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# Simple organocatalyst component system for asymmetric hetero Diels–Alder reaction of isatins with enones†

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A simple two catalyst component system consisting of primary  $\beta$ -amino alcohols as a catalyst and amino acids as a co-catalyst put together works as an efficient organocatalyst system in the hetero Diels–Alder reaction of isatins with enones to afford the chiral spirooxindole–tetrahydropyranones in good chemical yields and stereoselectivities (up to 86%, up to 85 : 15 dr., up to 95% ee).

## 1. Introduction

Spirooxindoles **A** are considered to be promising scaffolds in drug discovery.<sup>1</sup> The structure of **A** is contained in many compounds having pharmacological activities such as contraceptive,<sup>2</sup> anti-HIV,<sup>3</sup> anticancer,<sup>4</sup> antituberculosis,<sup>5</sup> antimalarial,<sup>6</sup> and antiproliferative drugs.<sup>9</sup> Therefore, the development of an effective strategy for the preparation of highly optically pure spirooxindole **Z** is a significantly challenging task in research.<sup>1</sup> The hetero Diels–Alder (HDA) reaction is a versatile tool for effectively forming heterocyclic compounds.<sup>7</sup> Especially, the catalytic asymmetric version of this reaction is the most efficient and convenient method for constructing a chiral heterocyclic skeleton, which acts as a precursor for many biologically active compounds and drugs.<sup>8</sup> In this class of HDA reactions, the reaction of isatins **X** with enones **Y** is one of the superior organic transformations for providing unique chiral spirooxindole–tetrahydropyranones **Z** containing quaternary chiral carbon center on the structure (Scheme 1).<sup>9</sup> Most recently, Tanaka and co-workers have reported an efficient organocatalyzed asymmetric HDA reaction of **X** with **Y** using three catalysts component system being composed with chiral amine as a catalyst, amino acid and thiourea as co-catalysts for affording Spirooxindole **Z** with satisfactory chemical yield and stereoselectivity (Scheme 1).<sup>9</sup> However, the favourable

geometric combination of three catalysts system of complex chiral cinchona alkaloid **A** as a catalyst and both the prepared complex chiral amino acids **B** and thioureas **C** as co-catalysts require time and effort for controlling the enantioselective reaction course for obtaining satisfactory chemical yield and stereoselectivity. Therefore, the development of a more convenient and easier catalytic component system for this versatile reaction is deeply required significantly.

Based on these backgrounds, we have designed a simple two catalysts component system for this reaction (Scheme 1). About the catalysts system, we focused on a concept of the combination of simple  $\beta$ -amino alcohol **D** as an organocatalyst for the generation of a diene species and common simple amino acid **E** as a co-catalyst for the activation of isatin substrate acting as



**Scheme 1** Asymmetric HDA reaction of isatins with enones using catalysts component system.

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Scheme 2 Concept of our two catalysts component system.

a dienophile comparatively to the complex catalyst system of Tanaka and co-workers having one catalyst and two co-catalysts. Recently, we have reported that simple  $\beta$ -amino alcohols **D** and their derivatives work as an efficient organocatalyst in various asymmetric reactions.<sup>10</sup> As an advantage of catalyst **D**, it can be easily prepared from commercially available amino acids in a single step and also contains the primary amino group as covalent site, hydroxyl group as a non-covalent site and steric influence site in the single molecule (Scheme 2). Furthermore, simple amino acids as co-catalyst are commercially available. Therefore, combined these properties of amino alcohols as a catalyst and amino acids as a co-catalyst may enable the formation of a simple catalytic component system. This organocatalysed asymmetric HDA reaction might proceed *via* transition state II (comparing to Tanaka's proposed reaction course I)<sup>9</sup> in which the diene species **D'** is formed by the reaction of primary amino group on catalyst **D** with enones **Y**, and then isatin dienophile **X** is activated by amino acids co-catalyst **E** by the two points of hydrogen bonding interactions (Scheme 2). In this transition state II, diene species **D'** might attack stereoselectively from less sterically hindered site of the incoming generated dienes to afford the chiral spirooxindoles **Z**.

Herein, we describe a simple two catalysts component system, primary  $\beta$ -amino alcohols **D** having only one chiral carbon center on the molecule as a catalyst and simple non-chiral *N*-protected amino acids **E** as a co-catalyst, together acts as an efficient component organocatalysts system in the HDA reaction of **X** with **Y** to afford the chiral **Z** in good chemical yields (up to 86%) and with excellent stereoselectivities (up to 85 : 15 dr., 95% ee).

