-DC reaction between nitrone **22** and α,β-unsaturated aldehyde **23** using the above mentioned amino alcohol catalysts was examined under various conditions (Scheme 8). The obtained adducts **24,24'** were converted into alcohols **25,25'** by using $NaBH_4$ to determine their chemical yields and the enantioselectivities. The reaction in the presence of **1q** having the bulkiest TTMSS group on the γ-oxygen atom and a co-catalyst trifluoromethanesulfonic acid (TfOH) provided the corresponding DC adduct *endo*-(3*R*,4*S*,5*R*)-**24** afforded in the best chemical yield and enantioselectivity (73%, 95% ee).

Next, to expand the substrate applicability of the amino alcohol catalyst, the 1,3-DC reaction between substituted nitrones **22**, **26a-k** and α,β-unsaturated aldehydes **23**,**27** in the presence of catalyst **1q** was examined (Table 2). All reactions afforded the corresponding DC adducts **28a-l** in good chemical yields and enantioselectivity. This finding suggested the broad applicability of the amino alcohol catalysts in this reaction.

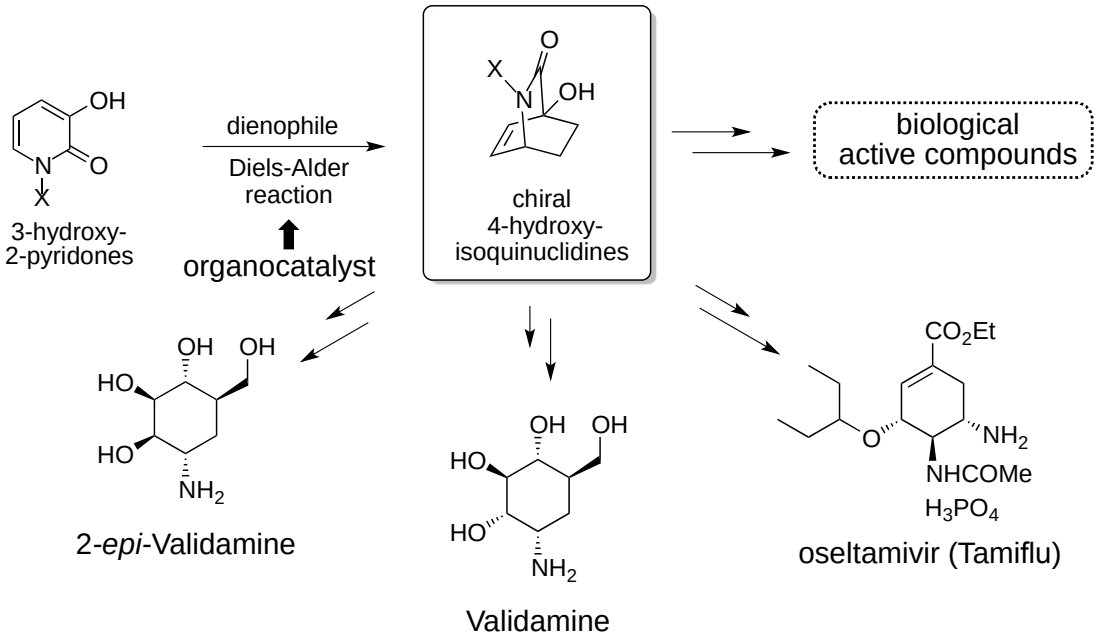
Table 2. 1,3-Dipolar cycloaddition between nitrones and α,β-unsaturated aldehydes using β-amino alcohol organocatalysts



entry	nitrone **22**,**26**	R^1	R^2	aldehyde	DC adduct **28**	yield (%)	*endo*/*exo*	*endo ee* (%)
1	**26a**	4-MePh	Bn	**23**	**28a**	67	95:5	94
2	**26b**	4-*i*PrPh	Bn	**23**	**28b**	75	96:4	64
3	**26c**	4-OMePh	Bn	**23**	**28c**	76	96:4	64
4	**26d**	4-ClPh	Bn	**23**	**28d**	59	89:11	89
5	**26e**	4-BrPh	Bn	**23**	**28e**	44	90:10	90
6	**26f**	2-ClPh	Bn	**23**	**28f**	49	93:7	93
7	**26g**	4-CF_3Ph	Bn	**23**	**28g**	58	92:8	62
8	**26h**	1-Naph	Bn	**23**	**28h**	59	92:8	71
9	**26i**	2-Naph	Bn	**23**	**28i**	63	92:8	92
10	**26j**	Ph	Me	**23**	**28j**	65	96:4	97
11	**26k**	4-ClPh	Me	**23**	**28k**	37	90:10	96
12	**22**	Ph	Bn	**27**	**28l**	79	61:39	70

