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A New Class of Enantioselective Catalytic 2-Pyrone Diels–Alder Cycloadditions

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Abstract: A highly enantioselective catalytic Diels–Alder (DA) cycloaddition of 2*H*-pyran-2,5-diones (synthon of 5-hydroxy-2-pyrones) has been developed with a *Cinchona*-derived thiourea as the catalyst. The conditions were optimized by using 0.2 equiv. of the catalyst and 0.1 equiv. of formic acid in 2-propanol at room temperature, which afforded the DA products in yields of up to 90% (*exo*/*endo* = 5.5:1, 98% *ee*) with *trans*-β-nitrostyrene derivatives as the dienophiles. The structure/activity relationships of the bifunctional catalyst and the effects of the steric, electronic and hydrogen-bonding properties of the dienophiles have been studied.

Keywords: asymmetric Diels–Alder reaction; enantioselectivity; nitrostyrenes; organocatalysis; 2*H*-pyran-2,5-diones; thiourea-*Cinchona* derivatives

Introduction

The Diels–Alder (DA) cycloaddition of 2-pyrones is a useful method in organic synthesis since it can provide functionalized cyclohexadienes or bridged bicyclic lactones in a single operation.[1] Indeed, this class of DA cycloadditions has been successfully utilized in natural product synthesis.[2] However, examples of highly enantioselective catalytic 2-pyrone DA cycloadditions are still very limited, probably due to the partial aromatic character of 2-pyrones and their low reactivity towards common dienophiles.[1,3] In 2007, Deng's group reported a highly enantioselective catalytic DA cycloaddition of 3-hydroxy-2-pyrone using a *Cinchona*-derived bifunctional catalyst.[4] They proposed that the hydrogen bonding between the C-3 hydroxy group of the 2-pyrone and the Brønsted base moiety of the catalyst is important for the high enantioselectivity.[4a] This reaction was first reported by Nakatani's group using a Brønsted base as the catalyst in 1995.[5] Recently, Tan's group reported an analogous DA cycloaddition of 3-hydroxy-2-pyridone dienes using an aminoindanol catalyst with excellent enantioselectivity.[6]

In the course of developing new methods for construction of the tricyclic core of basiliolide B,[7] we have found that 2*H*-pyran-2,5-diones can be used as a synthon of 5-hydroxy-2-pyrones for DA cycloadditions.[8] As shown in Figure 1, 2*H*-pyran-2,5-dione **1** reacted with *trans*-disubstituted dienophiles in the presence of a catalytic amount of dicyclohexylmethylamine or pyrrolidine in *t*-BuOH and afforded modest to good yields of the DA products with excellent *exo* selectivity. We herein report the development of this class of 2-pyrone DA cycloadditions into a highly enantioselective catalytic transformation.

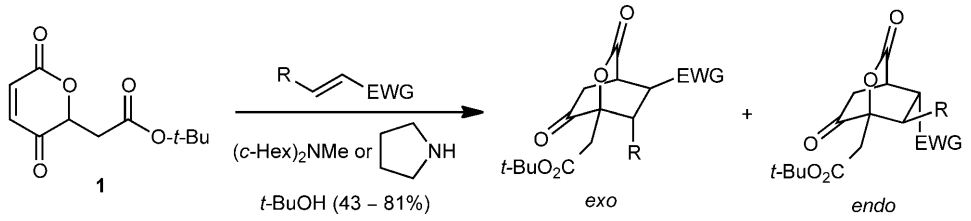


Figure 1. DA cycloaddition of 2*H*-pyran-2,5-dione **1**.

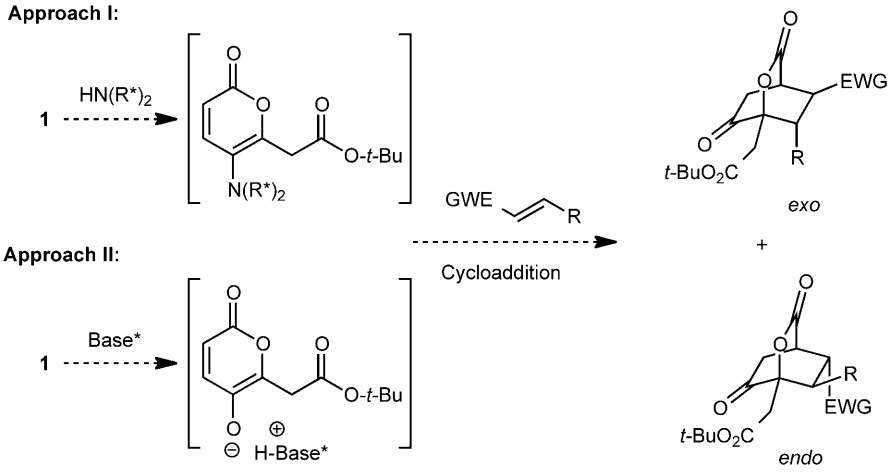


Figure 2. Approaches for developing enantioselective catalytic DA cycloaddition of 2*H*-pyran-2,5-dione **1**.

Activation of the substrates *via* enamine or iminium formation has been a popular approach in developing organocatalytic transformations.[9] Recently, organic Brønsted acids and Brønsted bases have been shown to be a promising alternative in the field of organocatalysis.[10] Since our previous study showed that dicyclohexylmethylamine and pyrrolidine are effective catalysts for the DA cycloaddition of 2*H*-pyran-2,5-diones, two approaches base on the structural frameworks of the catalysts could be employed. As shown in Figure 2, the enone moiety of **1** could be either converted to an enamine diene with a chiral cyclic secondary amine or to an enolate diene with a chiral Brønsted base. These resulting diene intermediates are anticipated to undergo DA cycloadditions stereoselectively.