## 2. Results and discussion

### 2.1. Preparations of catalysts 2a-e and 4a-e

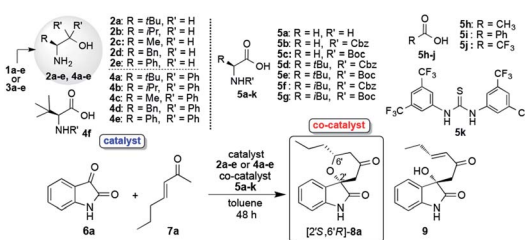
$\beta$ -Amino alcohol organocatalysts **2a-e** and **4a-e** were easily prepared by the reductions of the corresponding amino acids **1a-e** and Grignard reactions of the corresponding amino esters **3a-e**, respectively (Table 1).<sup>10a</sup> Furthermore, *N*-Cbz- and *N*-Boc-amino acids **5b-g** as co-catalyst were also easily derived from the corresponding commercially available non-protected amino acids.

### 2.2. Screening of catalysts 2a-e and 4a-e

Firstly, we examined the HDA reaction of isatin **6a** as a dienophile with heptene-2-one **7a** as a diene source, using only amino alcohol organocatalysts **2a** with primary hydroxyl methyl or **4a** with bulkier hydroxyl diphenylmethyl groups (entries 1 and 2, Table 1). The reaction was carried out with catalysts **2a** or **4a** in toluene at room temperature for 48 h for comparison with the catalytic efficiency of three catalysts component system by Tanaka and co-workers.<sup>9</sup> Simple amino alcohol **2a** showed good catalytic activity in this reaction and the corresponding HDA adduct [2'*S*,6'*R*]-**8a** was obtained in excellent enantioselectivity (92% ee) and with good diastereoselectivity (85 : 15), although the chemical yield was extremely low (15%) (entry 1). On the other hand, the use of bulkier amino alcohol catalyst **4a** did not show catalytic activity in this reaction condition (entry 2). These results deeply suggested the necessity of co-catalyst for the activation of isatin dienophile, and also the structure of amino alcohol catalyst may be important for showing a good catalytic activity.

Just in case, the catalytic activity of amino acid **1a** (*L*-*tert*-leucine) with the primary amino group for generating diene species was also examined under the same reaction condition (entry 3). However, its catalytic activity was not confirmed at all, for a reason that neutral amino acids exist in betaine form which might not work for the generation of the diene species. The most curious thing is that enantioselectivity was controlled almost completely (92% ee) to afford the HDA adduct **8a** using simple small  $\beta$ -amino alcohol molecules independently. Thus, amino alcohol alone worked as a catalyst for almost completely shielding one side of the enantiotopic face when diene attack to dienophile. These results indicated the necessity of our two catalysts component system comprising of amino alcohol catalyst for generating diene species and for controlling stereoselective reaction course and amino acid co-catalyst for activating isatin dienophile. Based on the results in entries 1 and 3, we next examined this reaction using the combinations of catalyst **2a** (20 mol%) with amino acids **5a-g** or common organic acids **5h-j** as co-catalysts (40 mol%) at room temperature for 48 h (entries 4–13). First, the reaction using the simplest amino acid **5a** having free amino group as a co-catalyst was carried out in the presence of catalyst **2a** (entry 4). Contrary to expectation, neutral acid **5a**, which hardly worked as co-catalyst for activating of isatin dienophile **7a**, showed excellent enantioselectivity (95% ee) with good diastereoselectivity, although chemical yield was quite low (14% ee). Interestingly, the use of **2a** and **5a** combined together increased the enantioselectivity (95% ee) then the result (92% ee) of the independently use of amino alcohol **2a** (entry 1). Amino acid **5a** might act as steric factor for controlling the attacking direction of diene to afford **8a** with superior enantioselectivity. Next, we tried the combinations of superior catalyst **2a** with other *N*-protected amino acids **5b-g** or common organic acids **5h-j** as co-catalysts in this reaction condition (entries 5–13). All of co-catalysts **5b-g** assisted the progress of the reaction for affording chiral **8a** with moderate to good results. Especially, highly satisfactory results for chemical yields and stereoselectivities were obtained when