2-4. Asymmetric Diels-Alder reaction of 3-hydroxy-2-pyridones

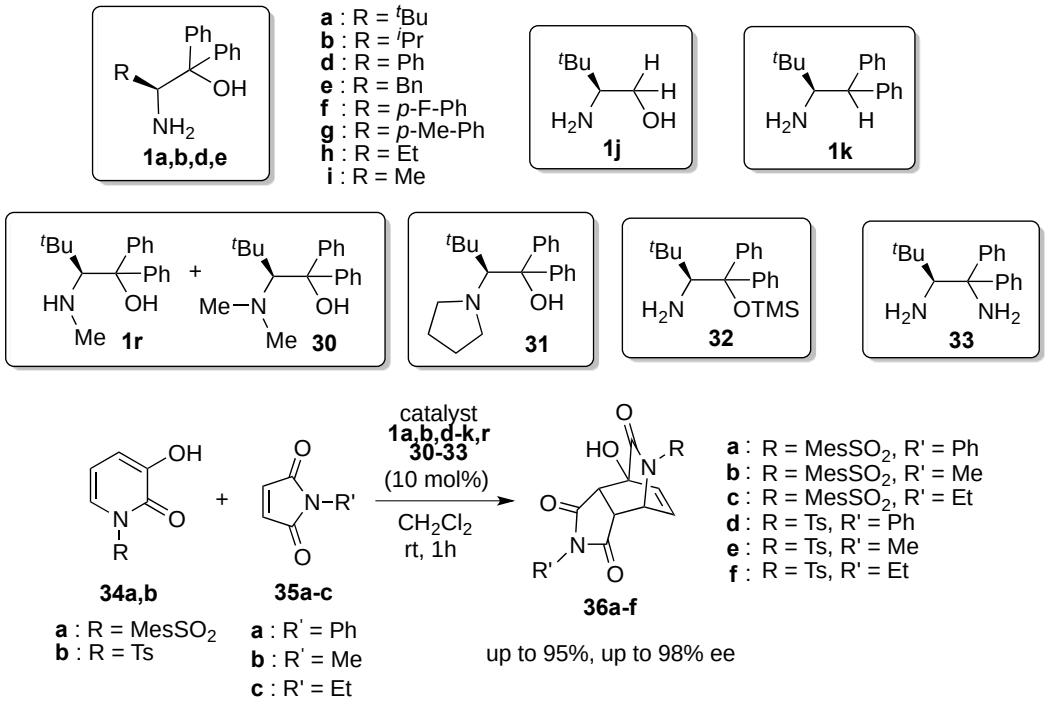
The DA reaction using 3-hydroxy-2-pyridones as diene is a useful reaction for providing 4-hydroxyisoquinuclidine derivatives which are synthetic intermediates for bioactive compounds such as the anti-influenza drug Tamiflu and the anti-glucosidase inhibitor Validamine, which show a glucosidase



Scheme 9. Utility of 4-hydroxy-isoquinuclidines

inhibitory activity, in a single step (Scheme 9).[9] However, almost no reports have been presented till date on this useful asymmetric DA reaction.[6a] We examined the asymmetric DA reaction using 3-hydroxy-2-pyridones[4a] as diene and β-amino alcohol organocatalysts as Brønsted bases to develop organocatalysts useful for this DA reaction (Scheme 10).

