Enantioselective Catalysis of the Hetero-Diels–Alder Reaction between Brassard's Diene and Aldehydes by Hydrogen-Bonding Activation: A One-Step Synthesis of (*S*)-(+)-Dihydrokawain

Haifeng Du, Dongbo Zhao, and Kuiling Ding*[a]

Abstract: The first catalytic enantioselective hetero-Diels–Alder reaction between Brassard's diene and aldehydes has been achieved through hydrogen-bonding activation using TADDOL derivatives as catalysts to afford the corresponding δ-lactone derivatives in moderate-to-good yields and with high enantioselectivities (up to 91% *ee*). The reactions can be carried out either under solvent-free conditions or in toluene. On the basis of the absolute configurations of the products and the hydrogen-bonding interaction pattern between TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol) and the carbonyl group disclosed by X-ray diffraction analysis, a possible mechanism for the catalytic reaction has been proposed. To demonstrate the usefulness of the methodology, a natural product, (*S*)-(+)-dihydrokawain, has also been prepared in 50% isolated yield and with 69% enantioselectivity in one step starting from 3-phenylpropionaldehyde by using this methodology. Therefore, this catalytic system is one of the most direct approaches to the construction of δ-lactone units, which will make the methodology very attractive for the synthesis of a variety of biologically important compounds and natural products.

Keywords: asymmetric catalysis · hetero-Diels–Alder reactions · hydrogen-bonding activation · lactones · organo catalysis · TADDOL

Introduction

Since the pioneering work of List, Barbas, and MacMillan and their co-workers in 2000,[1] the enantioselective catalysis of organic reactions involving small organic molecules as catalysts has become a rapidly growing area of research in the field of chiral chemistry because these reactions mimic enzyme processes.[2] In most of the asymmetric reactions involving carbonyl compounds, a central tenet is the selective activation of the carbonyl group by the catalyst through the coordination of its lone pair with a Lewis acid.[3] In principle, the proton can be considered the smallest hard Lewis acid. Accordingly, carbonyl activation by hydrogen bonding could be a viable strategy for catalysis and pave the way for asymmetric carbonyl reactions.[4] Several catalytic enantioselective reactions have been achieved very recently by hydrogen-bonding activation.[5] Of these, one of the most exciting developments is the 1-naphthyl-TADDOL-promoted hetero-Diels–Alder (HDA) reaction of 1-amino-3-siloxybutadiene with aldehydes reported by Rawal and co-workers (TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol), which affords the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones in excellent yields and enantioselectivities.[5b] Although a variety of catalytic asymmetric HDA reactions between dienes and carbonyl compounds have been reported to give dihydropyrones,[6] that can be converted to the corresponding δ-lactone derivatives, a type of heterocycle with extensive synthetic applications in biologically important natural and unnatural products,[7] the enantioselective HDA reaction of electron-rich 1,3-dimethoxy-1-(trimethylsiloxy)butadiene (Brassard's diene) with aldehydes to directly give δ-lactones has not yet been successful. Herein, we report our results on the development of the catalytic enantioselective HDA reaction of Brassard's diene with aldehydes through asymmetric hydrogen-bonding activation, as well as a one-step synthesis of (*S*)-(+)-dihydrokawain.

Results and Discussion

This research was inspired by our recent discovery during the optical resolution of the *anti* head-to-head coumarin dimer through molecular complexation with the diol host

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molecule, (*R*,*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (TADDOL, (*R*,*R*)-**1a**).[8,9] Decomposition of the molecular crystals formed between (*R*,*R*)-**1a** and the coumarin dimer in *N*,*N*-dimethylformamide (DMF) results in the formation of a new molecular complex, (*R*,*R*)-**1a**·DMF (**2**), and releases the enantiopure coumarin dimer. X-ray crystal structural analysis of the molecular crystal **2** showed that intramolecular hydrogen bonding exists between the two hydroxy groups of TADDOL and that a DMF molecule is included in the TADDOL host molecule through an intermolecular hydrogen-bonding interaction between one of the hydroxy groups and the lone pair of electrons of the carbonyl oxygen atom in DMF (Figure 1).[10] This structural information encouraged us to

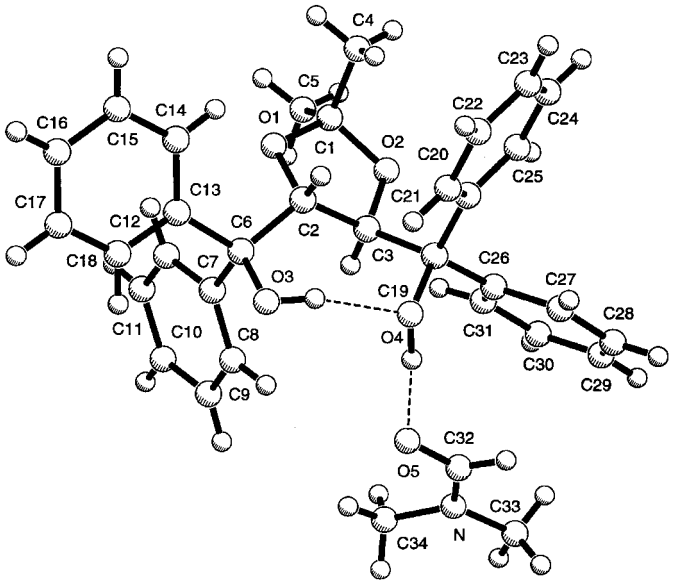
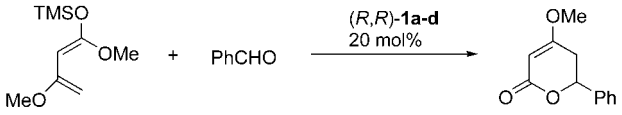


Figure 1. Molecular structure of (*R*,*R*)-**1a**·DMF (**2**).

carry out further asymmetric reactions involving activation of the carbonyl group through hydrogen bonding by replacing the DMF in the molecular complex with other carbonyl substrates, such as aldehydes or ketones.