Table 1 Catalyst screening of HDA reaction



| Entry | Enone 7a, (eq.) | Cat. 2a–e, 4a–e (mol%) | Co-cat. 5a–k (mol%) | Temp. (°C) | Yield <sup>a</sup> (%) | dr <sup>b</sup> | Ee <sup>c</sup> (%) |
|-------|-----------------|------------------------|---------------------|------------|------------------------|-----------------|---------------------|
| 1     | 4               | 2a (20)                | —                   | rt         | 15                     | 85 15           | 92                  |
| 2     | 4               | 4a (20)                | —                   | rt         | trace                  | —               | —                   |
| 3     | 4               | 1a (20)                | —                   | rt         | —                      | —               | —                   |
| 4     | 4               | 2a (20)                | a (40)              | rt         | 14                     | 75 25           | 95                  |
| 5     | 4               | 2a (20)                | b (40)              | rt         | 80                     | 79 21           | 91                  |
| 6     | 4               | 2a (20)                | c (40)              | rt         | 86                     | 80 20           | 92                  |
| 7     | 4               | 2a (20)                | d (40)              | rt         | 61                     | 82 18           | 88                  |
| 8     | 4               | 2a (20)                | e (40)              | rt         | 87                     | 81 19           | 87                  |
| 9     | 4               | 2a (20)                | f (40)              | rt         | 90                     | 82 18           | 88                  |
| 10    | 4               | 2a (20)                | g (40)              | rt         | 97                     | 75 25           | 84                  |
| 11    | 4               | 2a (20)                | h (40)              | rt         | 68                     | 75 25           | 86                  |
| 12    | 4               | 2a (20)                | i (40)              | rt         | 68                     | 84 16           | 87                  |
| 13    | 4               | 2a (20)                | j (40)              | rt         | tra                    | —               | —                   |
| 14    | 4               | 2a (20)                | k (40)              | rt         | 19                     | 73 27           | 75                  |
| 15    | 4               | 2b (20)                | c (40)              | rt         | 16                     | 75 25           | 86                  |
| 16    | 4               | 2c (20)                | c (40)              | rt         | 66                     | 55 45           | 72                  |
| 17    | 4               | 2d (20)                | c (40)              | rt         | 78                     | 64 36           | 81                  |
| 18    | 4               | 2e (20)                | c (40)              | rt         | 61                     | 50 50           | 88                  |
| 19    | 4               | 4b (20)                | c (40)              | rt         | 14                     | 75 25           | 24                  |
| 20    | 4               | 4c (20)                | c (40)              | rt         | 18                     | 74 26           | 41                  |
| 21    | 4               | 4d (20)                | c (40)              | rt         | 28                     | 83 17           | 14                  |
| 22    | 4               | 4e (20)                | c (40)              | rt         | 24                     | 78 22           | 6                   |
| 23    | 2               | 2a (20)                | c (40)              | rt         | 47                     | 77 23           | 90                  |
| 24    | 1               | 2a (20)                | c (40)              | rt         | 17                     | 73 27           | 89                  |
| 25    | 4               | 2a (20)                | c (40)              | 0          | 56                     | 81 19           | 93                  |
| 26    | 4               | 2a (20)                | c (20)              | rt         | 54                     | 78 22           | 89                  |
| 27    | 4               | 2a (20)                | c (10)              | rt         | 52                     | 79 21           | 87                  |
| 28    | 4               | 2a (10)                | c (10)              | rt         | 54                     | 77 22           | 89                  |
| 29    | 4               | 2a (10)                | c (20)              | rt         | 60                     | 88 19           | 89                  |
| 30    | 4               | 2a (10)                | c (5)               | rt         | 52                     | 79 21           | 87                  |

<sup>a</sup> Isolated yield. <sup>b</sup> Diastereoselectivity (dr) was determined by <sup>1</sup>HNMR of the crude reaction mixture (major diastereomer: **8a**). <sup>c</sup> The ee value were determined by HPLC (Daicel chiralpak IB column).

