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RESEARCH ARTICLE

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Simple amino silyl ether organocatalyst for asymmetric hetero Diels–Alder reaction of isatins with enones

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Abstract

New two catalysts component system comprising of a primary β-amino silyl ethers as an organocatalyst and *N*-protected amino acids as a co-catalyst put together worked as an efficient organocatalyst system in the hetero Diels–Alder reaction of isatins with enones affording the chiral spirooxindole-tetrahydropyranones in good chemical yields and stereoselectivities (up to 94%, up to *dr* 78:22., up to 85% *ee*).

KEYWORDS

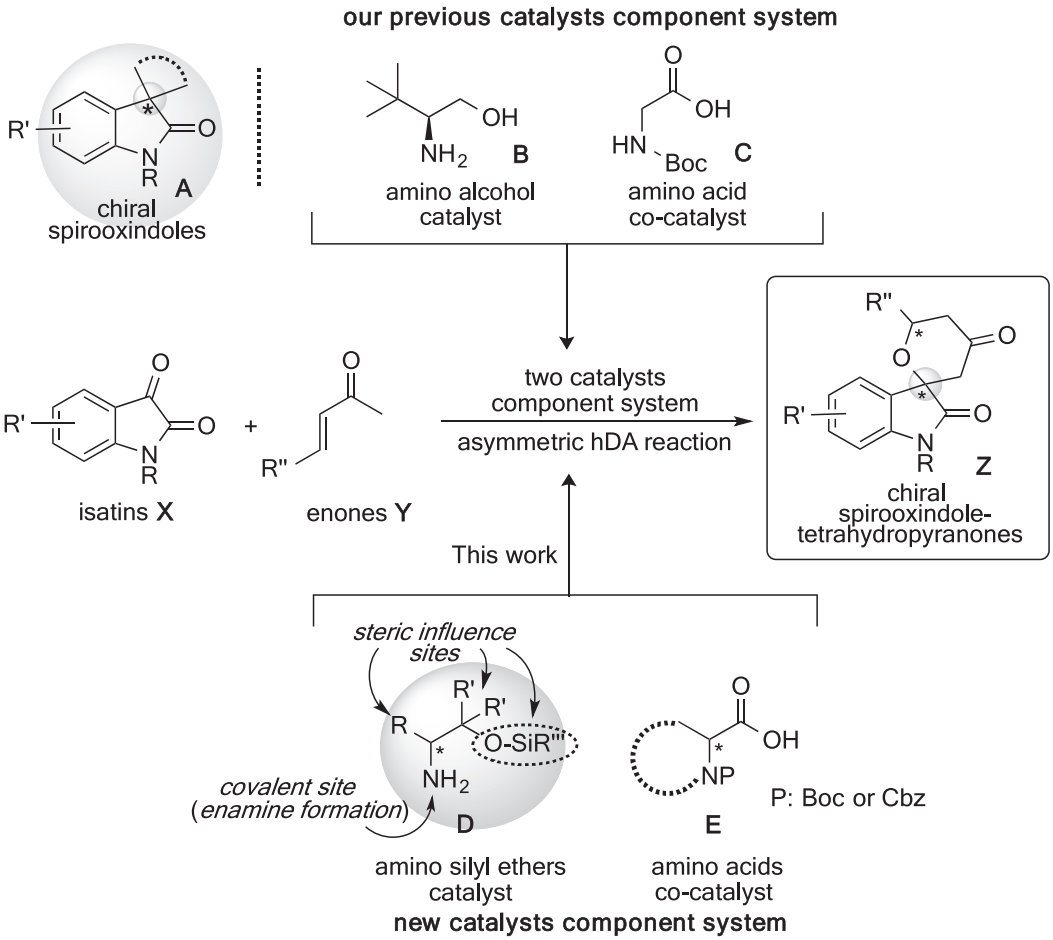
hetero Diels–Alder reaction, organocatalysis, spirooxindole, β-amino alcohol, β-amino silyl ether

1 | INTRODUCTION

Spirooxindole skeleton **A** is found in many biologically active natural compounds[1–7]and drugs[8–10] such as anti-malarial,[11–13] anti-cancer,[14,15] anti-viral,[16] anti-tuberculosis,[17] and anti-proliferative[18] (Scheme 1). Therefore, it is important to establish an effective asymmetric synthetic methodology for the synthesis of chiral spirooxindoles **A**. In the past decade, the study of organocatalysis has immensely attracted wide range of researchers in creating and exploring new chiral compounds as organocatalysts in synthetic organic chemistry,[19,20] due to their ease of handling, inert to atmosphere, low toxic nature. Organocatalyzed asymmetric hetero Diels–Alder (hDA) reaction has been found to be an efficient synthetic protocol for the synthesis of various pharmaceutically and biologically active chiral compounds.[21,22] However, enantioselective hDA reaction, for the synthesis of chiral spirooxindoles still remains a challenging task in the field of synthetic organic chemistry in terms of drug discovery.