Results and Discussions

Thus the catalytic activities of a variety of cyclic secondary amines[9] for the DA cycloaddition of 2*H*-pyran-2,5-dione **1** with *trans*-β-nitrostyrene in *t*-BuOH were investigated (Figure 3). As shown in Table 1, L-proline (**3a**) gave only 15% yield of the DA products (*exo*/*endo* = 4.2:1) and very poor enantioselectivity (entry 1). Switching to L-prolinol (**3b**) improved the yield to 46% (*exo*/*endo* = 5.8:1) with 22% *ee* for the *exo* product (entry 2). This encouraging result prompted us to evaluate the catalytic activities of other L-proline derivatives. However, *O*-methyl-L-prolinol (**3c**) could only slightly improve the *ee* value (entry 3) and the enantioselectivities obtained by using **3d–f** were disappointing (entries 4–6). MacMillan's catalysts (**4a** and **4b**)[11] were found to be not effective for this DA cycloaddition, providing only trace amount of the DA products in 7 days (entries 7 and 8). These results indicated that the L-phenylalanine derivatives could be too bulky for enamine formation with **1**. Since derivatives of *Cinchona* alkaloids, which possess both hydrogen bond donor and acceptor moieties, have been demonstrated to be versatile Brønsted base catalysts in many enantioselective reactions,[12] we decided to study the catalytic activities of a variety of *Cinchona* derivatives in the DA cycloaddition. When quinine (**5a**) was used as the catalyst, the DA cycloaddition was finished in 7 h and afforded a 33% yield of the DA products (*exo*/*endo* = 2.5:1) with −35% *ee* for the *exo* product (entry 9). *Cinchona* derivative **5b**[4b,13] afforded a similar yield of the DA products with a higher *exo*/*endo* ratio but a lower *ee* value (entry 10). As thioureas are known to be able to activate carbonyl and nitro groups *via* efficient hydrogen bonding interactions,[14–16] *Cinchona* thiourea **6a**[16e] was employed. This bifunctional catalyst successfully led to a complete reaction in 9 h and furnished 73% yield of the DA products (*exo*/*endo* = 6.0:1) with 72% *ee* for the *exo* product (entry 11).

The DA cycloaddition conditions were then further optimized by examining the effects of different solvents. Among the alcohol solvents used, *i*-PrOH showed the best result, providing 88% yield of the DA products (*exo*/*endo* = 7.0:1) with 94% *ee* for the *exo* product (entry 3, Table 2). The DA cycloaddition went much moreslowly in toluene or CH_2Cl_2 and gave poor *exo*/*endo* ratios and modest enantioselectivity (entries 5 and 6). Switching the solvent to CH_3CN, ethyl acetate, diethyl ether or THF led to higher diastereoselectivities (entries 7–10). Among these solvents, THF gave the highest *exo*/*endo* ratio (17:1) with 85% *ee* for the *exo* product (entry 10). After the study of the solvent effects, the effects of catalyst loading and reaction temperature were also examined with *i*-PrOH as the solvent. As shown in Table 2, reducing the catalyst loading to 0.05 or 0.1 equiv. decreased the reaction rate dramatically (7–11 days) and gave low yields and poor selectivities (entries 11 and 12). The DA cycloaddition proceeded much faster