the reactions were carried out in the presence of simple non-chiral amino acids, *N*-Cbz-protected **5b** and *N*-Boc-protected **5c** with good chemical yields and stereoselectivities (**5b**: 80%, 79 : 21 dr., 91% ee, **5c**: 86%, 80 : 20, 92% ee) (entries 5 and 6). On the other hand, the uses of common organic acids **5h**, **i** brought about the decrease of chemical yield, even though good stereoselectivities were obtained (entries 11 and 12). Furthermore, strongest trifluoro acetic acid (TFA) **5j** did not work as a co-catalyst in this reaction condition (entry 13). Moreover, thioureas **5k** that was used as co-catalyst in Tanaka's three catalysts component system<sup>9</sup> was also applied with amino alcohol organocatalyst **2a** in this reaction. However, this component system of **2a** and **5k** did not work effectively in this reaction (19%, 73 : 27 dr., 75% ee) (entry 14). In addition, three

catalysts component system of catalyst **2a** and co-catalysts of both amino acid **5c** and thiourea **5k** also did not show better catalytic activity (85%, 75 : 25 dr., 82% ee) than two catalysts component system of **2a** and **5c** (86%, 80 : 20 dr., 92% ee). We next examined the reaction of **6a** with **7a** in the presence of  $\beta$ -amino alcohols **2b–e** (20 mol%) as catalysts along with superior simple non-chiral *N*-Boc-amino acid **5c**, as a co-catalyst (40 mol%) in this reaction condition (entries 15–18). Although, all catalysts combination systems, of catalysts **2b–e** and co-catalyst **5c** showed good catalytic activities to afford the HDA adduct **8a** with moderate to good chemical yields, diastereoselectivities and enantioselectivities, but showed inferior results compared to catalyst **2a** and co-catalyst **5c** (entry 6). Moreover, the utility of combination of the catalysts bulkier



amino alcohol catalysts **4a–e** and superior simplest non-chiral *N*-Boc-amino acid co-catalyst **5c** were also examined in this reaction condition (entries 19–22). However, better catalytic activities were not confirmed at all than that of the combination of simple catalysts **2a–e** with a primary hydroxyl group and **5c** (entry 6). From these results, it was revealed that the best catalyst combination was  $\beta$ -amino alcohols **2a** with primary hydroxyl group as a catalyst and non-chiral *N*-Boc-amino acid as a co-catalyst **5c**. Next, the ratio of substrate amounts **6a** and **7a** (**6a** : **7a** = 1 : 2 and **6a** : **7a** = 1 : 1) were examined in the presence of optimised **2a** and co-catalyst **5c** under same reaction condition (entries 23 and 24). However, these results displayed considerable decrease in chemical yields and the reaction temperature performed at 0 °C also showed a large decrease in chemical yield up to 56% (entry 25). Next, we examined the molar ratio of catalyst **2a** and co-catalyst **5c** in this reaction of **6a** with **7a** (4 equiv.) at room temperature (entries 26–30). Satisfactory enantioselectivities and diastereoselectivities were confirmed under all of the molar ratios of **2a** and **5c**. However, chemical yields comparatively decreased when the reaction was carried out under the molar ratio of 20 mol% of catalyst **2a** and 40 mol% of co-catalyst **5c** (entry 6).

We also examined the effects of various solvents and the reaction times to this reaction with an optimized catalyst combination of **2a** (20 mol%) and **5c** (40 mol%) at room temperature (Table 2). As a result, aromatic solvents performed better giving satisfactory chemical yields and stereoselectivities (entries 1–3). Particularly, toluene was found to be effective in

this reaction (entry 1). Furthermore, no significant improvement in chemical yields and stereoselectivities was observed when the reaction times were shortened for 24 h and prolonged for 72 h and 96 h, respectively (entries 14–16). From these results, it was revealed that the catalyst combination of simple catalyst **2a** (20 mol%) and simple non-chiral *N*-Boc-glycine **5c** (40 mol%), toluene as solvent, room temperature and 48 h reaction time was best reaction condition for this reaction. This reaction using three catalysts component system by Tanaka and co-workers mainly afforded HDA adduct **8a** which was obtained by concerted HDA cycloaddition, while this reaction also slightly afforded aldol product **9** which is obtained by aldol reaction as a by-product. Similarly, our catalysts component system also slightly afforded similar aldol product **9** in low chemical yield (12%) and stereoselectivities (72 : 28 dr, 16% ee) like Tanaka and co-workers.<sup>9</sup>

### 2.3. Substrate scope

After optimizing the reaction conditions, we examined the generality of the developed superior two catalysts component system of **2a** and **5c** in the reactions of different isatins **6a–f** with enones **7a–e** (Scheme 3). This system also showed better catalytic activity in the reactions and afforded the corresponding chiral spirooxindole-tetrahydropyranones **8b–j** in good to excellent stereoselectivities with moderate to good chemical yields, except the result from the reaction of **6a** with **7e** to did not afford the adduct **8j**. From the results, it is strongly indicated that our simple two catalysts component system works effectively in this reaction using variety of substrates.