Recently, asymmetric cooperative catalysis has attracted immense interest, in which two catalysts work simultaneously to form products which cannot be accomplished by the use of a single catalyst alone.[23–28] Most recently, we have also reported a simple two catalysts component system consisting of a primary β-amino alcohol **B** as a catalyst and *N*-protected amino acid **C** as a co-catalyst for this asymmetric hDA reaction.[29] This dual component system showed efficient catalytic activity affording the chiral spirooxindole-tetrahydropyranone **Z**, which acts as a synthetic precursor for many biologically active compounds. Based on these backgrounds, we have designed a new, simple two catalysts component system, using simple amino silyl ether **D** as an organocatalyst and amino acid **C** as a co-catalyst for this reaction (Scheme 1).

As of catalyst **D**, it can be prepared easily from the commercially available amino acids in few steps and also **D** contains a primary amino group as a covalent site and both a silyl ether group and an alkyl or an aryl group at α- and/or β-positions as steric influence sites in the single molecule (Scheme 1).



SCHEME 1 Concept of organocatalyst

Furthermore, simple amino acids as co-catalysts **C** also can be easily prepared from the corresponding amino acids. Herein, we describe the utility of the two catalysts component system using primary β-amino silyl ethers **D** having only one chiral carbon center on the molecule as a catalyst and simple *N*-protected amino acids **E** as a co-catalyst in the hDA reaction of **X** with **Y** to afford chiral **Z** in good chemical yields (up to 94%) with satisfactory stereoselectivities (up to *dr* 78:22, up to 85% *ee*).

2 | MATERIALS AND METHODS

2.1 | 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_{254} plates and the analytes were identified under UV light. Flash column chromatography was performed using silica gel pore size 60_N (40–100 μm). Melting points were recorded with a micro-melting point apparatus. Infrared (IR) spectra were recorded with a JASCO-4100 Fourier transform infrared spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data were recorded using a JEOL JNM-ECA500 instrument with tetramethylsilane as the internal standard. High-performance liquid chromatography (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.

2.2 | General procedure for the asymmetric hetero Diels–Alder reaction

To a solution of the corresponding isatins **4a–f** (0.2 mmol, 1 eq) and enones **5a–e** (0.8 mmol, 4 eq) in anhydrous toluene (0.3 ml) were added catalysts **2a–o** (0.04 mmol, 20 mol %) and co-catalysts **3a–s** (0.08 mmol,

40 mol %) at room temperature and the mixture was stirred at that temperature for 48 h. After the completion of reaction, the mixture was purified by flash column chromatography (SiO_2, hexane: ethyl acetate = 7:3) to afford the corresponding major hDA adducts **6a–i**. The diastereoselectivity (*dr*) of the obtained hDA adducts were determined by the crude reaction mixture by ^{1}H NMR. The enantiomeric excess (*ee*) of **6a–i** were determined by HPLC (CHIRALPAK IB, hexane: *i*PrOH = 90:10 or 95:5, 0.6 ml,1.0 ml/min, λ = 245 nm).

2.3 | General procedure for the synthesis of catalysts 2a–o

To a solution of the corresponding amino alcohol **1a–o** (6.79 mmol, 1 eq) in dry CH_2Cl_2, cooled at 0 C or −30 C were added corresponding trialkyl silyl chloride or trifluoromethane sulfonate (1.2 eq) and triethylamine (1.2 eq) for 10 min under argon atmosphere. The solution was stirred for 24 h at room temperature. After the completion of reaction, the reaction mixture was diluted with water and extracted with dichloromethane. Organic layer was separated and dried with sodium sulfate. Solvent was evaporated under reduced pressure, the obtained crude mixture was purified by flash column chromatography (SiO_2, hexane: ethyl acetate = 7:3 and MeOH:CH_2Cl_2 = 9:1) to give the corresponding amino silyl ether catalysts **2a–o**.

2.4 | (*S*)-1-phenyl-3-([triethylsilyl]oxy) propane-2-amine (2l)

Light yellow oil. 89% yield. $[\alpha]_D^{24} = +6.24$ (c = 0.48, CH_2Cl_2). IR (neat) cm^{-1}: 3027, 2875, 1602, 1495, 1097, 794, 699.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.30 (m, 2H), 7.20 (td, J = 5.0, 2.1 Hz, 3H), 4.11 (s, 2H), 3.62 (q, J = 4.6 Hz, 1H), 3.49 (dd, J = 9.7, 6.3 Hz, 1H), 3.21 (qd, J = 6.8, 4.3 Hz, 1H), 2.81 (dq, J = 46.5, 6.9 Hz, 2H), 0.92–0.99 (m, 9H), 0.56–0.63 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.31, 129.37, 128.61, 126.56, 77.41, 77.17, 76.91, 65.35, 54.62, 38.90, 6.90, 4.42. MS (FAB): *m/z*: 265 $[M]^+$, HRMS (FAB): calcd. for $C_{15}H_{27}N_1O_1Si_1$ *m/z* 265.47; found: 265.69.