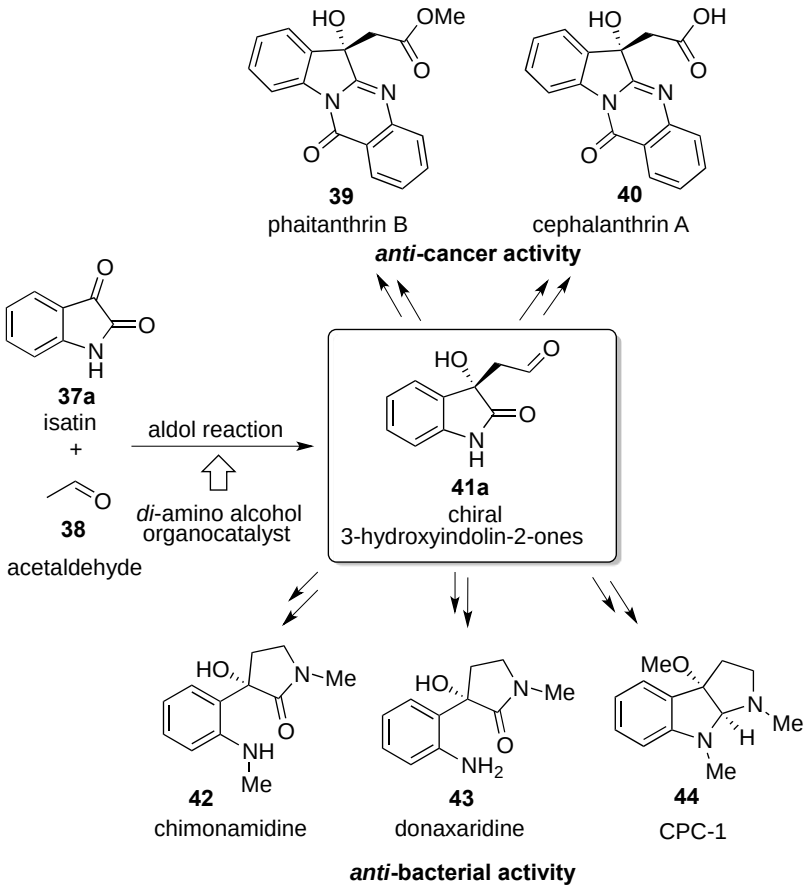
We examined the asymmetric DA reaction between 3-hydroxy-2-pyridones **34a**,**b** and maleimides **35a-c** in the presence of amino alcohol organocatalysts **1a**,**b**,**d-k**,**r**, **30-33** (Scheme 10). The DA reaction between pyridone **34b** and maleimide **35b** in the presence of catalyst **1a** with a *tert*-butyl group at the β-position afforded the desired isoquinuclidine derivative **36e** in an excellent chemical yield and almost complete enantioselectivity (95%, 98% ee, respectively). We are now trying to develop the new hybrid type anti-influenza drug candidates using the obtained DA adducts as the synthetic intermediates.



Scheme 10. DA reaction between 3-hydroxy-2-pyridones and maleimides using β-amino alcohol organocatalysts

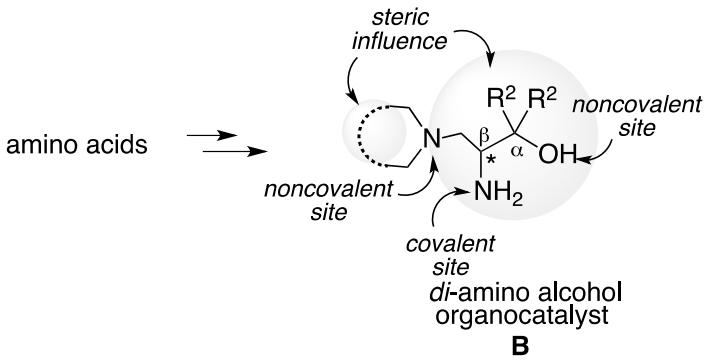
2-5. Asymmetric aldol reaction of isatins with acetaldehyde