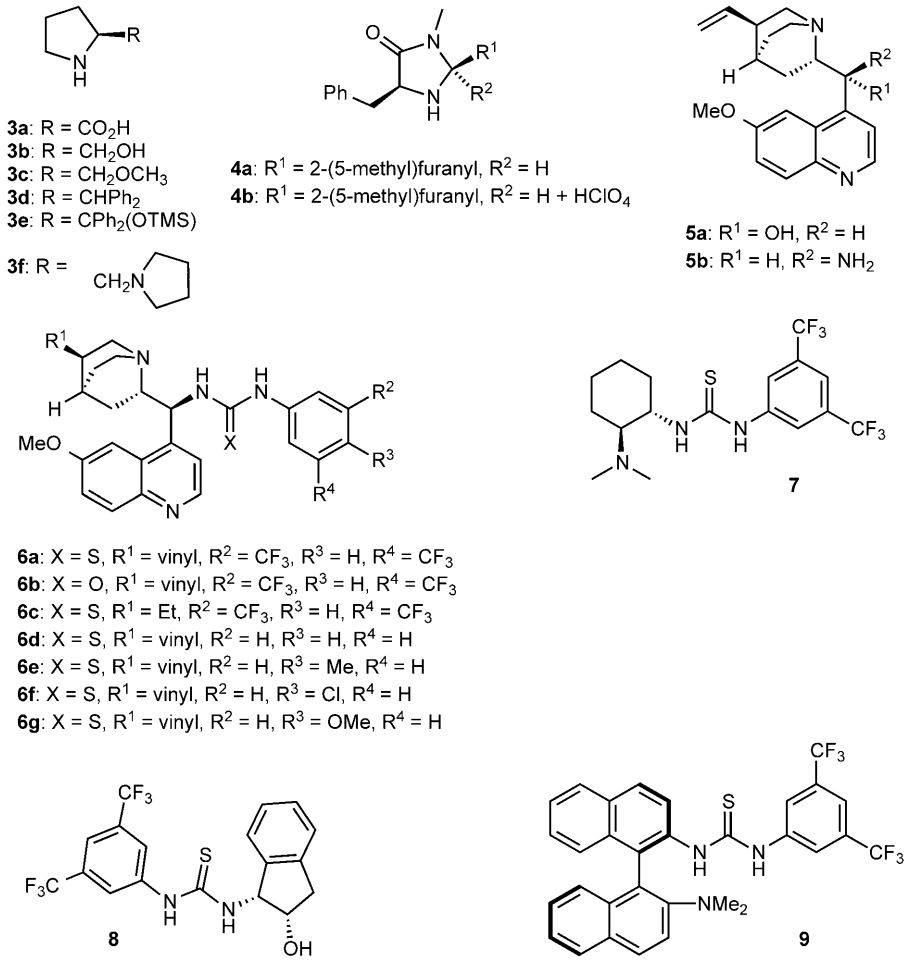


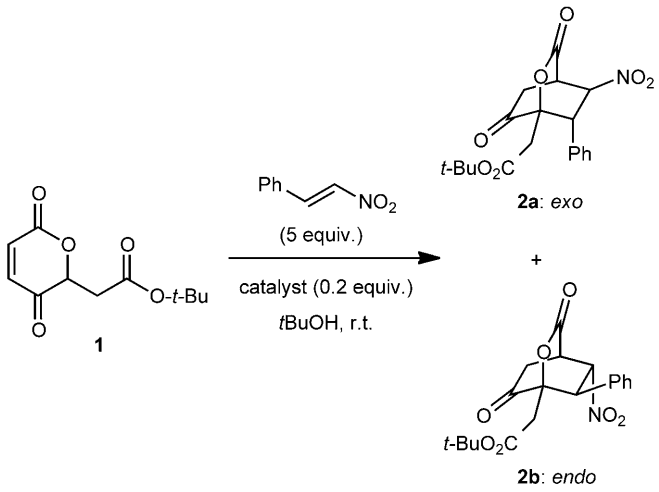
Figure 3. Structures of the catalysts.

with 0.15 equiv. of the catalyst, but only a slightly higher enantioselectivity was observed (entry 13). Surprisingly, a brief survey on the temperature effects showed that either increasing or decreasing the reaction temperature led to significant drops in *ee* values (entries 14 and 15).

To investigate the structure/activity relationships of the catalyst, a variety of *Cinchona* derivatives was employed as the catalyst for the DA cycloaddition. As shown in Table 3, varying the catalyst structures did not affect the yields of the DA products but led to significant changes in *exo*/*endo* ratios and *ee* values. Urea **6b** gave only modest selectivities (*exo*/*endo* = 4.8:1 with 66% *ee* for the *exo* product) (entry 2), suggesting the thiourea is important for high selectivities. Switching to the hydrogenated derivative (**6c**) led to a higher *exo*/*endo* ratio but a slightly lower *ee* value (entry 3). Replacing the bis(trifluoro)phenyl by a phenyl group (**6d**)[17] also led to a lower *exo*/*endo* ratio and a lower *ee* value (entry 4). Introducing a methyl (**6e**), a halo or a methoxy substitute (**6g**) to the 4-position of the phenyl group caused significant drops in diastereoselectivity and enantioselectivity (entries 5–7). Only the 4-chlorophenyl derivative (**6f**)[17] provided a satisfactory *ee* value (86% *ee*) for the *exo* product (entry 7). The 4-fluoro- and 4-bromophenyl derivative just gave 55 and 76% *ee*, respectively (data not shown). These results suggested that the electronic properties of the aromatic moiety of the catalyst can considerably affect the enantioselectivity of the DA product. The effects of the skeleton of different Brønsted bases were also examined. Takemoto's catalyst[16c] (**7**) afforded a higher yield of the DA products but a lower *exo*/*endo* ratio and a lower *ee* value (entry 9). However, both Sibi's catalyst[18] (**8**) and Wang's catalyst[19] (**9**) were found to be not effective for the DA cycloaddition (entries 10 and 11), which indicated that the basicity of the Brønsted base is essential for the 2-pyrone DA cycloaddition.

Since addition of acid may affect the basicity of the Brønsted base and the hydrogen bondings between the substrates and the catalyst, the effects of acid additives in the DA cycloadditions with *i*-PrOH as the solvent were first studied with different amounts of formic acid. As shown in Table 4, the yields and enantioselectivity of the DA cycloaddition were found to

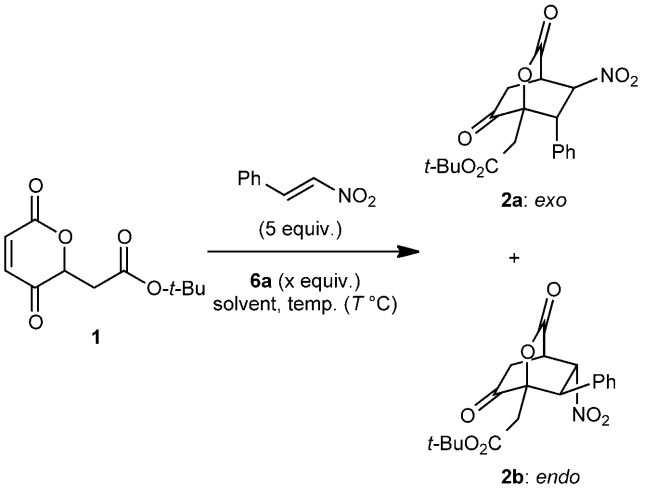
Table 1. Enantioselective DA cycloaddition of 2*H*-pyran-2,5-dione **1**.[a]



No.	Catalyst	Time	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**3a**	5 d	15	4.2:1	<5
2	**3b**	3 d	46	5.8:1	22
3	**3c**	3 d	40	5.5:1	26
4	**3d**	2 d	51	5.1:1	<5
5	**3e**	18 h	53	6.3:1	<5
6	**3f**	7 d	36	5.7:1	<5
7	**4a**	7 d	trace	n.d.[e]	n.d.[e]
8	**4b**	7 d	trace	n.d.[e]	n.d.[e]
9	**5a**	7 h	33	2.5:1	−35
10	**5b**	10 h	37	4.2:1	20
11	**6a**	9 h	73	6.0:1	72

[a] The general procedures were followed with *t*-BuOH as the solvent.
[b] Total isolated yields [%] of *exo* and *endo* products after silica gel column chromatography.
[c] *dr* = *exo*/*endo* ratios, which were estimated by ^{1}H NMR (δ_{exo} = 3.75 ppm and δ_{endo} = 3.99 ppm).
[d] The% *ee* of the *exo* product, determined by chiral HPLC.
[e] n.d. = not determined.