Although the synthesis of optically active δ-lactones through the reaction of Brassard's diene (**3**) with optically active aldehydes has been achieved in the presence of Lewis acid catalysts,[11] to the best of our knowledge, no successful catalytic enantioselective HDA reactions of **3** with aldehydes (**4**), by using either organometallic catalysts or organocatalysts, have been reported. On the basis of the interaction between TADDOL (**1a**) and DMF mentioned above, we decided to investigate the viability of the catalytic enantioselective HDA reaction between **3** and **4** using TADDOL[8] as the catalyst. The reaction was carried out at room temperature with 0.5 mmol of **3** and 2.5 mmol of benzaldehyde (**4a**) using 20 mol% of (*R*,*R*)-**1a** under solvent-free conditions. The reaction proceeded enantioselectively to give 4-methoxy-6-phenyl-5,6-dihydropyran-2-one [(−)-**5a**] in 30% yield although the enantioselectivity was low (Table 1, entry 1). This result encouraged us to improve the enantioselectivity of the reaction by tuning the structure of the catalysts and the reaction conditions. As shown in Table 1, the use of catalyst (*R*,*R*)-**1b**, which was found to be highly efficient in Rawal's system,[5b] enhanced the yield and enantioselectivity of the reaction (Table 1, entry 2) under the same experimental conditions. By lowering the reaction temperature to −30 °C, the enantioselectivity was further improved to 71% with a yield of 70% if the reaction time was extended to 24 h (Table 1, entry 3). When the catalyst loading was reduced to 10 mol%, the enantioselectivity of the reaction remained constant although the yield dropped to 50% (Table 1, entry 4). In contrast, the use of 2-naphthyl-TADDOL derivative (*R*,*R*)-**1c** as catalyst gave the racemic product (Table 1, entry 5), which clearly demonstrates that aryl groups have a significant impact on the efficiency of asymmetric induction. Moreover, changing the R group in the backbone of TADDOL from methyl [(*R*,*R*)-**1b**] to 1,4-butylene (*R*,*R*)-**1d**] (Scheme 1) affected the enantioselectivity only slightly, but resulted in a lower yield (Table 1, entry 6). Therefore, from the performances of catalysts (*R*,*R*)-**1a–d**, the TADDOL derivative (*R*,*R*)-**1b** is evidently the best choice for the present reaction system in terms of both enantioselectivity and reactivity. Because the solvent-free reaction system was very viscous at a low reaction temperature (the melting point of benzaldehyde is −56 °C), toluene was added to the reaction system in order to reduce

Table 1. Enantioselective hetero-Diels–Alder reaction between Brassard's diene (**3**) and benzaldehyde (**4a**).[a]



3 **4a** **5a**

Entry	Catalyst	Solvent [mL]	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	free	RT	12	30	7
2	**1b**	free	RT	12	40	50
3	**1b**	free	−30	24	70	71
4[d]	**1b**	free	−30	24	50	72
5[d]	**1c**	free	−30	24	40	0
6[d]	**1d**	free	−30	24	37	74
7	**1b**	toluene (0.05)	−30	24	70	75
8	**1b**	toluene (0.1)	−30	24	68	76
9	**1b**	toluene (0.2)	−60	48	67	83
10	**1b**	toluene (0.4)	−60	48	50	86
11	**1b**	toluene (0.2)	−78	48	26	89

[a] All the reactions were carried out with 2.5 mmol of benzaldehyde and 0.5 mmol of Brassard's diene. [b] Yield of isolated product based on Brassard's diene. [c] The enantiomeric excesses of the products were determined by HPLC on a Chiralpak AD column; the sign of the optical rotation is "−". [d] 10 mol% of catalyst was used.

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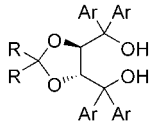


1a: Ar = phenyl R = CH_3
1b: Ar = 1-naphthyl R = CH_3
1c: Ar = 2-naphthyl R = CH_3
1d: Ar = 1-naphthyl R-R = $(CH_2)_4$

Scheme 1. The chiral diol catalysts employed in asymmetric catalysis.

the viscosity of the mixture. It was found that the addition of a small amount of toluene was favorable for the enantioselectivity (Table 1, entries 7 and 8), and it also allowed the reaction temperature to be further decreased to −60 °C, which afforded (−)-**5a** with 83–86 % *ee* without a significant reduction in yield (Table 1, entries 9 and 10). Although the enantioselectivity of the reaction could be improved to 89 % by reducing the reaction temperature to −78 °C, the yield of (−)-**5a** was poor (Table 1, entry 11).

BINOL-Ti and BINOL-Zn complexes have previously been reported to be efficient catalysts in the enantioselective hetero-Diels–Alder reaction of Danishefsky's diene and aldehydes.[12] These organometallic catalysts were also employed in the asymmetric hetero-Diels–Alder reactions between Brassard's diene (**3**) and benzaldehyde (**4a**) in order to compare the two catalytic systems. The optimized results are summarized in Table 2, and clearly demonstrate the advantages of organocatalysis over organometallic catalysis in this reaction system. Moreover, the reactions catalyzed by the organometallic catalysts hardly gave reproducible yields, which is probably due to the fact that Brassard's diene (**3**) decomposed in the presence of the Lewis acid before it reacted with the aldehydes.[13]