The asymmetric aldol reaction is one of the important methods for carbon-carbon bond formation,[10] therefore, in the last decade, there is a significant progress in the development of enantioselective organocatalyzed aldol reaction of various aldehydes.[11] But the direct crossed aldol reaction of acetaldehyde, which is the simplest enolizable carbonyl compound, has been known to be a challenging task.[12,13] This reaction between acetaldehyde as a nucleophile and ketone as an electrophile has great significance since it results in a chiral quaternary carbon center, which is immensely valuable in synthetic chemistry.[14] Specifically, enantioselective crossed aldol reaction of isatin **37a** with acetaldehyde **38** is a straightforward method to acquire chiral 3-substituted 3-hydroxyindolin-2-one **41a**, which is a valuable building block for the synthesis of broad range of biologically important compounds (Scheme 11). Owing to its significance as a pharmacophore, in recent years, few research groups have developed the asymmetric crossed aldol reaction of acetaldehyde with isatins to afford 3-substituted 3-hydroxyindolin-2-one derivatives **41**[15] that are versatile synthetic intermediate for the synthesis of tryptanthrin architecture based indoloquinazoline alkaloids, phaitanthrin B **39** and cephalanthrin A **40**, isolated recently from *Phaius mishmensis* (Orchidaceae)[16a] and *Cephalantheropsis gracilis*,[16b] with potential anticancer and antiviral activities.[16,17] Furthermore, the intermediate **41a** were expected to work for the synthesis of *anti*-bacterial indolidine alkaloids such as chimonamidine **42**, donaxaridine **43** and CPC-1 **44**.



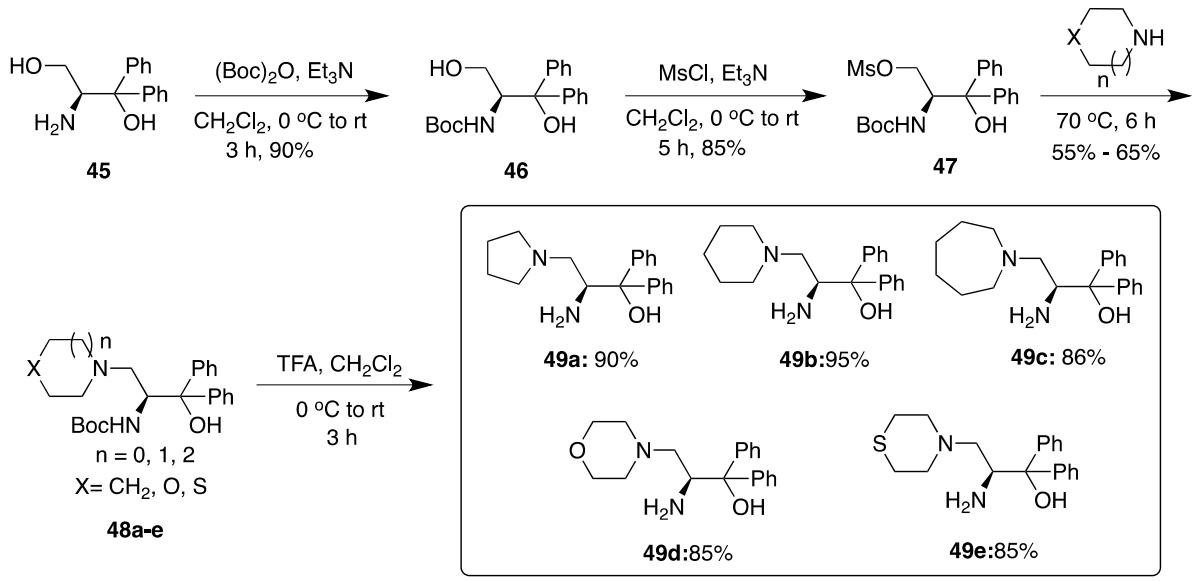
Scheme 11. Utility of 3-hydroxyindolin-2-ones

We designed and prepared a series of new type of *di*-amino alcohols **B** (Scheme 12) with two kinds of covalents and a non-covalent bonding and steric influence sites for the enantioselective crossed aldol reaction of isatin **37a** with acetaldehyde **38**. These new type of *di*-amino alcohols **B** might coordinate with acetaldehyde **38** through enamine formation and with isatin **37a** through hydrogen bonding between carbonyl oxygen of isatin and cationized nitrogen of pyrrolidine ring of the ethenamine derivative. Moreover, we also tried the total synthesis of biologically active compounds **39-43** and the formal synthesis of **44** *via* intermediate **41** that is obtained from the reaction of **37a** with **38**.