2.5 | (*S*)-1-phenyl-3-([triisopropylsilyl] oxy)propane-2-amine (2m)

Light yellow oil. 90% yield. $[\alpha]_D^{24} = +1.81$ (c = 0.55, CH_2Cl_2). IR (neat) cm^{-1}: 2941, 2864, 1558, 1105, 782, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.30 (m, 2H), 7.19–7.22 (m, 3H), 3.67 (q, J = 4.6 Hz, 1H), 3.56 (dd, J = 10.0, 6.0 Hz, 1H), 3.31 (s, 2H), 3.12–3.18 (m, 1H), 2.83 (q, J = 6.7 Hz, 1H), 2.66 (dd, J = 13.5, 7.7 Hz, 1H), 1.04–1.06 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.26, 129.38, 128.68, 126.66, 77.39, 77.15, 76.89, 66.24, 54.89, 38.94, 18.06, 11.96. MS (FAB): *m/z*: 307 $[M]^+$, HRMS (FAB): calcd. for $C_{18}H_{33}N_1O_1Si_1$ *m/z* 307.55; found: 307.64.

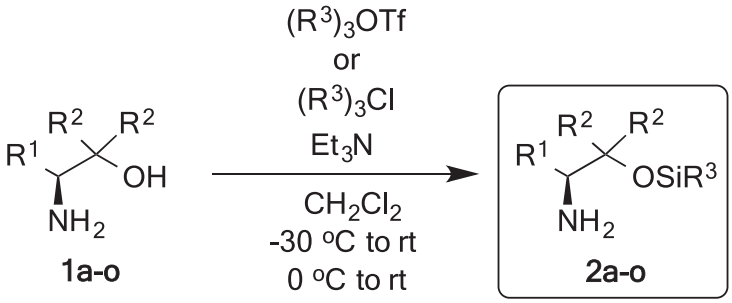
2.6 | (*S*)-1-([1,1,1,1,3,3,3-heptamethyl-2-{trimethylsilyl}-1-trisilan-2-yl]oxy) 3-phenylpropane-2-amine- propane-2-amine (2o)

Colorless liquid. 88% yield. $[\alpha]_D^{24} = -17.24$ (c = 0.58, CH_2Cl_2). IR (neat) cm^{-1}: 2947, 2892, 1558, 1540, 1070, 769, 699. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.29 (m, 2H), 7.17–7.20 (m, 3H), 3.37 (q, J = 4.6 Hz, 1H), 3.31 (dd, J = 9.5, 6.6 Hz, 1H), 2.99–3.04 (m, 1H), 2.72 (q, J = 6.3 Hz, 1H), 2.54 (q, J = 6.9 Hz, 1H), 1.45 (d, J = 22.3 Hz, 2H), 0.17 (s, 27H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.16, 129.38, 128.53, 126.31, 77.39, 77.15, 76.89, 71.98, 54.82, 40.47, 0.39. MS (FAB): *m/z*: 397 $[M]^+$, HRMS (FAB): calcd. for $C_{18}H_{39}N_1O_1Si_4$ *m/z* 397.86; found: 397.91.

3 | RESULTS AND DISCUSSION

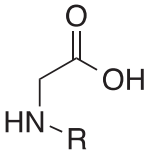
3.1 | Preparation of catalysts and co-catalysts

The desired amino silyl ethers **2a–n**[30,31] having several trialkylsilyl groups on oxygen atom at α-position were easily prepared by the reactions of the corresponding β-amino alcohols **1a–n** with XOTf (X: TMS [trimethylsilyl]),[30] XCl (X: TES [triethylsilyl]),[31] XOTf (X: TIPS [triisopropylsilyl]),[31] and XCl (X: TBDMS [*tert*-butyldimethylsilyl]),[31] respectively, in moderate to good yields (46%–90%)(Scheme 2). Furthermore, the bulkiest β-amino silyl ether catalyst **2o** having a super silyl TTMSS (tris[trimethylsilyl] silyl)[31] group on oxygen atom was also easily prepared from the reaction of the corresponding amino alcohol with TTMSSCl in good yield (88%). Furthermore, several *N*-Cbz[32] and *N*-Boc-amino acids **3a–s** as co-catalysts were also easily derived from the corresponding commercially available nonprotected acyclic and sterically bulky cyclic amino acids, respectively (Scheme 2).