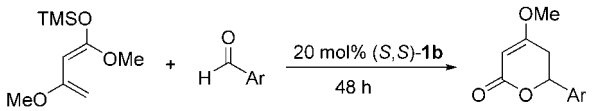
Table 2. Enantioselective HDA reactions between Brassard's diene (**3**) with benzaldehyde (**4a**) using chiral Lewis acids as the catalysts.[a]

Entry	Ligand	Metal	Solvent	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**7**	(*R*)-BINOL-Ti[d]	toluene	RT	24	38	70
2	**7**	(*R*)-BINOL-Ti[e]	toluene	RT	24	50	17
3	**8**	(*R*)-6,6′-Br_2-BINOL-Zn[f]	DME[g]	−30	24	50	62

[a] The reactions were carried out with 0.25 mmol of benzaldehyde and 0.5 mmol of Brassard's diene in 1.0 mL of solvent using 10 mol % of the catalyst. [b] Yield of isolated product of **5a**. [c] The enantiomeric excesses of the products were determined by HPLC on a Chiralpak AD column. The optical rotation of **5a** is "+". [d] BINOL/[Ti(O*i*Pr)$_4$] = 2:1. [e] BINOL/[Ti(O*i*Pr)$_4$] = 1:1. [f] 6,6′-Br_2-BINOL/Et_2Zn = 1:1.4. [g] DME = ethylene glycol dimethyl ether.

Under the optimized conditions, the substrate scope of this reaction system was then examined using **1b** as the catalyst. As shown in Table 3, this catalyst was effective for the reactions of a variety of aromatic aldehydes to give the corresponding 6-substituted 4-methoxy-5,6-dihydropyran-2-ones in 45–85 % yields and with 68–91 % *ee*. When solid aldehydes were employed as the substrates, it was necessary to use more toluene to ensure that the reaction mixture was an homogeneous solution (Table 3, entries 4–7). In particular, when 3-phenylpropionaldehyde **4i** was used as the substrate,

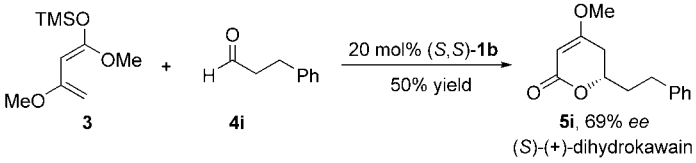
Table 3. The reaction of Brassard's diene with aldehydes catalyzed by **1b**.[a]



Entry	Ar	Toluene [mL]	Temp. [°C]	Yield [%][c]	*ee* [%][d]
1[b]	Ph **5a**	0.2	−60	67	83 (*S*)
2[b]	furyl **5b**	0.2	−60	80	87 (*S*)
3	*o*-MeC_6H_4 **5c**	0.2	−30	54	68 (*R*)
4	*p*-ClC_6H_4 **5d**	0.4	−30	85	76 (*R*)
5	*p*-BrC_6H_4 **5e**	0.4	−30	72	78 (*R*)[e]
6	*m*-BrC_6H_4 **5f**	0.4	−60	67	89 (*R*)
7	*o*-BrC_6H_4 **5g**	0.4	−60	75	82 (*R*)
8	*m*-$MeOC_6H_4$ **5h**	0.2	−60	45	91[f]

[a] All the reactions were carried with 2.5 mmol of benzaldehyde and 0.5 mmol of Brassard's diene. [b] The catalyst employed in this case was (*R*,*R*)-**1b**. [c] Yield of isolated product. [d] The enantiomeric excesses of the products were determined by HPLC on a Chiralpak AD column. The absolute configurations were assigned by comparing the Cotton effect of the CD spectra with that of **5e**. [e] The absolute configuration was determined by X-ray crystal structural analysis of **5e** on the basis of the anomalous dispersion of the heavy bromine atom. [f] The absolute configuration was not assigned.

a natural product, (*S*)-(+)-dihydrokawain (**5i**),[14] was obtained in one step in 50 % isolated yield and with 69 % *ee* (Scheme 2). Therefore, this catalytic system has provided one of the most direct and convenient approaches to the synthesis of δ-lactone derivatives, which are very useful in the synthesis of natural products and chiral drugs (for example, all of the Statin drugs, such as Lipitor, Zocor, and Pravacol, contain the chiral β-hydroxy-δ-lactone subunit).[15] Hence, this methodology will be very attractive from a synthetic point of view.



Scheme 2. One-step synthesis of (*S*)-(+)-dihydrokawain (**5i**).

The absolute configuration of (+)-**5e** was determined unambiguously by the Bijvoet method to be *R* with a Flack parameter of −0.004(15) on the basis of the anomalous dispersion of the bromine heavy atom (Figure 2). To determine the absolute configurations of the other products, the CD spectra of **5a**–**g** and **5i** were measured in $CHCl_3$. As shown in Figure 3, compounds (+)-**5c**–**g** exhibited a similar (+)

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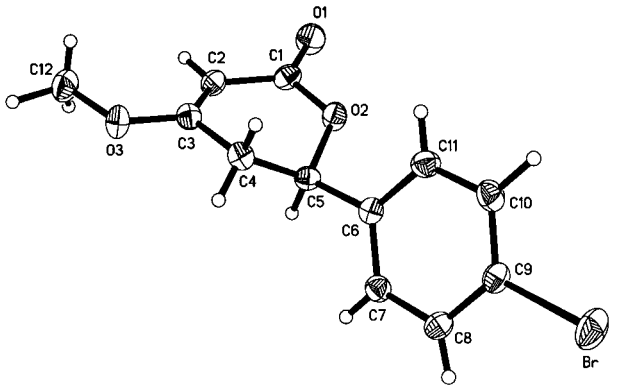

Figure 2. Molecular structure of (*R*)-(+)-**5e** in the crystal.