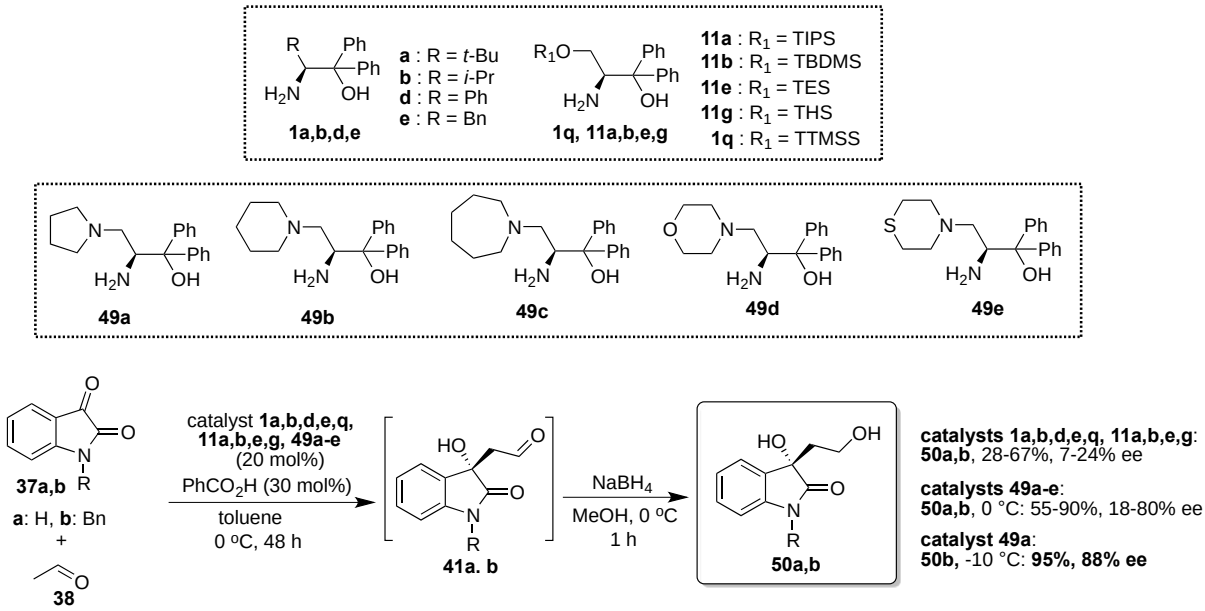
Scheme 12. Functionality of *di*-amino alcohol organocatalysts

New catalyst was prepared by the following methodology. The protection of primary amine of compound **45** with $(Boc)_2O$ followed by masking of primary hydroxy group with mesyl chloride afforded compound **46** in good yield. Subsequently, the substitution reaction of mesylate **47** with various cyclic amines (pyrrolidine, piperidine, azepane, morpholine and thiomorpholine) under neat reaction conditions provided **48a-e** in moderate to good yields. Finally, deprotection of Boc group of **48a-e** by treating with TFA furnished the targeted new type of multifunctional organocatalysts **49a-e** in good overall yields (Scheme 13).



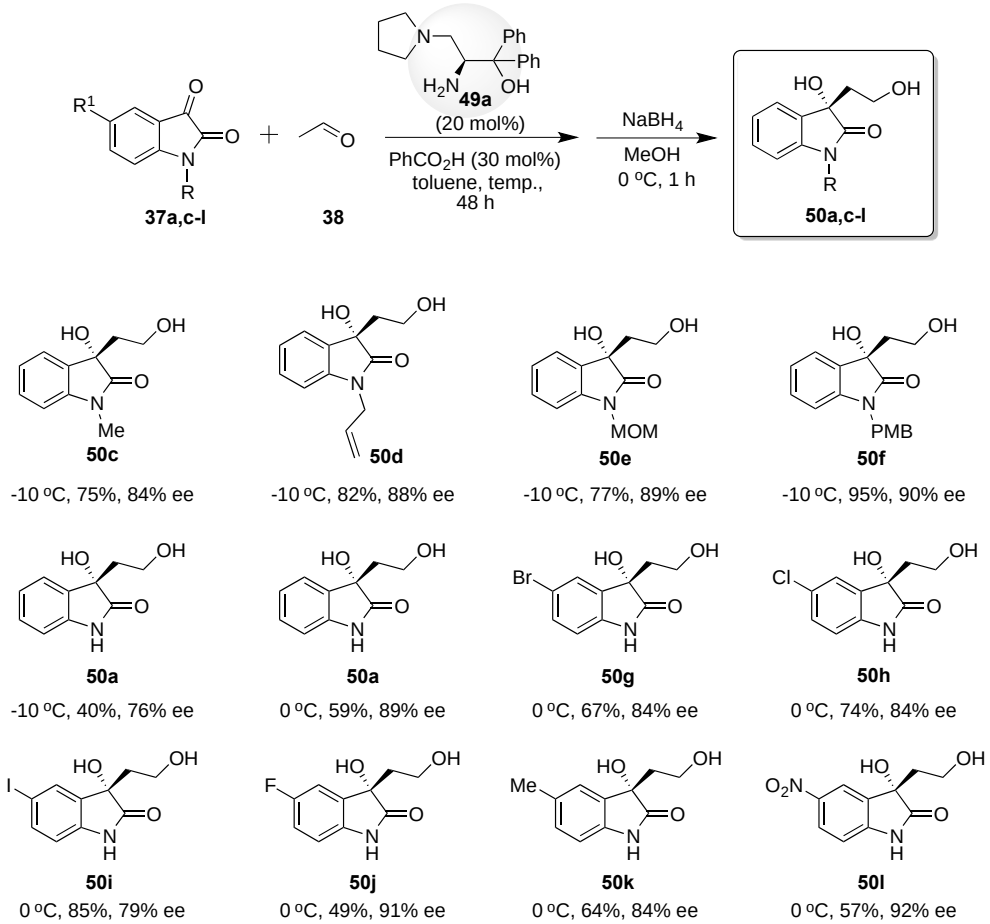
Scheme 13. Preparations of new *di*-amino alcohol organocatalysts