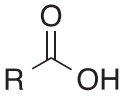


2a:	R^1 = Me,	R^2 = H,	R^3 = TMS,	88%
2b:	R^1 = Et,	R^2 = H,	R^3 = TMS,	90%
2c:	R^1 = *i*Pr,	R^2 = H,	R^3 = TMS,	80%
2d:	R^1 = *t*Bu,	R^2 = H,	R^3 = TMS,	85%
2e:	R^1 = Bn,	R^2 = H,	R^3 = TMS,	89%
2f:	R^1 = Ph,	R^2 = H,	R^3 = TMS,	84%
2g:	R^1 = Me,	R^2 = Ph,	R^3 = TMS,	80%
2h:	R^1 = *i*Pr,	R^2 = Ph,	R^3 = TMS,	76%
2i:	R^1 = *t*Bu,	R^2 = Ph,	R^3 = TMS,	80%
2j:	R^1 = Bn,	R^2 = Ph,	R^3 = TMS,	68%
2k:	R^1 = Ph,	R^2 = Ph,	R^3 = TMS,	46%
2l:	R^1 = Bn,	R^2 = H,	R^3 = TES,	89%
2m:	R^1 = Bn,	R^2 = H,	R^3 = TIPS,	90%
2n:	R^1 = Bn,	R^2 = H,	R^3 = TBDMS,	89%
2o:	R^1 = Bn,	R^2 = H,	R^3 = TTMSS,	88%

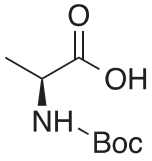
co-catalysts



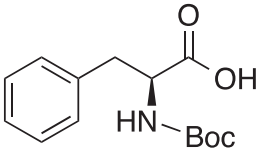
3a: R = Boc
3b: R = Cbz



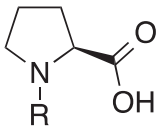
3c: R = Ph
3d: R = 4-NO_2-Ph
3d: R = 4-F-Ph
3f: R = 4-Me-Ph
3g: R = 1-napthyl
3h: R = 2-napthyl
3i: R = 1-pyranyl
3j: R = 1-adamantyl
3k: R = Me
3l: R = CF_3



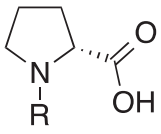
3m



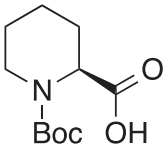
3n



3o: R = Boc
3p: R = Cbz



3q: R = Boc
3r: R = Cbz



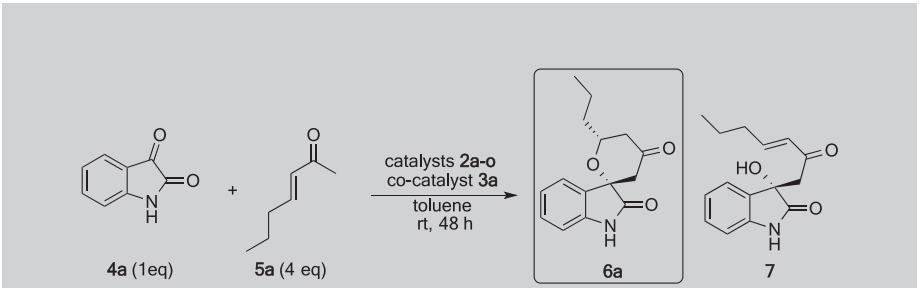
3s

SCHEME 2 Synthesis of catalysts **2a–o** and co-catalysts **3a–s**

3.2 | Optimization of catalysts

First, we examined the hDA reaction of isatin **4a** as a dienophile with heptene-2-one **5a** as a diene using β-amino silyl ether organocatalysts **2a–f** with primary trimethylsiloxy (OTMS) group or **2g–o** with tertiary OTMS groups (20 mol %) and the simplest *N*-Boc-amino acid **3a** as a co-catalyst (40 mol %) at room temperature for 48 h (Table 1). Two equivalents of co-catalyst against catalyst was used for a reason that, co-catalyst may work in both way, in the acceleration of the formation of diene and also in the activation of isatin. Amino silyl ethers **2a–f** showed catalytic activities in this reaction and the corresponding chiral hDA adduct [2′*S*,6′*R*]-**6a** was obtained in good enantioselectivities (72%–85% *ee*) and moderate diastereoselectivities (53:47–67:33) with chemical yields in the range of extremely low to good (2%–77%) (Entries 1–6). Among these catalysts **2a–f**, the use of catalysts **2e–f** with bulkier Bn or Ph groups at β-position on the molecules showed better catalytic activity than others (Entries 5 and 6). Particularly, the catalyst **2e** showed best catalytic activity to afford chiral adduct **6a** in good chemical yield (74%) and enantioselectivity (81% *ee*) with moderate diastereoselectivity (67:33, Entry 5). When only catalyst **2e**, without a co-catalyst was used in this reaction satisfactory result was not obtained (Entry 7). On the other hand, the reactions using catalysts **2g–k** with tertiary OTMS groups hardly proceeded and enantioselectivity was considerably decreased (Entries 8–12). Next, based on these results, the reaction using catalysts **2l–o** having different bulkier silyl groups on oxygen atom and co-catalyst **3a** were carried out under same reaction condition (Entries 13–16). However, these catalysts **2l–o** did not show better catalytic activity than

TABLE 1 Asymmetric hetero Diels–Alder reaction of 4a with 5a using catalysts 2a–o and co-catalyst 3a