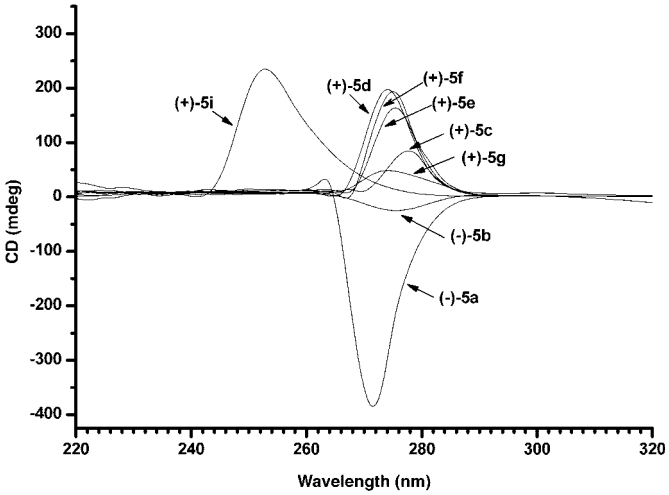

Figure 3. CD spectra of compounds **5a–g** and **5i** ($c = 0.01$ M in $CHCl_3$).

Cotton effect in their CD spectra. It can be deduced that these compounds possess the same *R* configuration as (+)-**5e**. On the other hand, compound (−)-**5a** and -**5b**, which were obtained with the opposite enantiomer of catalyst (*R*,*R*)-**1b**, exhibited a (−) Cotton effect and hence their absolute configurations can be assigned as *S*. Accordingly, it can be concluded that the reaction of the aromatic aldehydes afforded (*R*)-5,6-dihydropyran-2-one derivatives when (*S*,*S*)-**1b** was used whilst the reaction of the aliphatic aldehyde **4i** gave (*S*)-**5i** with the same catalyst.

On the basis of the observed absolute configurations of the products and the hydrogen-bonding interaction pattern in the crystal structure of **2**, a possible mechanism for asymmetric induction in this catalytic system can be outlined (Figure 4). When (*S*,*S*)-**1b** was used as the catalyst, the steric hindrance of the naphthyl moiety shields the *Si* face of the aldehyde, while the *Re* face is available to accept the attacking diene to give the products with the *R* configuration as expected. Although this model cannot quantitatively explain the impact of the aryl groups of TADDOL derivatives on their asymmetric induction in HDA reactions, it is evident that the strength of the intermolecular hydrogen bonding between the catalyst and the substrate, the greater steric hindrance of the 1-naphthyl group, and the π–π interaction between the naphthyl ring and the carbonyl group of the substrate all play important roles in the control of the enantioselectivity of the catalytic reactions.[5b]

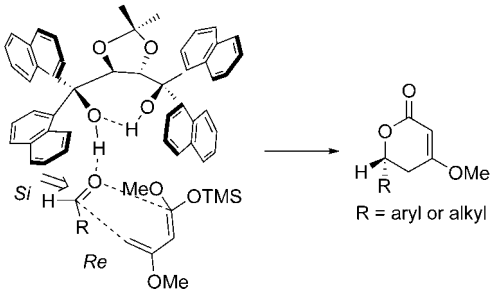

Figure 4. Possible mechanism for asymmetric induction in the enantioselective HDA reaction between Brassard's diene and aldehydes.

Conclusions

In conclusion, the first catalytic enantioselective hetero-Diels–Alder reaction of Brassard's diene with aldehydes has been achieved by catalysis with TADDOL derivatives through hydrogen-bonding activation to afford the corresponding δ-lactone derivatives in moderate-to-good yields and with high enantioselectivities (up to 91 % *ee*). On the basis of the absolute configurations of the products and the hydrogen-bonding interaction pattern between TADDOL and the carbonyl group disclosed by X-ray diffraction analysis, a possible mechanism for the enantioselective catalytic reaction has been proposed. Moreover, a natural product, (*S*)-(+)-dihydrokawain, has also been prepared in one step by using this methodology. Therefore, this catalytic system has provided one of the most direct and convenient approaches to the construction of δ-lactone units, which will make the methodology very attractive for the synthesis of a variety of biologically important compounds and natural products.[15]

Experimental Section

General considerations: ^{1}H NMR spectra were recorded on a Bruker AM300 NMR spectrometer (300 MHz) with $CDCl_3$ or [D_6]DMSO as solvent; chemical shifts are measured in ppm and coupling constants, *J*, in hertz. Mass spectra (EI, 70 eV) were recorded on a HP5989A spectrometer. HRMS data were measured on a Kratos Concept instrument. Elemental analysis was preformed on an Elemental VARIO EL apparatus. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 automatic polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. CD spectra were recorded on a JASCO 810 spectrometer in $CHCl_3$ at room temperature. HPLC analyses were carried out on a JASCO 1580 liquid chromatograph with a JASCO CD-1595 detector ($\lambda = 254$ nm) and AS-1555 autosampler. Toluene and tetrahydrofuran were distilled from sodium benzophenone ketyl under argon and degassed before use. All reactions were performed under argon.