We examined the aldol reaction of isatins **37a,b** with acetaldehyde **38** in the presence of usual amino alcohols **1a,b,d,e,q, 11a,b,e,g** and new desired *di*-amino alcohol catalysts **49a-e** (Scheme 14). The obtained adducts **41a,b** were changed to alcohols **50a,b** by $NaBH_4$ reduction to determine the chemical yield and enantioselectivity. As a result, the usual amino alcohol catalysts **1, 11** did not work effectively in this reaction (up to 67%, up to 24% ee). On the other hand, the new designed *di*-amino alcohol catalysts **49** showed good catalytic activity (up to 90%, up to 80% ee) in this reaction. Especially, the use of catalyst **49a** bearing pyrrolidine ring showed an excellent asymmetric catalytic activity in this reaction at lower temperature (-10 °C) led to the aldol product **50b** in excellent yield (95%) and good enantioselectivity (88% ee). Although the several reaction conditions for improving the chemical and optical yield of the desired aldol product **50b** using the superior catalyst **49a** were examined, unfortunately, no improvement was observed regarding either chemical yield or optical yield than the previous obtained results (95%, 88% ee).



Scheme 14. Aldol reaction using *di*-amino alcohol organocatalysts

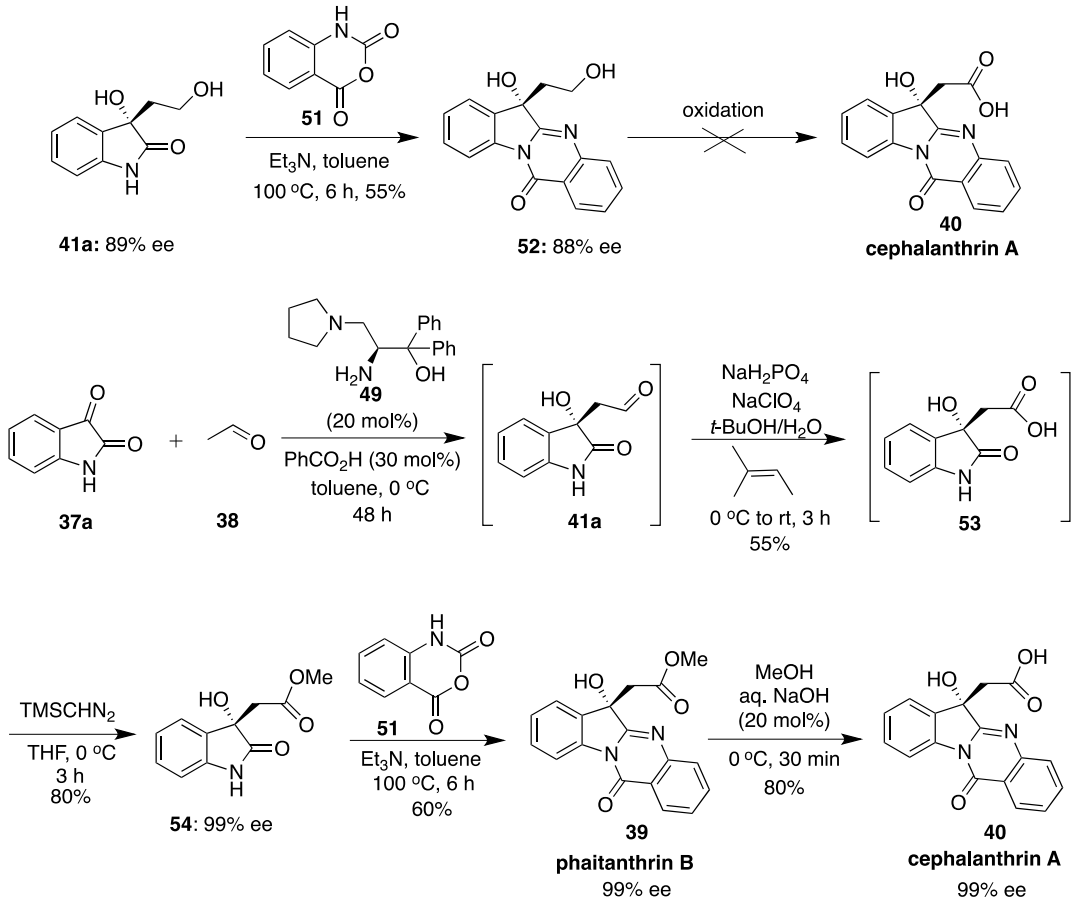
This superior catalyst applied to the reactions using some isatins and acetaldehyde under the optimized



Scheme 15. Substrate scope of crossed-aldol reaction

conditions (Scheme 15). All reactions smoothly proceeded and afforded the corresponding aldol products in good chemical yields and enantioselectivities. Thus *N*-protected isatins such as *N*-methyl, *N*-allyl, *N*-MOM and *N*-PMB isatins **37c-f** afforded the corresponding aldol products **50c-f** in good chemical and optical yields (up to 75-95%, up to 84-90% ee). Isatin **37a** was also tested using catalyst **49a**, which is essential for utility of this method effectively for natural product synthesis. The respective product **50a** was afforded with good enantioselectivity (76% ee). Furthermore, the temperature from -10 °C to 0 °C afforded the product **50a** with notable improvement in chemical yield (59%) and enantioselectivity (89% ee). Halogen-substituted isatins **37g-j**, were also compatible with this protocol and satisfactory results were obtained (up to 49-85%, up to 79-91% ee). Moreover, 5-methylisatin **37k** afforded the product **50k** in moderate yield and selectivity (64%, 84% ee). The best result was obtained with 5-nitrisatin **37l** to afford the corresponding product **50l** (57%, 92% ee).

From these satisfactory results in hand, we aimed our attention towards total synthesis of biologically active natural products (Scheme 16). We attempted for direct synthesis of cephalanthrin A **40** from the aldol product **41a**. Condensation of diol **41a** with isatoic anhydride **51** yielded the coupled product **52** in