Table 2. Optimization of the DA cycloaddition conditions.[a]



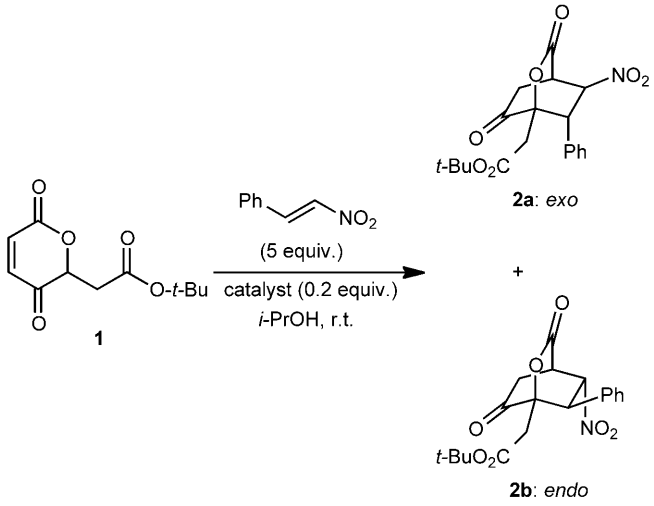
No.	Solvent	*T*[b] [°C]	x[c]	Time	Yield [%][d]	*dr*[e]	*ee* [%][f]
1	MeOH	r.t.	0.2	12 h	48	2.0:1	39
2	EtOH	r.t.	0.2	12 h	70	6.0:1	79
3	*i*-PrOH	r.t.	0.2	9 h	88	7.0:1	94
4	*t*-BuOH	r.t.	0.2	9 h	73	6.0:1	72
5	toluene	r.t.	0.2	24 h	27	2.0:1	56
6	CH_2Cl_2	r.t.	0.2	24 h	60	2.0:1	66
7	CH_3CN	r.t.	0.2	6 h	78	8.0:1	71
8	EtOAc	r.t.	0.2	7 h	72	12:1	75
9	Et_2O	r.t.	0.2	9 h	80	14:1	75
10	THF	r.t.	0.2	9 h	72	17:1	85
11	*i*-PrOH	r.t.	0.05	11 d	45	3.2:1	40
12	*i*-PrOH	r.t.	0.1	7 d	57	3.6:1	46
13	*i*-PrOH	r.t.	0.15	27 h	83	4.4:1	55
14	*i*-PrOH	40	0.2	9 h	74	5.6:1	57
15	*i*-PrOH	−20	0.2	3 d	25	2.6:1	43

[a] The general procedures were followed with the indicated solvent.
[b] *T* = reaction temperature.
[c] x = equivalents of the catalyst used.
[d] Total isolated yields [%] of *exo* and *endo* products after silica gel column chromatography.
[e] *dr* = *exo*/*endo* ratios, which were estimated by ^{1}H NMR (δ_{exo} = 3.75 ppm and δ_{endo} = 3.99 ppm).
[f] The% *ee* of the *exo* product, determined by chiral HPLC.

be very sensitive to the catalyst/acid ratio (entries 1–4). The optimal ratio of catalyst/formic acid is 2:1, which gave 90% yield of the DA products (*exo*/*endo* = 5.5:1) with 98% *ee* for the *exo* product (entry 2). Switching to acetic acid or benzoic acid decreased the yields and *ee* values gently (entries 5 and 6). Strong acid, such as TFA and TsOH led to much slower reactions with low yields and poor enantioselectivity (entries 7 and 8). Since THF afforded the optimal *exo*/*endo* ratio, the effects of the acid additive in THF were also studied. Although the enantioselectivity was slightly improved, only a modest yield of the DA products was obtained (entry 9).

With the optimal reaction condition in hand, the 2-pyrone DA cycloadditions of **1** with a variety of *trans*-β-nitrostyrene derivatives as the dienophile were studied and the results are summarized in Table 5. Dienophiles with 4-methyl- or 4-halophenyl substituents generally proceeded much more slowly (3-6 days) at room temperature and gave slightly lower yields of the DA products with comparable *exo*/*endo* ratios and *ee* values (entries 1–4, and 7). On the other hand, a strong electron-donating group (OMe) at the 4-position led to a much lower *ee* value (entry 8). Interestingly, switching the OMe to OH provided a much higher enantioselectivity (entry 11). Moreover, dieno-

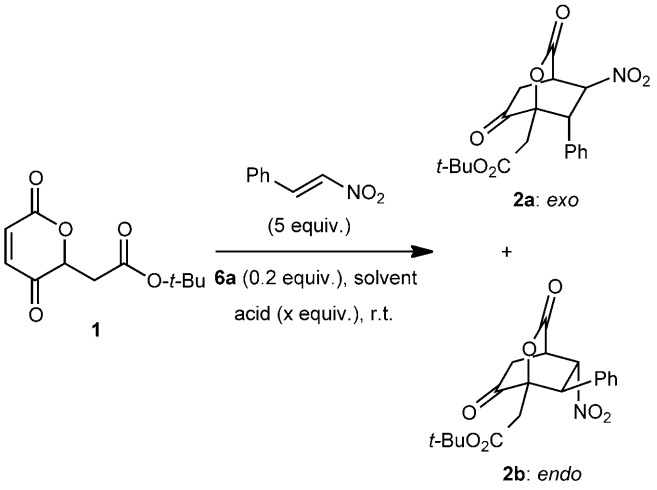
Table 3. DA cycloaddition with various catalysts.[a]



No.	Catalyst	Time	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**6a**	9 h	88	7.0:1	94
2	**6b**	12 h	88	4.8:1	66
3	**6c**	12 h	82	8.0:1	83
4	**6d**	12 h	86	3.6:1	63
5	**6e**	12 h	85	3.4:1	67
6	**6f**	12 h	88	3.6:1	86
7	**6g**	12 h	85	3.7:1	55
8	**7**	14 h	92	4.9:1	63
9	**8**	10 d	–	n.d.[e]	n.d.[e]
10	**9**	10 d	trace	n.d.[e]	n.d.[e]

[a] The general procedures were followed with *i*-PrOH as the solvent.
[b] Total isolated yields [%] of *exo* and *endo* products after silica gel column chromatography.
[c] *dr* = *exo*/*endo* ratios, which were estimated by ^{1}H NMR (δ_{exo} = 3.75 ppm and δ_{endo} = 3.99 ppm).
[d] The% *ee* of the *exo* product, determined by chiral HPLC.
[e] n.d. = not determined.