Entry	Cat 2a–o (mol %)	Co-cat 3a mol %	Yield (%)[a]	*dr*[b]	*ee*[c] (%)
1	2a (20)	40	11	54:46	72
2	2b (20)	40	9	64:36	79
3	2c (20)	40	44	67:33	85
4	2d (20)	40	2	63:37	76
5	2e (20)	40	74	67:33	81
6	2f (20)	40	77	53:47	72
7	2e (20)	—	31	56:44	59
8	2g (20)	40	2	65:35	40
9	2h (20)	40	*trace*	—	—
10	2i (20)	40	*trace*	—	—
11	2j (20)	40	*trace*	—	—
12	2k (20)	40	9	74:26	14
13	2l (20)	40	64	61:39	75
14	2m (20)	40	46	69:31	15
15	2n (20)	40	65	66:34	18
16	2o (20)	40	84	51:49	51

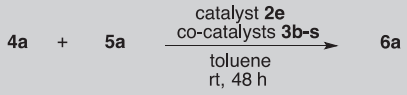
[a]Isolated yields.
[b]*Dr* was determined by ^{1}H nuclear magnetic resonance (NMR).
[c]*Ee* were determined by high-performance liquid chromatography (HPLC) using a Daicel CHIRALPAK IB column.

2e. From these results, it was revealed that the best catalyst was β-amino silyl ether **2e** with primary OTMS group in this reaction. This catalysts component system also slightly afforded an aldol product **7** as by product in low chemical yield (10%) and enantioselectivity (9% *ee*).

3.3 | Optimization of co-catalysts

We next examined this reaction using the combinations of superior catalyst **2e** (20 mol %) with several acids **3b–s** as co-catalysts (40 mol %) at room temperature for 48 h

TABLE 2 Asymmetric hetero Diels–Alder reaction of **4a** with **5a** using catalyst **2e** and co-catalyst **3b–s**



Entry	Enone 5a eq	Cat 2e mol %	Co-cat 3b–s (mol %)	Yield (%)[a]	*dr*[b]	*ee*[c] (%)
1	4	20	**3b** (40)	69	65:35	82
2	4	20	**3c** (40)	85	69:31	79
3	4	20	**3d** (40)	76	68:32	79
4	4	20	**3e** (40)	94	69:21	80
5	4	20	**3f** (40)	85	70:30	78
6	4	20	**3g** (40)	91	65:35	78
7	4	20	**3h** (40)	90	68:32	80
8	4	20	**3i** (40)	53	65:35	81
9	4	20	**3j** (40)	80	67:33	80
10	4	20	**3k** (40)	82	65:35	80
11	4	20	**3l** (40)	*trace*	—	—
12	4	20	**3m** (40)	79	76:24	80
13	4	20	**3n** (40)	78	68:22	81
14	4	20	**3o** (40)	85	77:23	82
15	4	20	**3p** (40)	79	67:33	81
16	4	20	**3q** (40)	76	77:23	80
17	4	20	**3r** (40)	87	68:32	78
18	4	20	**3s** (40)	75	57:43	78
19[c]	4	20	**3o** (40)	35	82:18	84
20[d]	4	20	**3o** (40)	79	77:23	76
21	4	20	**3o** (20)	85	75:25	80
22	4	20	**3o** (10)	82	72:28	79
23	4	10	**3o** (10)	30	71:29	82
24	4	10	**3o** (20)	50	69:31	82
25	4	10	**3o** (5)	17	72:28	83
26	1	20	**3o** (40)	48	70:30	81
27	2	20	**3o** (40)	78	78:22	79
28	3	20	**3o** (40)	84	78:22	78
29	5	20	**3o** (40)	92	76:24	76

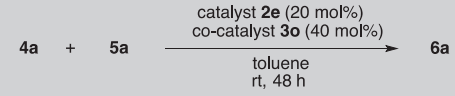
[a]Isolated yields.
[b]*Dr* was determined by ^{1}H nuclear magnetic resonance (NMR).
[c]Reaction was carried out at 0°C.
[d]Reaction was carried out at 40°C.
[e]*Ee* were determined by high-performance liquid chromatography (HPLC) using a Daicel CHIRALPAK IB column.