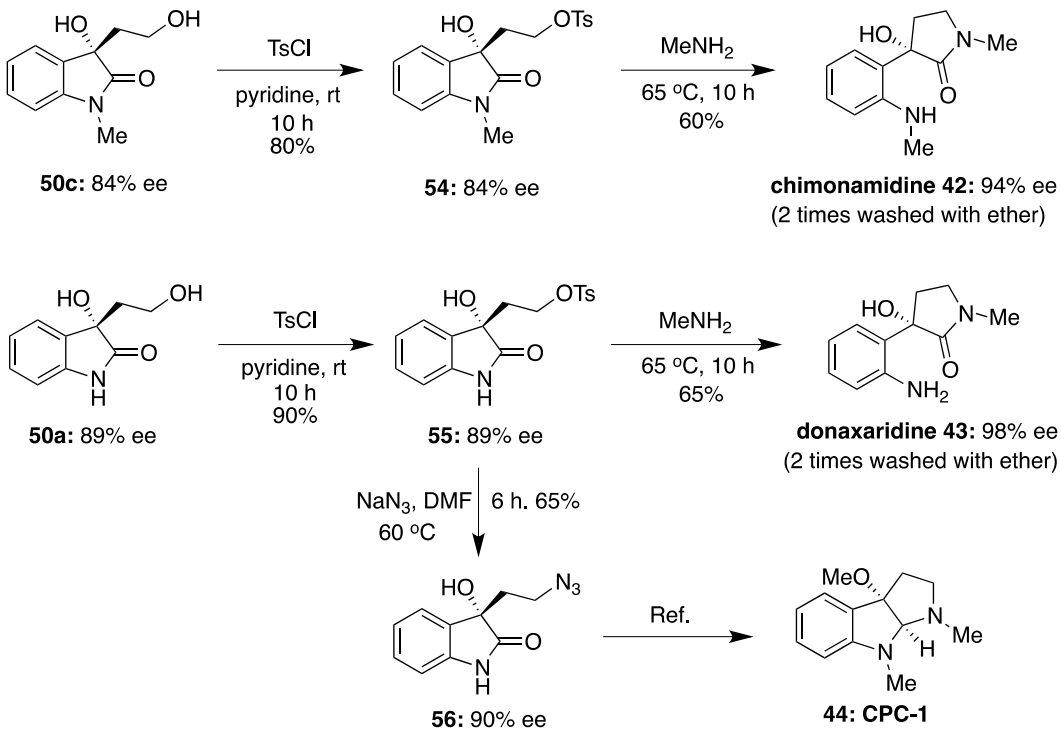


Scheme 16. Total synthesis of phaitanthrin B and cephalanthrin A

moderate chemical yield without loss of enantioselectivity (88% ee). Then, we anticipated that oxidation of primary alcohol of **52** could result in cephalanthrin A **40**. However, the oxidation conditions using TEMPO/BAIB did not afford the desired product. Also, the use of either Jones reagent,[18] $KMnO_4$ in strong alkali condition[19] or Cornforth reagent,[20] unfortunately, did not result in the desired product **40** (Scheme 5).

After these failed attempts, synthetic route was changed. Pinnick oxidation[21] of aldehyde **41a** (aldol product), followed by esterification by treating with $TMSCHN_2$ afforded the *β*-hydroxy ester **54** in good yield without loss of enatioselectivity. Condensation of **54** with isatoic anhydride **51** offered the targeted phaitanthrin B **39** without affecting the enantioselectivity. Afterwards, cephalanthrin A **40** was conveniently obtained from phaitanthrin B **39** by its treatment with base. After single recrystallization in diethyl ether the two targeted molecules phaitanthrin B **39** and cephalanthrin A **40** were obtained in 99% ee.

We next synthesized the proposed 3-hydroxy-2-oxindole derived natural products. Tosylated product **54** was obatained by treatment of diol **50c** with tosyl chloride. Tosylate **54** was then converted to the desired (*S*)-chimonamidine **42** by treatment with methylamine under refluxing conditions. Following the same path, donaxaridine **43** was also obtained from **50a** through tosylation followed by treatment with



Scheme 17. Total synthesis of chimonamidine, donaxaridine and formal synthesis of CPC-1

methylamine. The resulted final compounds *i.e.* chimonamidine **42** and donaxaridine **43** were washed with diethyl ether (two times) to increase to the sufficient *ee* values (chimonamidine **42:** 94% *ee*,

donaxaridine **43:** 98% *ee*). Azidation of tosylate **55** using NaN_3 yielded the azide **56** in good yield without loss of enantioselectivity. CPC-1 **44** could be synthesized from **56** *via* reported procedure (Scheme 17).[15c]

3. CONCLUSION

Up to this point, we have described the synthesis of the β-amino alcohol organocatalysts that we developed and their applications to asymmetric additions. Our catalysts showed excellent asymmetric catalytic activity in each reaction we tried. We will apply our catalysts to other asymmetric catalytic reactions to find further usefulness. We are also trying to develop the novel bioactive compounds, including anti-influenza drug candidates that can be synthesized from the chiral asymmetric adducts obtained from the reactions that we examined.

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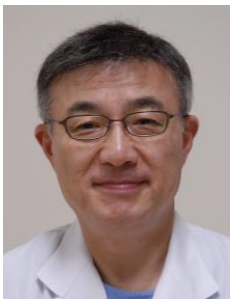

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