Table 4. DA cycloaddition with various acid additives.[a]



No.	Acid/Solvent	x[b]	Time	Yield [%][c]	*dr*[d]	*ee* [%][e]
1	HCO_2H/*i*-PrOH	0.05	7 h	65	5.0:1	65
2	HCO_2H/*i*-PrOH	0.1	44 h	90	5.5:1	98
3	HCO_2H/*i*-PrOH	0.2	2 d	43	5.4:1	61
4	HCO_2H/*i*-PrOH	0.4	2 d	65	5.0:1	74
5	AcOH/*i*-PrOH	0.1	17 h	85	5.0:1	80
6	$PhCO_2H$/*i*-PrOH	0.1	37 h	74	6.0:1	80
7	TFA/*i*-PrOH	0.1	5 d	38	8.0:1	32
8	TsOH/*i*-PrOH	0.1	16 d	13	n.d.[f]	30
9	HCO_2H/THF	0.1	16 h	66	13:1	90

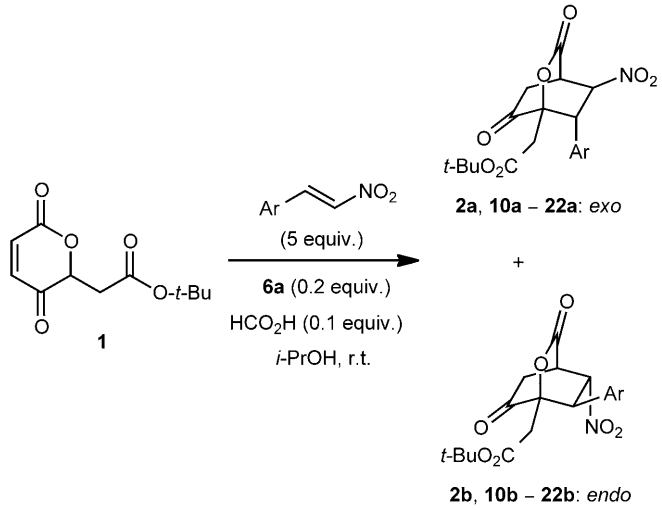
[a] The general procedures were followed with an acid additive in the indicated solvent.
[b] x = equivalent of the catalyst used.
[c] Total isolated yields [%] of *exo* and *endo* products after silica gel column chromatography.
[d] *dr* = *exo*/*endo* ratios, which were estimated by ^{1}H NMR (δ_{exo} 3.75 ppm and δ_{endo} 3.99 ppm).
[e] The% *ee* of the *exo* product, determined by chiral HPLC.
[f] n.d. = not determined.

philes with the chloro group at different positions of the benzene ring did not show any significant effects on the efficiency and selectivities (entries 4–6) which was similar to those bearing OMe or OH at the 3, 4-positions of the phenyl group (entries 8, 9 and 10, 11). However, dienophiles with OMe or OH at the 2-position of the phenyl group gave a very sluggish reaction (entry 10) or a non-selective reaction (entry 13). These results indicated that the hydrogen-bond donating or accepting group of the dienophile closer to the reaction site showed greater influences on the reactivity and the selectivities of the DA cycloaddition. Finally, replacing the phenyl group with other aromatic rings (2-furanyl group) also provided good yields and high enantioselectivity (entry 14).

DA product **2a** can be readily converted to an optically enriched and highly functionalized α-hydroxycyclohexanone, which could be useful building blocks for natural product synthesis. As shown in Scheme 1, lactone ring opening of **2a** using sodium methoxide in methanol afforded an 86% yield of **23**, which is a single diastereomer.

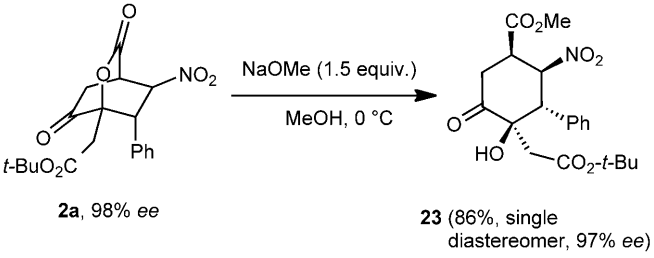
Finally, the absolute configurations of DA product **2a** were determined by means of X-ray crystallography (Figure 4, **b**)[20] of the single crystals that were obtained by recrystallization of **2a** (98% *ee*) from a hexanes/dichloromethane solution. A transition state with **6a** acting as a bifunctional catalyst was proposed. As shown in Figure 4, **c**, the Brønsted base of the *Cinchona* derivative induced the enolization of 2*H*-pyran-2,5-dione to 5-hydroxy-2-pyrone and activated the diene *via* hydrogen bondings with the 5-hydroxy

Table 5. DA cycloaddition with various dienophiles.[a]