Preparation of Brassard's diene (3):[11c] A solution of anhydrous THF (100 mL) and diisopropylamine (12.0 g, 118 mmol, 17.0 mL) was cooled to 0 °C, and *n*BuLi (1.6 M in hexane, 70 mL, 112 mmol) was added dropwise over 10 min. The pale yellow solution was stirred at 0 °C for 1 h and then cooled to −78 °C. Methyl 3-methoxy-2-butenoate (12.0 g, 100 mmol) was added slowly to the lithium diisopropylamide (LDA) solution, which

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was then stirred for 30 min at −78 °C. Chlorotrimethylsilane (20.0 mL, 16.9 g, 156 mmol) was slowly added to the solution at −78 °C, and the solution was stirred for 10 min. Then the mixture was allowed to warm to room temperature over 1 h. The solution was diluted with hexane (100 mL) and filtered. The solution was then concentrated to remove the solvent and the residue was distilled in vacuo (60–62 °C/2 mmHg) to afford Brassard's diene (**3**) (13.6 g, 78 % yield) as a colorless liquid ($E/Z > 95$ %). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.36$ (d, $J = 1.5$ Hz, 1H), 4.03 (d, $J = 1.2$ Hz, 1H), 3.99 (d, $J = 1.2$ Hz, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 0.26 (s, 9H) ppm.

Preparation of (*R*,*R*)-1-naphthyl-TADDOL [(*R*,*R*)-1b]:[16] Magnesium (2.0 g, 84 mmol), anhydrous THF (24 mL), and a grain of iodine were added to a flame-dried three-necked flask. 1-Bromonaphthane (16.6 g, 80 mmol) in THF (80 mL) was then added dropwise to prepare 1-naphthylmagnesium bromide. (*R*,*R*)-*O*,*O*′-Isopropylidene-L-tartaric acid diethyl ester (2.46 g, 10 mmol) in THF (50 mL) was added dropwise to the solution of 1-naphthylmagnesium bromide at room temperature over 1 h, and then the reaction mixture was refluxed for an additional 6 h. The reaction mixture was cooled to room temperature, and saturated NH_4Cl aqueous solution was added carefully to quench the reaction. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic phase was then dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel using toluene as eluent to give (*R*,*R*)-**1b** (3.3 g, 50 % yield) as a white solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 8.50$ (br s, 1H), 8.36 (br s, 1H), 7.98–7.64 (br m, 18H), 7.27–6.98 (br m, 8H), 6.72 (br s, 2H), 5.20 (br s, 2H), 0.05 (br s, 6H) ppm; IR (KBr): $\nu =$ 3569, 3352, 3047, 1598, 1509, 1395, 1381, 1370, 1235, 1216, 1168, 1057, 778 cm^{-1}.

By following the same procedure as described above, TADDOL derivatives **1a**, **1c**, and **1d** were prepared and their spectral data are summarized below.

(*R*,*R*)-1a: Yield 76 %; m.p. 195–196 °C (lit.[16] 195–196 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$–7.60 (m, 20H), 4.60 (s, 2H), 3.95 (s, 2H), 1.00 (s, 6H) ppm; IR (KBr): $\nu = 3589$, 3398, 3055, 2976, 2904, 2872, 1494, 1448, 1441, 1336, 1270, 1206, 1178, 1156, 1109 cm^{-1}

(*R*,*R*)-1c: Yield 82 %; m.p. 213–215 °C (lit.[16] 213–214.5 °C); ^{1}H NMR (300 MHz, [D$_6$]DMSO):[16] $\delta = 8.21$ (s, 2H), 7.97–7.91 (m, 8H), 7.80–7.72 (m, 6H), 7.65–7.43 (m, 12H), 7.32 (d, $J = 8.7$ Hz, 2H), 4.78 (s, 2H), 1.13 (s, 6H) ppm; IR (KBr): $\nu = 3550$, 3248, 3056, 2985, 1631, 1599, 1505, 1454, 1434, 1380, 1371, 1273, 1241, 1217, 1165, 1124, 1093, 1060, 1018, 886, 858, 815, 792, 756, 746 cm^{-1}.

(*R*,*R*)-1d: Yield 60 %; m.p. 187–189 °C; $[\alpha]_D^{20} = -24.7$ ($c = 1.0$ in $CHCl_2$); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 8.50$ (br m, 2H), 8.47–7.71 (br m, 18H), 7.23–6.95 (m, 8H), 6.72–6.70 (br m, 2H), 5.17 (br s, 2H), 1.01–0.97 (br m, 4H), 0.45–0.40 (br m, 2H), 0.02 to −0.02 (br m, 2H) ppm; MALDI-MS [M^++Na): 715.3; HRMS (MALDI): calcd for $C_{49}H_{40}O_4Na$: 715.2849; found: 715.2819; elemental analysis calcd. (%) for $C_{49}H_{40}O_4$: C 84.94, H 5.82; found: C 84.64, H 5.79; IR (KBr): $\nu = 3569$, 3350, 3047, 2955, 1598, 1509, 1395, 1334, 1199, 1121, 964, 899, 778 cm^{-1}.

General procedure for the catalytic asymmetric hetero-Diels–Alder reaction between Brassard's diene and aldehydes using 1b as catalyst: TADDOL derivative (*R*,*R*)-**1b** (66.6 mg, 0.1 mmol), freshly distilled benzaldehyde (**4a**) (265 mg, 2.5 mmol), and toluene (0.2 mL) were added to a dried Schlenk tube filled with argon. The Schlenk tube was then immersed in a cooling bath for 30 min to attain a temperature of −60 °C, and finally Brassard's diene (**3**) (102 mg, 0.5 mmol) was quickly added. The reaction mixture was stirred at −60 °C for 48 h, and then methanol (0.5 mL) was added. Evaporation of the solvent in vacuo gave the crude product which was purified by flash chromatography on silica gel with hexanes/ethyl acetate (2:1) as eluent to afford (*S*)-4-methoxy-6-phenyl-5,6-dihydropyran-2-one ((*S*)-**5a**) (68 mg, 67 % yield) as a white solid with 83 % *ee* (determined by HPLC on a Chiralpak AD column using hexane/2-propanol (85:15) as eluent, flow rate = 1.0 mL min^{-1}, $t_{R1} = 13.5$ min (minor), $t_{R2} = 15.4$ min (major)). $[\alpha]_D^{20} = -156.0$ ($c = 1.17$ in $CHCl_3$); m.p. 124–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$–7.36 (m, 5H), 5.44 (dd, $J = 12.0$, 3.6 Hz, 1H), 2.25 (d, $J = 0.9$ Hz, 1H), 3.79 (s, 3H), 2.89–2.79 (m, 1H), 2.64–2.57 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.5$, 166.8, 138.1, 128.6, 128.5, 125.9, 90.5, 77.4, 56.1, 35.0 ppm; EI-MS: *m*/*z* (%): 204 ([M]$^+$, 16.83), 98 (100), 68 (55.91), 69 (33.84), 40 (21.59), 77 (18.65), 39 (17.47), 105 (16.18); HRMS (EI): calcd for $C_{12}H_{12}O_3$: 204.0781; found: 204.0787; IR (KBr): $\nu = 3064$, 2983, 2947, 2913, 1718, 1620, 1456, 1384, 1290, 1228, 1070, 1025, 997, 761, 702 cm^{-1}.