(Table 2). First, the reactions using *N*-Cbz-amino acids **3b** and also common aromatic and aliphatic acids **3c–l** as co-catalysts were carried out respectively (Entries 1–11). Almost all co-catalysts **3b–k** assisted the progress of the reaction, affording chiral **6a** with moderate to good chemical yields and stereoselectivities. However, only bulkier aromatic acid **3i** afforded **6a** in moderate chemical yields, although no change in the stereoselectivities was observed (Entry 8). Furthermore, the strongest trifluoro acetic acid **3l** as a co-catalyst did not work in this reaction condition (Entry 11). Next, the reactions using chiral *N*-Boc-amino acids **3m**,**n** as co-catalysts were examined and these **3m**,**n** also showed good co-catalytic activities (Entries 12 and 13). Moreover, the combinations of catalyst **2e** with bulkier chiral cyclic amino acids, *N*-Boc-, *N*-Cbz-prolines **3o–r**, and *N*-Boc-piperidine **3s**, were also examined in this reaction condition (Entries 14–18), respectively. The use of chiral co-catalysts **3o–s** having bulkier cyclic structure and specific steric configuration might be effective for increasing the stereoserectivities in this reaction to afford chiral **6a**. As a result, **3o–s** showed good catalytic activities affording **6a**, but chemical yields and stereoselectivities were almost the same as the results of general acyclic amino acids **3a**,**b**,**m**,**n** and common organic acids **3c–k**. In **3o–s**, *N*-Boc-L-proline **3o** showed best co-catalytic activity and afforded **6a** in good chemical yield (85%) and stereoselectivities (*dr* 77:23, 82% *ee*) (Entry 14). However, this combination of **2e** with **3o** at 0°C brought about a large decrease in chemical yield up to 35%, although good stereoselectivity (*dr* 82:18, 84% *ee*) was maintained (Entry 19). On the other hand, the reaction at 40°C afforded **6a** with good chemical yield and stereoselectivity (Entry 20). From these results, it was revealed that the combination of **2e** with **3o** was the best one in this reaction.

Next, we examined the molar ratio of catalyst **2e** and co-catalyst **3o**, in this reaction of **4a** (1 equiv.) with **5a** (4 equiv.) at room temperature (Entries 21–25). Satisfactory enantioselectivities and diastereoselectivities were observed under all of the molar ratios of **2e** and **3o**. However, chemical yields were comparatively lowered, when the reaction was carried out with 10 mol % of catalyst **2e** and 5%–20% of co-catalyst **3o** (Entries 23–25). On the other hand, the use of the equivalent ratio of catalyst (20 mol %) and co-catalyst (10 mol % or 20 mol %) were relatively effective (Entries 21 and 22). Furthermore, the ratio of substrates **4a** and **5a** were examined in the presence of optimized catalyst **2e** (20 mol %) and co-catalyst **3o** (40 mol %) system under the same reaction condition (Entries 26–29). Good chemical yields and stereoselectivities were observed except, when 1 equivalent of **5a** to **2e** was used, which brought about the decrease in chemical yield (48%, Entry 26).

We also examined the effects of various solvents to this reaction using the optimized catalysts combination of **2e** (20 mol %) and **3o** (40 mol %) at room temperature (Table 3). 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) affording high enantioselectivity (Entry 1). From these results, it was revealed that the catalysts combination of **2e** (20 mol %) as a catalyst and chiral *N*-Boc-L-proline **3o** as a co-catalyst (40 mol %), toluene as a solvent, at room temperature and 48 h reaction time was the best reaction condition for this reaction. Furthermore, in order to demonstrate the practical utility of the catalysts combination of **2e** and **3o**, the reaction of **4a** with **5a** was conducted on gram scale (**4a**: 1 g) using the above optimized reaction conditions, the corresponding product **6a** was obtained in good chemical yield (88%), diastereoselectivity (*dr* 78:22), and enantioselectivity (79% *ee*). This result indicated that the catalysts

TABLE 3 Solvent screening for optimized reaction condition



Entry	Solvent	Yield (%)[a]	*dr*[b]	*ee*[c] (%)
1	Toluene	85	77:23	82
2	Benzene	92	77:23	77
3	Xylene	92	77:23	79
4	Cyclohexane	86	51:49	74
5	Hexane	75	67:33	64
6	Et_2O	62	67:33	75
7	iPr_2O	82	55:46	71
8	THF	35	70:30	74
9	CH_2Cl_2	82	61:39	78
10	$CHCl_3$	86	61:39	80
11	$C_2H_4Cl_2$	74	65:35	80
12	CH_3CN	30	53:47	79
13	MeOH	25	79:21	67
14	Neat	82	63:37	73

[a]Isolated yields.
[b]*Dr* was determined by ^1H nuclear magnetic resonance (NMR).
[c]*Ee* value were determined by high-performance liquid chromatography (HPLC) using a Daicel CHIRALPAK IB column.