No.	Ar	Product[b]	Time	Yield [%][c]	*dr*[d]	*ee* [%][e]
1	Ph	**2a,b**	32 h	90	5.5:1	98
2	4-Me-C_6H_4	**10a,b**	5 d	78	5.3:1	96
3	4-F-C_6H_4	**11a,b**	3 d	85	5.8:1	96
4	4-Cl-C_6H_4	**12a,b**	4 d	83	6.2:1	94
5	3-Cl-C_6H_4	**13a,b**	3 d	78	5.5:1	82
6	2-Cl-C_6H_4	**14a,b**	3 d	80	5.8:1	93
7	4-Br-C_6H_4	**15a,b**	6 d	76	5.8:1	91
8	4-MeO-C_6H_4	**16a,b**	7 d	62	5.4:1	63
9	3-MeO-C_6H_4	**17a,b**	7 d	60	5.6:1	63
10	2-MeO-C_6H_4	**18a,b**	7 d	trace	n.d.[f]	n.d.[f]
11	4-HO-C_6H_4	**19a,b**	26 h	72	5.2:1	91
12	3-HO-C_6H_4	**20a,b**	3 d	70	5.0:1	89
13	2-HO-C_6H_4	**21a,b**	3 d	61	5.0:1	<5
14	2-furanyl	**22a,b**	3 d	81	5.3:1	96

[a] The general procedures were followed.
[b] The circular dichroism spectra of DA adducts **2a**, **10a**–**17a**, **19a**–**20a** and **22a** showed a negative Cotton effect with absorption bands at 282–291 nm, indicating analogous absolute configurations of these DA adducts. These results are also consistent with the orders of elution in HPLC.
[c] Total isolated yields [%] of *exo* and *endo* products after silica gel column chromatography.
[d] *dr* = *exo*/*endo* ratios, which were estimated by ^{1}H NMR.
[e] The% *ee* of the *exo* product, determined by chiral HPLC.
[f] n.d. = not determined.



Scheme 1. Preparation of highly functionalized α-hydroxycyclohexanone from the DA product.

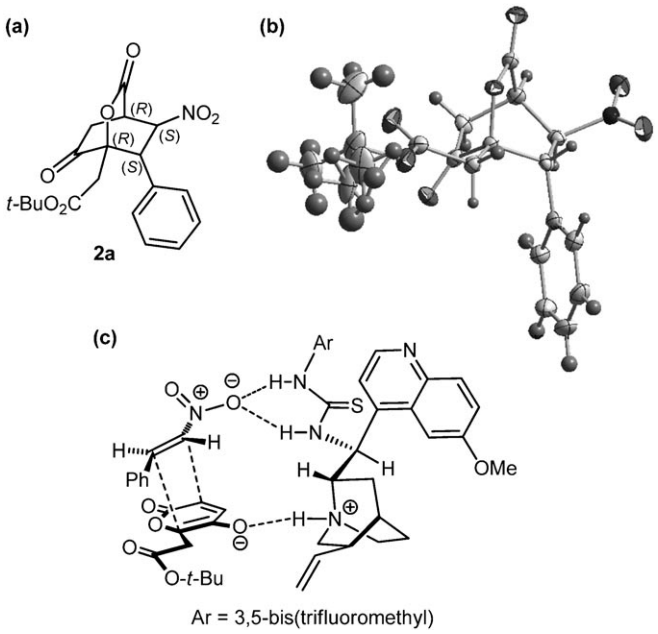


Figure 4. (**a**) The absolute configurations of **2a**, (**b**) X-ray crystal structure of **2a**, and (**c**) a proposed transition state for the DA cycloaddition.

moiety and the thiourea moiety of the catalyst activated the dienophile *via* hydrogen bondings with the nitro moiety.[21] The extensive hydrogen-bonding network in this transition state should provide a good environment for high enantioselectivity.

Conclusions

In summary, we have developed a new class of enantioselective catalytic 2-pyrone DA cycloaddition reactions using *Cinchona*-derived thiourea **6a** as the catalyst. This bifunctional catalyst induced the equilibration of 2*H*-pyran-2,5-dione to the 5-hydroxy-2-pyrone, which underwent DA cycloaddition with *trans*-β-nitrostyrene derivatives in high efficiency and very good stereoselectivities. With **6a** (0.2 equiv.) and formic acid (0.1 equiv.) in 2-propanol at room temperature, this optimal condition afforded the DA cycloadducts in yields up to 90% (*exo*/*endo* = 5.5:1, 98% *ee*). The results of the DA cycloaddition with a variety of *trans*-β-nitrostyrene derivatives showed that the electronic and hydrogen-bonding properties of the substituent of the phenyl group exhibited great influence on the yields and selectivities of the DA cycloaddition. Moreover, this enantioselective transformation provided a quick access to highly functionalized bridged bicyclic lactones and α-hydroxycyclohexanone derivatives in high optical purity. The utilities of this reaction in natural product synthesis are being actively explored in our research group.

Experimental Section

General Remarks

All air- and water-sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel plates (60F-254) that were analyzed by staining with $KMnO_4$ (200 mL H_2O of 1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 mL of 10% aqueous NaOH). Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All the chemicals were purchased commercially and used without further purification. Anhydrous THF was distilled from sodium-benzophenone, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically, unless otherwise stated.

NMR spectra were recorded on either a Bruker Advance 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz), or Bruker Advance 500 (^{1}H: 500 MHz, ^{13}C: 125.8 MHz). The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra were obtained from Applied Biosystems (ABI) Q-Star Elite MALDI-TOF Mass Spectrometer. High performance liquid chromatography analysis was performed on an Agilent Technologies 1200 Series instrument, using a Daicel Chiralcel OD-H column (250 × 4.6 mm) or Chiralpak AD-H column (250 × 4.6 mm) with *i*-PrOH/hexane as the eluent. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Melting points were uncorrected and determined on X-6 micro-melting point meter (Beijing Tech Instrument Co., Ltd.). Crystallographic data were obtained from an Oxford diffraction single crystal X-ray diffractometer (Gemini S Ultra). All the IR spectra were recorded with Nicolet 380 FT-IR spectrometer. Circular dichroism spectra were obtained in dichloromethane with a Biologic MOS-450 spectropolarimeter.