General procedure for the catalytic asymmetric hetero-Diels–Alder reaction between Brassard's diene and benzaldehyde using chiral metal complexes as catalysts: A chiral diol ligand (**7** or **8**, 0.025 mmol), dried toluene or DME (1.0 mL), and a specific amount of [Ti(O*i*Pr)$_4$] or Et$_2$Zn were added to a dried Schlenk tube filled with argon (see Table 2). The mixture was stirred at room temperature for 0.5 h and then freshly distilled benzaldehyde (**4a**) (26.5 mg, 25 mmol, 25 μL) was introduced. The temperature of the reaction system was adjusted to the appropriate temperature (see Table 2), and finally Brassard's diene **3** (102 mg, 0.5 mmol, 100 μL) was quickly added. The reaction mixture was stirred for 24 h, and then methanol (0.5 mL) was added to quench the reaction. Evaporation of the solvent in vacuo gave the crude product which was purified by flash chromatography on silica gel with hexanes/ethyl acetate (2:1) as eluent to afford (*R*)-4-methoxy-6-phenyl-5,6-dihydropyran-2-one ((*R*)-**5a**) as a white solid. The results are summarized in Table 2.

(*S*)-4-Methoxy-6-(2-furyl)-5,6-dihydropyran-2-one ((*S*)-5b): A white solid prepared in 80 % yield and 87 % *ee* (determined by HPLC on a Chiralpak AD column using hexane/2-propanol (85:15) as eluent, flow rate = 1.0 mL min^{-1}, $t_{R1} = 21.2$ min (minor), $t_{R2} = 22.8$ min (major)); $[\alpha]_D^{20} = -56.0$ ($c = 0.95$ in $CHCl_3$); m.p. 124–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.44 (s, 1H), 6.45–6.44 (m, 1H), 6.40–6.38 (m, 1H), 5.47 (dd, $J = 11.4$, 4.2 Hz, 1H), 5.22 (s, 1H), 3.76 (s, 3H), 3.13–3.03 (m, 1H), 2.68–2.61 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.2$, 166.2, 150.1, 143.0, 110.4, 108.9, 90.2, 70.3, 56.1, 31.0 ppm. EI-MS: *m*/*z* (%): 194 ([M]$^+$, 16.83), 39 (100), 68 (83.59), 69 (45.55), 38 (25.45), 55 (24.19), 98 (16.15); HRMS (EI): calcd for $C_{10}H_{10}O_4$: 194.0574; found: 194.0572; IR (KBr): $\nu = 3143$, 3129, 3113, 3029, 2930, 1709, 1621, 1597, 1379, 1347, 1289, 1233, 1201, 1026, 1013, 823, 761 cm^{-1}.

(*R*)-4-Methoxy-6-(2-tolyl)-5,6-dihydropyran-2-one ((*R*)-5c): This product was obtained by using (*S*,*S*)-**1b** as the catalyst: a white solid prepared in 54 % yield and 68 % *ee* (determined by HPLC on a Chiralpak AD column using hexane/2-propanol (85:15) as eluent, flow rate = 1.0 mL min^{-1}, $t_{R1} = 12.6$ min (major), $t_{R2} = 14.5$ min (major)); $[\alpha]_D^{20} =$ +146.2 ($c = 1.17$ in $CHCl_3$); m.p. 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.51$–7.48 (m, 1H), 7.28–7.22 (m, 2H), 7.19–7.16 (m, 1H), 5.61 (dd, $J = 12.3$, 3.6 Hz, 1H), 5.25 (d, $J = 1.5$ Hz, 1H), 3.79 (s, 3H), 2.86–2.76 (m, 1H), 2.54–2.47 (m, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.8$, 167.1, 136.1, 134.7, 130.6, 128.4, 126.4, 126.0, 90.4, 74.6, 56.1, 33.8, 19.0 ppm; EI-MS *m*/*z* (%): 218 ([M]$^+$, 5.33), 98 (100), 68 (88.54), 172 (75.07), 91 (59.59), 69 (58.52), 130 (39.40), 99 (38.06), 119 (36.97); HRMS (EI): calcd for $C_{13}H_{14}O_3$: 218.0937; found: 218.0940; IR (KBr): $\nu = 2978$, 2975, 1711, 1620, 1386, 1287, 1244, 1231, 1070, 1026, 991, 780 cm^{-1}.