We also examined this reaction using a large amount of substrate (**6a**: 1 g, **7a**: 3.05 g) to demonstrate the practical utility of the two component system in best reaction condition. As a result, the HDA adduct **8a** was successfully obtained with 87% chemical yield with good stereoselectivities (dr = 80 : 20, 85% ee), although a slight decrease of ee was observed. From this result, it is expected that this HDA reaction using our two catalyst components system may be useful for practical aspect.

### 2.4. Reaction mechanism

Based on the observed highly enantiopurity of the obtained HDA adduct **[2S,6R]-8a** (rt: 92% ee, 0 °C: 93% ee, entries 6 and

Table 2 Solvent screening for HDA reaction

| $\text{6a} + \text{7a} \xrightarrow[\text{solvent, rt, time}]{\text{catalyst 2a (20 mol\%)}, \text{co-catalyst 5c (40 mol\%)}} \text{[2'S,6'R]-8a Major}$ |                                               |          |                        |                 |                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------|------------------------|-----------------|---------------------|
| Entry                                                                                                                                                     | Solvent                                       | Time (h) | Yield <sup>a</sup> (%) | dr <sup>b</sup> | Ee <sup>c</sup> (%) |
| 1                                                                                                                                                         | Toluene                                       | 48       | 86                     | 80 : 20         | 92                  |
| 2                                                                                                                                                         | Benzene                                       | 48       | 60                     | 78 : 22         | 90                  |
| 3                                                                                                                                                         | Xylene                                        | 48       | 73                     | 77 : 23         | 88                  |
| 4                                                                                                                                                         | Cyclohexane                                   | 48       | 66                     | 74 : 26         | 89                  |
| 5                                                                                                                                                         | Hexane                                        | 48       | trace                  | —               | —                   |
| 6                                                                                                                                                         | Et <sub>2</sub> O                             | 48       | 55                     | 78 : 22         | 90                  |
| 7                                                                                                                                                         | iPr <sub>2</sub> O                            | 48       | 68                     | 77 : 23         | 89                  |
| 8                                                                                                                                                         | THF                                           | 48       | 40                     | 79 : 21         | 82                  |
| 9                                                                                                                                                         | CH <sub>2</sub> Cl <sub>2</sub>               | 48       | 74                     | 79 : 21         | 90                  |
| 10                                                                                                                                                        | CHCl <sub>3</sub>                             | 48       | 34                     | 84 : 16         | 92                  |
| 11                                                                                                                                                        | C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub> | 48       | 75                     | 77 : 23         | 88                  |
| 12                                                                                                                                                        | CH <sub>3</sub> CN                            | 48       | 70                     | 75 : 25         | 88                  |
| 13                                                                                                                                                        | MeOH                                          | 48       | 38                     | 68 : 32         | 83                  |
| 14                                                                                                                                                        | Toluene                                       | 24       | 73                     | 79 : 21         | 90                  |
| 15                                                                                                                                                        | Toluene                                       | 72       | 86                     | 78 : 22         | 86                  |
| 16                                                                                                                                                        | Toluene                                       | 96       | 78                     | 78 : 22         | 86                  |
| 17                                                                                                                                                        | Neat                                          | 24       | 87                     | 71 : 29         | 86                  |
| 18                                                                                                                                                        | Neat                                          | 48       | 75                     | 68 : 32         | 82                  |

<sup>a</sup> Isolated yield. <sup>b</sup> Diastereoselectivity (dr) was determined by <sup>1</sup>HNMR of the crude reaction mixture (major diastereomer: **8a**). <sup>c</sup> The ee value were determined by HPLC (Daicel chiralpak IB column).



Scheme 3 Substrate scope for asymmetric HDA reaction.





Scheme 4 Plausible reaction course for asymmetric HDA reaction.