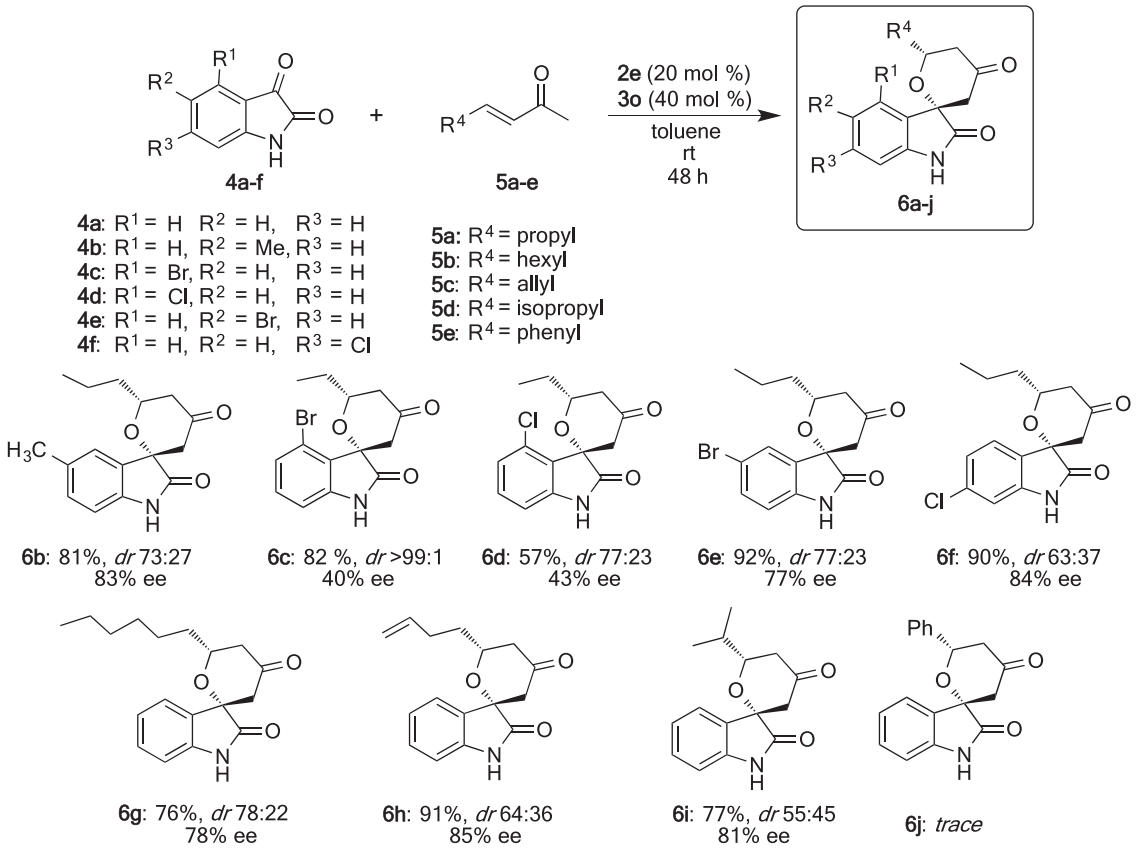
component system of **2e** and **3o** can also be effective on practical scale.

3.4 | Substrate scope for the asymmetric hDA reaction

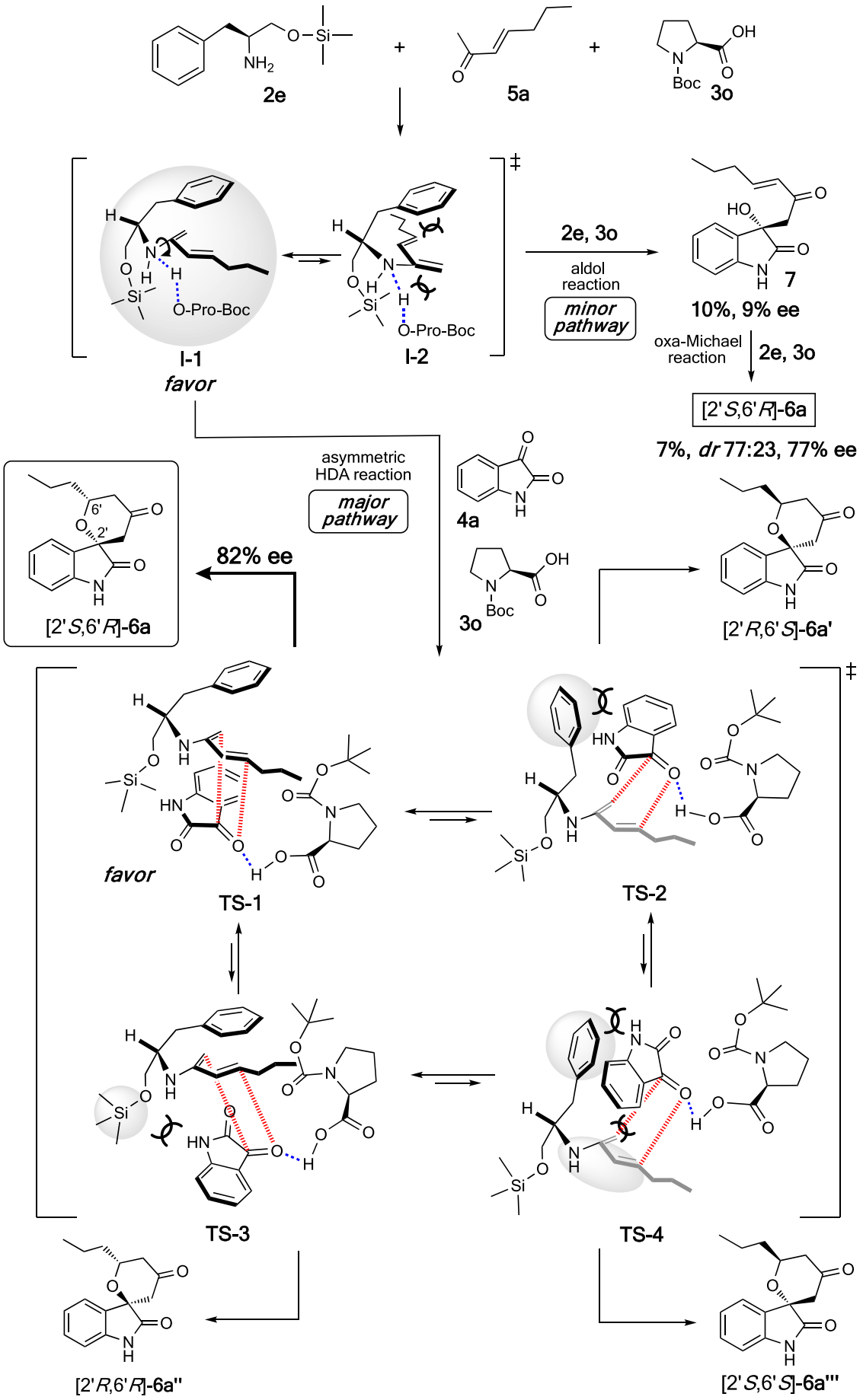
We examined the generality of the developed superior two catalysts component system of **2e** and **3o** in the reactions of different isatins **4a–f** with enones **5a–e** (Scheme 3). This component system also showed good catalytic activity in the reactions and afforded the corresponding chiral spirooxindole-tetrahydropyranones **6a–i** in moderate to good chemical yields and stereoselectivities as shown in Scheme 3. However, the reactions of **4a** with enones **5e** with bulky phenyl group hardly proceeded in this reaction condition to afford the corresponding adduct **6j**, respectively.