General Procedure for the Racemic Base-Catalyzed Diels–Alder Cycloadditions

To a stirred solution of **1** (23 mg, 0.1 mmol) and the appropriate dienophile (0.5 mmol) in *t*-BuOH (1.5 mL) was added (*c*-Hex)$_2$NMe (2.2 μL, 0.01 mmol). The resulting mixture was stirred at room temperature and monitored by TLC until the starting material was consumed. The reaction was worked up by addition of a saturated aqueous NH_4Cl solution and the aqueous layer was extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was then purified by silica gel flash column chromatography and subsequently subjected to HPLC analysis. The relative configurations of racemic **2a** were determined by X-ray crystallography,[20] and the relative configurations of **10a**–**22a** were determined by comparison with the ^{1}H NMR of **2a**.

General Procedure for the Asymmetric Diels–Alder Cycloadditions

To a solution of catalyst **6a** (17.8 mg, 0.03 mmol) in *i*-PrOH (1.0 mL, HPLC grade) was added formic acid (0.015 mmol, 0.6 μL). After stirring at room temperature for 30 min, the appropriate dienophile (0.75 mmol) was added. After another 30 min, **1** (33.9 mg, 0.15 mmol) was added. The resulting mixture was monitored by TLC until the starting material was consumed. The reaction was worked up by addition of a saturated aqueous NH_4Cl solution and the aqueous layer was extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was then purified by silica gel flash column chromatography and subsequently subjected to HPLC analysis.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-8-Nitro-3,6-dioxo-7-phenyl-2-oxabicyclo[2.2.2]octan-1-yl}acetate (2a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.5:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.75 ppm, δ_{endo} = 3.99 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a pale yellow solid; yield: 43 mg (76% yield, 98% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column: hexane/*i*-PrOH = 75:25, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 39.06 min, t_{major} = 43.62 min; $[\alpha]_D^{20}$: −15.6 (*c* 0.50 in $CHCl_3$); mp 190–191 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (m, 3H), 7.06 (m, 2H), 5.10 (dd, *J* = 7.0 Hz, 1.8 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 3.75 (d, *J* = 2.1 Hz, 1H), 3.06 (dd, *J* = 19.5 Hz, 3.2 Hz, 1H), 2.92 (dd, *J* = 19.5 Hz, 2.7 Hz, 1H), 2.64 (d, *J* = 17.2 Hz, 1H), 2.37 (d, *J* = 17.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.0, 166.9, 166.8, 133.8, 129.8, 129.5, 128.7, 87.6, 86.6, 82.4, 51.0, 41.1, 36.5, 35.3, 28.2; IR (KBr): ν = 3068, 2982, 2940, 2919, 1779, 1753, 1732, 1458, 1379, 1368, 1246, 1232, 1103, 1022, 707 cm^{-1}; HR-MS (ESI/[M+H]$^+$): *m/z* = 376.1411, calcd. for $C_{19}H_{22}NO_7$: 376.1396.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-8-Nitro-3,6-dioxo-7-*p*-tolyl-2-oxabicyclo[2.2.2]octan-1-yl}acetate (10a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.3:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.73 ppm, δ_{endo} = 3.96 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a white solid; yield: 38 mg (66%, 96% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column: hexane/*i*-PrOH = 75:25, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 28.50 min, t_{major} = 31.06 min; $[\alpha]_D^{20}$: −12.6 (*c* 0.53 in $CHCl_3$); mp = 197–198 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 8.1 Hz, 2H), 5.08 (dd, *J* = 7.0 Hz, 2.0 Hz, 1H), 4.66 (d, *J* = 7.0 Hz, 1H), 3.73 (m, 1H), 3.05 (dd, *J* = 19.4 Hz, 3.3 Hz, 1H), 2.90 (dd, *J* = 19.4 Hz, 2.9 Hz, 1H), 2.63 (d, *J* = 17.2 Hz, 1H), 2.38 (d, *J* = 17.2 Hz, 1H), 2.35 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.1, 167.0, 166.8, 139.6, 130.6, 130.5, 128.5, 87.7, 86.7, 82.3, 50.7, 41.1, 36.5, 35.3, 28.2, 21.2; IR (KBr): ν = 3053, 2987, 2831, 2685, 2521, 2410, 2305, 2155, 2126, 2055, 1788, 1603, 1551, 1422, 1271, 1156, 986, 896, 708 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): *m/z* = 412.1366, calcd. for $C_{20}H_{23}NO_7Na$: 412.1367.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(4-Fluorophenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (11a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.8:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.75 ppm, δ_{endo} = 3.98 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a white solid; yield: 45 mg (76%, 96% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak AD-H column: hexane/*i*-PrOH = 85:15, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 22.01 min, t_{major} = 26.90 min; $[\alpha]_D^{20}$: −18.2 (*c* 0.52 in $CHCl_3$); mp 209–210 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (m, 4H), 5.02 (dd, *J* = 7.2 Hz, 1.9 Hz, 1H), 4.76 (d, *J* = 7.2 Hz, 1H), 3.75 (m, 1H), 3.06 (dd, *J* = 19.5 Hz, 3.3 Hz, 1H), 2.90 (dd, *J* = 19.5 Hz, 2.9 Hz, 1H), 2.64 (d, *J* = 17.2 Hz, 1H), 2.35 (d, *J* = 17.2 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.2, 166.8, 166.7, 130.6, 130.5, 117.0, 116.9, 87.6, 86.5, 82.5, 50.2, 41.0, 36.6, 35.1, 28.2; IR (KBr): ν = 3054, 2987, 2831, 2685, 2521, 2411, 2306, 2156, 2126, 2055, 1788, 1605, 1551, 1422, 1263, 1156, 986, 896, 693 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): *m/z* = 416.1120, calcd. for $C_{19}H_{20}NO_7FNa$: 416.1121.