(*R*)-4-Methoxy-6-(4-chlorophenyl)-5,6-dihydropyran-2-one ((*R*)-5d): This product was obtained by using (*S*,*S*)-**1b** as the catalyst: a white solid prepared in 85 % yield and 76 % *ee* (determined by HPLC on a Chiralpak AD column using hexane/2-propanol (85:15), flow rate = 1.0 mL min^{-1}, $t_{R1} = 18.2$ min (major), $t_{R2} = 21.9$ min (minor)); m.p. 180–182 °C; $[\alpha]_D^{20} =$ +141.0 ($c = 1.07$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$ (s, 1H), 5.42 (dd, $J = 12.0$, 3.9 Hz, 1H), 5.25 (d, $J = 1.5$ Hz, 1H), 3.80 (s, 3H), 2.84–2.74 (m, 1H), 2.63–2.56 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.3$, 166.5, 136.7, 134.3, 128.8, 127.3, 90.5, 76.3, 56.2, 34.9. EIMS *m*/*z* (relative intensity): 238 ([M]$^+$, 13.57), 98 (100), 68 (56.07), 69 (32.77), 139 (16.57), 111 (11.84), 127 (5.73); HRMS (EI): calcd for $C_{12}H_{11}ClO_3$: 238.0392; found: 238.0390; elemental analysis calcd (%) for $C_{12}H_{11}ClO_3$: C 60.39, H 4.65; found: C 60.38, H 4.66; IR (KBr): $\nu = 3085$, 3035, 2993, 2945, 2899, 1705, 1620, 1493, 1456, 1441, 1386, 1288, 1230, 1176, 1072, 1029, 1013, 999, 834 cm^{-1}.

(*R*)-4-Methoxy-6-(4-bromophenyl)-5,6-dihydropyran-2-one ((*R*)-5e): This product was obtained by using (*S*,*S*)-**1b** as the catalyst: a white solid prepared in 72 % yield and 78 % *ee* (determined by HPLC on a Chiralpak AD column using hexane/2-propanol (85:15), flow rate = 1.0 mL min^{-1}, $t_{R1} = 19.4$ min (major), $t_{R2} = 23.6$ min (minor)); m.p. 165–167 °C; $[\alpha]_D^{20} =$ +117.2 ($c = 1.09$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.56$ (d, $J =$ 8.4 Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 5.43 (dd, $J = 12.3$, 4.2 Hz, 1H), 5.28 (s, 1H), 3.82 (s, 3H), 2.85–2.75 (m, 1H), 2.65–2.68 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.3$, 166.5, 137.2, 131.7, 127.6, 122.5, 90.4,

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76.3, 56.2, 34.8 ppm; EI-MS: *m/z* (%): 282 ([*M*]$^+$, 11.93), 98 (100), 68 (54.94), 69 (31.96), 183 (12.03), 284 (11.78), 155 (7.91); HRMS (EI): calcd. for $C_{12}H_{11}BrO_3$: 281.9886; found: 281.9892; elemental analysis calcd (%) for $C_{12}H_{11}BrO_3$: C 50.91, H 3.92; found: C 50.76, H 3.84; IR (KBr): ν = 3085, 2991, 2943, 2898, 1703, 1620, 1490, 1440, 1384, 1286, 1230, 1177, 1072, 1029, 1010, 924, 842, 829 cm^{-1}.

(*R*)-4-Methoxy-6-(3-bromophenyl)-5,6-dihydropyran-2-one ((*R*)-5 f): This product was obtained by using (*S*,*S*)-**1b** as the catalyst: a white solid prepared in 67% yield and 89% *ee* (determined by HPLC on a Chiralpak AD column using hexane/2-propanol (85:15), flow rate = 1.0 mL min^{-1}, t_{R1} = 14.0 min (major), t_{R2} = 17.0 min (minor)); m.p. 88–90 °C; $[\alpha]_D^{20}$ = +162.2 (*c* = 1.09 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.34–7.22 (m, 2H), 5.38 (dd, *J* = 12.0, 0.9 Hz, 1H), 5.24 (s, 1H), 3.78 (s, 3H), 2.82–2.76 (m, 1H), 2.62–2.55 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 166.4, 140.4, 131.6, 130.2, 129.0, 124.5, 122.7, 90.5, 76.2, 56.2, 34.9 ppm; EI-MS: *m/z* (%): 282 ([*M*]$^+$, 11.94), 98 (100), 68 (47.51), 69 (29.18), 40 (11.64), 284 (11.55), 183 (7.99), 155 (5.17); HRMS (EI): calcd for $C_{12}H_{12}O_3$: 204.0781; found: 204.0787; elemental analysis calcd (%) for $C_{12}H_{11}BrO_3$: C 50.91, H 3.92; found: C 51.11, H 3.92; IR (KBr): ν = 3106, 3014, 2942, 1712, 1626, 1568, 1386, 1355, 1227, 1174, 1072, 1028, 994, 877, 834, 802, 690 cm^{-1}.

(*R*)-4-Methoxy-6-(2-bromophenyl)-5,6-dihydropyran-2-one ((*R*)-5 g): This product was obtained by using (*S*,*S*)-**1b** as the catalyst: a white solid prepared in 75% yield and 82% *ee* (determined by HPLC on a Chiralpak AD column with hexane/isopropanol (85:15), flow rate = 1.0 mL min^{-1}, t_{R1} = 11.0 min (major), t_{R2} = 12.4 min (minor)); m.p. 142–144 °C; $[\alpha]_D^{20}$ = +210.4 (*c* = 1.04 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.29–7.24 (m, 1H), 7.57 (dd, *J* = 12.3, 3.6 Hz, 1H), 5.29 (s, 1H), 3.82 (s, 3H), 2.87–2.80 (m, 1H), 2.66–2.57 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 166.7, 137.6, 132.8, 129.9, 127.7, 121.0, 90.4, 76.4, 56.2, 33.7 ppm; EI-MS: *m/z* (%): 282 ([*M*]$^+$, 6.23), 98 (100), 68 (59.58), 69 (36.49), 40 (24.66), 159 (22.97), 115 (7.36), 183 (6.04); HRMS (EI): calcd. for $C_{12}H_{11}BrO_3$: 281.9886; found: 281.9885; IR (KBr): ν = 3078, 2979, 2947, 2854, 1712, 1620, 1386, 1233, 1184, 1073, 1022, 996, 850, 775 cm^{-1}.