3.5 | Plausible reaction mechanism

The hDA reaction of isatin **4a** with enone **5a** in the presence of catalyst **2e** without the superior co-catalyst **3o** afforded the corresponding chiral hDA adduct [2′*S*,6′*R*]-**6a** in low chemical yield and stereoselectivities (31%, *dr* 56:44, 59% ee) (Entry 7, Table 1). On the other hand, the same reaction in the presence of **2e** using **3o** afforded chiral hDA adduct **6a** in good results (85%, *dr* 77:23, 82% ee) (Entry 14, Table 2). Furthermore, in the absence of co-catalyst **3o**, the formation of diene intermediate **I** was not observed in the reaction of catalyst **2e** with enone **5a**, although the formation of **I** was observed using **3o**. These results may indicate that co-catalyst works as an acid for accelerating the formation of diene intermediate. Based on these experiment results and the high enantiopurity of the obtained hDA adduct [2′*S*,6′*R*]-**6a** (82% *ee*, Table 3), the model of the enantioselective reaction course was proposed as shown in Scheme 4. First, the reactions of catalyst **2e** with enone **5a** in the presence of co-catalyst **3o** as an acid forms the diene intermediate **I-1** that has less steric interaction between amino silyl ether part and substituted diene part than that of intermediate **I-2**. Furthermore, isatin **4a** is activated by the hydrogen bonding interaction with *N*-Boc-L-proline co-catalyst **3o**. Then, the reaction might proceed through **TS-1** to afford chiral **6a** that has a less steric interaction between **I-1** and dienophile **4a** than those of **TS-2**–**TS-4** to afford **6a′**–**6a‴** that have more steric interaction between **I-1** and **4a**. Thus, the diene **I-1** might



SCHEME 3 Substrate scope for the asymmetric hetero Diels–Alder (hDA) reaction



SCHEME 4 Plausible reaction mechanism for the asymmetric hDA reaction

attack stereoselectively from less sterically hindered site towards the incoming activated isatin dienophile **4a** to afford [2′*S*,6′*R*]-**6a** with good optically purity (82% *ee*). In this reaction, aldol product **7** was formed as a by product. From this result, the reaction of **2e** with **3o** also may proceed via aldol reaction followed by oxa-Michael addition. However, the chemical yields and optical purities of the obtained aldol product **7** and Michael adduct **6a** were quite low (**7**: 10%, 9% *ee*, **6a**: 7%, *dr* 77:23, 77% *ee*). Based on these results, it may be assumed that the reaction of **2e** with **3o** proceeds via hDA reaction pathway.

4 | CONCLUSION

We have developed a simple two catalysts component system consisting of a primary β-amino silyl ether **2e** as a catalyst and *N*-Boc-L-proline **3o** 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 **6a–i** in good chemical yields (up to 94%) and with enough stereoselectivities (up to *dr* 78: 22, up to 85% *ee*), which are expected to act as efficient synthetic intermediates for the synthesis of biologically active compound and also in drug discovery. The modification of the combination of β-amino silyl ether and detailed mechanistic study of this reaction using our catalysts system are in progress.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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