25, Table 1), the model of the enantioselective reaction course was proposed as shown in Scheme 4. First, the reaction of  $\beta$ -amino alcohol catalyst **2a** with enone **7a** forms the diene intermediate **I-1** that has less steric interaction of between amino alcohol that is fixed by intramolecular hydrogen bonding and substituted diene parts on generated diene **I-1** than that of intermediate **I-2**. Furthermore, isatin **6a** is activated by the two points of hydrogen bonding interactions with *N*-Boc amino acid co-catalyst **5c**. Then, the reaction might proceed through **TS-1** to afford **8a** that has a less steric interaction between **I-1** and dienophile **6a** than those of **TS-2-4** to afford **8a'-8a''** that have more steric interaction between **I-1** and **6a**. Thus, diene **I-1** might attack stereoselectively from less sterically hindered site of the incoming activated isatin dienophile **6a** to afford **[2S,6R]-8a** with excellent optical purity (93% ee). On the other hand, it is also expected that the formation of adduct **8a** via aldol reaction followed by oxa-Michael addition may be minor pathway based on the chemical yield and enantioselectivity of the obtained aldol product **9** and **8a** was quite low (**9**: 12%, 72 : 28 dr., 16% ee, **8a**: 8%, 80 : 20 dr., 86% ee).

### 3. Conclusion

We have developed a simple two catalysts component system consisting of primary  $\beta$ -amino alcohol **2a** as a catalyst and *N*-protected amino acid **5c** as a co-catalyst for the asymmetric HDA reaction of isatins with enones for the first time. This dual component system showed efficient catalytic activity to afford the chiral spirooxindole-tetrahydropyranones **8a-j** that are efficient synthetic intermediates for many biologically active compounds and drug discovery, in good chemical yields (up to 86%) and with enough stereoselectivities (up to 85 : 15 dr, 95% ee). In addition, the independent use of simple  $\beta$ -amino alcohol catalyst **2a** also showed good catalytic activity for affording **8a** with an excellent enantioselectivity (92% ee), although chemical yield was low. The modification of the combination of amino alcohols and detailed mechanistic study of this reaction using our catalysts system are in progress.

## 4. Experimental

### 4.1. General information

All reagents and dry solvents were purchased from commercial vendors and used directly without further purification. All reactions were placed in dried sample vials inserted with magnetic beads. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F<sub>254</sub> plates and the analytes were identified under UV light. Flash column chromatography was performed using silica gel pore size 60<sub>N</sub> (40–100  $\mu$ m). Melting points were recorded with a micro-melting point apparatus. IR spectra were recorded with a JASCO-4100 Fourier transform infrared spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data were recorded using a JEOL JNM-ECA500 instrument with tetramethyl silane as the internal standard. HPLC data were collected using the TOSOH instrument equipped with (UV-8020, DP-8020, and SD-8022) detectors using CHIRALPAK IB column. Optical rotations were recorded using a JASCO DIP-360 digital polarimeter. High-resolution mass spectrometry (HRMS) data were collected by electron impact (EI) modes using Hitachi RMG-GMG and JEOL JNX-DX303 sector instruments.

### 4.2. General procedure for the hetero Diels–Alder (HDA) reaction of isatins (**6a-f**) with enones (**7a-e**)

To a solution of the corresponding isatins **6a-f** (0.2 mmol, 1 eq.) and enones **7a-e** (0.8 mmol, 4 eq.) in anhydrous toluene (0.3 mL) were added catalysts **2a-e** or **4a-e** (0.04 mmol, 20 mol%) and co-catalysts **5a-k** (0.08 mmol, 40 mol%) at room temperature and the mixture were stirred at that temperature for 48 h. The mixture was purified by flash column chromatography (SiO<sub>2</sub>: hexane/ethyl acetate, 7 : 3) to afford the corresponding major HDA adducts **8a-j**.<sup>9</sup> The diastereoselectivity (dr) of the obtained HDA adducts were determined by the crude reaction mixture by <sup>1</sup>H-NMR.<sup>9</sup> The enantiomeric excess (ee) of **8a-j** were determined by HPLC (CHIRALPAK-IB, hexane/*i*-PrOH = 70 : 30, 90 : 10 and 95 : 5, 1.0 mL and 0.6 mL min<sup>-1</sup>,  $\lambda$  = 245 nm).<sup>9</sup>

## Conflicts of interest

There are no conflicts to declare.

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