4-Methoxy-6-(3-methoxyphenyl)-5,6-dihydropyran-2-one (5 h): This product was obtained by using (*S*,*S*)-**1b** as the catalyst: a white solid prepared in 45% yield and 91% *ee* (determined by HPLC on a Chiralpak AD column using hexane/2-propanol (85:15), flow rate = 1.0 mL min^{-1}, t_{R1} = 17.6 min (major), t_{R2} = 20.7 min (minor)); m.p. 90–92 °C; $[\alpha]_D^{20}$ = +167.2 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.8 Hz, 1H), 6.99–6.97 (m, 1H), 6.91–6.88 (m, 1H), 5.41 (dd, *J* = 12.3, 4.2 Hz, 1H), 5.26 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.83–2.78 (m, 1H), 2.64–2.56 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 166.8, 159.8, 139.8, 129.7, 118.1, 114.1, 111.4, 90.5, 76.9, 56.1, 55.3, 35.0 ppm; EI-MS: *m/z* (%): 234 (*M*$^+$, 63.44), 98 (100), 68 (86.24), 69 (50.88), 135 (35.81), 77 (31.80), 176 (7.93); HRMS (EI): calcd for $C_{13}H_{12}O_4$: 234.0887; found: 2234.0883; IR (KBr): ν = 3096, 3013, 2945, 2838, 1702, 1625, 1585, 1490, 1458, 1448, 1388, 1289, 1244, 1227, 1202, 1032, 998, 786 cm^{-1}.

(*S*)-4-Methoxy-6-(2-phenylethyl)-5,6-dihydropyran-2-one ((*S*)-5 i): This product was obtained by using (*S*,*S*)-**1b** as the catalyst: a white solid prepared in 50% yield and 69% *ee* (determined by HPLC on a Chiralcel OB-H column using hexane/isopropanol (85:15), flow rate = 1.2 mL min^{-1}, t_{R1} = 42.5 min (*R*, minor), t_{R2} = 56.1 min (*S*, major)). The absolute configuration of **5i** was determined to be *S* by comparison of its chiroptical rotation with that reported in the literature.[14] $[\alpha]_D^{20}$ = +18.5 (*c* = 0.97 in $CHCl_3$); m.p. 56–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 2H), 7.23–7.19 (m, 3H), 5.15 (d, *J* = 1.5 Hz, 1H), 4.40–4.34 (m, 1H), 3.74 (s, 1H), 2.90–2.79 (m, 2H), 2.58–2.48 (m, 1H), 2.34–2.29 (m, 1H), 2.18–2.10 (m, 1H), 1.92 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 167.3, 104.8, 128.5, 128.4, 126.1, 90.3, 74.7, 56.0, 36.3, 33.0, 30.9 ppm; EI-MS: *m/z* (%): 232 ([*M*]$^+$, 30.04), 127 (100), 91 (70.87), 39 (55.20), 117 (43.82), 68 (37.02), 200 (23.23), 141 (20.00), 155 (16.30); HRMS (EI): calcd. for $C_{14}H_{16}O_3$: 232.1094; found: 232.1102; IR (KBr): ν = 3087, 3063, 3028, 2943, 2857, 1708, 1625, 1605, 1497, 1456, 1444, 1396, 1374, 1295, 1396, 1374, 1249, 1224, 1039, 1000, 912, 824, 732, 701 cm^{-1}.

X-ray crystallographic analysis of 2:[10] A single crystal of **2** was obtained by recrystallization of TADDOL in DMF/H_2O (5:1). X-ray crystallographic analysis was performed at 20 °C by using a Rigaku AFC7R diffractometer with graphite monochromated $Mo_{K\alpha}$ radiation (λ = 0.71069 Å). A total of 3870 reflections were measured and 1933 were unique [$I > 2.50\sigma(I)$]. The structure was solved by direct methods (SHELX-97)[17] and refined by full-matrix least-squares to R = 0.063, wR = 0.072. Crystal data for **2** ($C_{34}H_{37}O_5N$): orthorhombic, $P2_12_12_1$, a = 10.277(4), b = 29.928(6), c = 9.616(3) Å, $\alpha = \beta = \gamma = 90°$, V = 2957(1) Å^3, ρ_{calcd} = 1.212 g cm^{-3}, Z = 4.

X-ray crystallographic analysis of (*R*)-(+)-5 e:[10] A single crystal of (+)-**5e** was obtained by slow evaporation of its solution in dichloromethane/hexane (1:2) at room temperature. X-ray crystallographic analysis was performed with a Bruker SMART CCD-APEX at 20 °C using graphite monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). A total of 6832 reflections were measured and 2517 were unique (R_{int} = 0.0800). The structure was solved by direct methods (SHELX-97)[17] and refined by full-matrix least-squares to R = 0.0455, wR = 0.1016. Crystal data for (+)-**5e** ($C_{12}H_{11}BrO_3$): orthorhombic, $P2_12_12_1$, a = 7.0582(9), b = 8.4182(11), c = 19.142(2) Å, $\alpha = \beta = \gamma = 90°$, V = 1137.3(3) Å^3, ρ_{calcd} = 1.653 g cm^{-3}, Z = 4. The absolute configuration of (+)-**5e** was determined unambiguously by the Bijvoet method to be *R* with a Flack parameter of −0.004(15) on the basis of the anomalous dispersion of the bromine heavy atom.

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