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(4-Chlorophenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (12a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 6.2:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.76 ppm, δ_{endo} = 3.99 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a white solid; yield: 44 mg (71%, 94% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak AD-H column: hexane/*i*-PrOH = 85:15, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 22.69 min, t_{major} = 32.16 min; $[\alpha]_D^{20}$: −13.8 (*c* 0.54 in $CHCl_3$); mp 191–192 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 5.01 (dd, *J* = 7.1 Hz, 1.9 Hz, 1H), 4.76 (d, *J* = 7.1 Hz, 1H), 3.75 (dd, *J* = 4.9 Hz, 2.7 Hz, 1H), 3.06 (dd, *J* = 19.5 Hz, 3.2 Hz, 1H), 2.90 (dd, *J* = 19.5 Hz, 2.8 Hz, 1H), 2.64 (d, *J* = 17.1 Hz, 1H), 2.35 (d, *J* = 17.1 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.1, 166.8, 166.6, 135.9, 132.3, 130.1, 130.0, 87.4, 86.4, 82.6, 50.3, 41.0, 36.5, 35.1, 28.2; IR (KBr): ν = 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2155, 2126, 2055, 1789, 1604, 1551, 1422, 1256, 1156, 987, 896, 693 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): *m/z* = 432.0829, calcd. for $C_{19}H_{20}NO_7ClNa$: 432.0826.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(3-Chlorophenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (13a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.5:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.77 ppm, δ_{endo} = 3.99 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a light yellow solid; yield: 41 mg (66%, 82% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak OD-H column: hexane/*i*-PrOH = 75:25, flow rate = 0.5 mL min^{-1}, λ = 210 nm); t_{minor} = 30.67 min, t_{major} = 42.28 min; $[\alpha]_D^{20}$: −11.9 (*c* 0.55 in $CHCl_3$); mp 168–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (m, 2H), 7.09 (m, 1H), 6.93 (m, 1H), 5.05 (dd, 1H, *J* = 7.1 Hz, 2.0 Hz), 4.77 (d, 1H, *J* = 7.1 Hz), 3.77 (m, 1H), 3.05 (dd, 1H, *J* = 19.5 Hz, 3.2 Hz), 2.93 (dd, 1H, *J* = 19.4 Hz, 2.9 Hz), 2.66 (d, 1H, *J* = 17.3 Hz), 2.36 (d, 1H, *J* = 17.3 Hz), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.9, 166.8, 166.7, 135.8, 135.6, 131.1, 129.9, 129.1, 126.5, 87.1, 86.2, 82.6, 50.2, 40.8, 36.4, 35.0, 28.2; IR (KBr): ν = 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2155, 2126, 2054, 1789, 1604, 1551, 1422, 1271, 1156, 986, 896, 693 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): *m/z* = 432.0818, calcd. for $C_{19}H_{20}NO_7NaCl$: 432.0821.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(2-Chlorophenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (14a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.8:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.75 ppm, δ_{endo} = 3.98 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a light yellow solid; yield: 44 mg (71%, 93% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak OD-H column: hexane/*i*-PrOH = 75:25, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 37.05 min, t_{major} = 45.84 min; $[\alpha]_D^{20}$: −13.2 (*c* 0.53 in $CHCl_3$); mp 180–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (m, 1H), 7.33 (m, 2H), 6.80 (m, 1H), 5.07 (d, 1H, *J* = 7.4 Hz), 4.99 (m, 1H), 3.75 (m, 1H), 3.13 (dd, 1H, *J* = 19.2 Hz, 2.9 Hz), 2.92 (m, 1H), 2.80 (d, 1H, *J* = 17.2 Hz), 2.55 (d, 1H, *J* = 17.3 Hz), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.2, 166.7, 166.3, 135.6, 131.1, 130.7, 128.2, 127.9, 87.0, 86.9, 82.3, 48.0, 41.2, 36.7, 35.4, 28.1; IR (KBr): ν = 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2155, 2126, 2055, 1789, 1604, 1551, 1422, 1271, 1156, 987, 896, 693 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): *m/z* = 432.0816, calcd. for $C_{19}H_{20}NO_7NaCl$: 432.0821.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(4-Bromophenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (15a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.8:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.76 ppm, δ_{endo} = 3.99 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a white solid; yield: 44 mg (65%, 91% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak AD-H column: hexane/*i*-PrOH = 90:10, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 41.93 min, t_{major} = 65.17 min; $[\alpha]_D^{20}$: −16.6 (*c* 0.51 in $CHCl_3$); mp 178–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 5.01 (d, *J* = 6.5 Hz, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 3.76 (m, 1H), 3.06 (dd, *J* = 19.5 Hz, 3.0 Hz, 1H), 2.90 (dd, *J* = 19.5 Hz, 2.5 Hz, 1H), 2.65 (d, *J* = 17.5 Hz, 1H), 2.35 (d, *J* = 17.5 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.0, 166.8, 166.6, 133.0, 132.8, 130.3, 124.0, 87.3, 86.3, 82.6, 50.3, 41.0, 36.5, 35.1, 28.2; IR (KBr): ν = 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2155, 2126, 2055, 1789, 1603,

1551, 1422, 1271, 1156, 986, 896, 691 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): m/z = 476.0317, calcd. for $C_{19}H_{20}NO_7BrNa$: 476.0315.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(4-Methoxyphenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (16a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.4:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.73 ppm, δ_{endo} = 3.95 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a yellow oil; yield: 32 mg (52%, 63% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak AD-H column: hexane/*i*-PrOH = 90:10, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 43.93 min, t_{major} = 50.46 min; $[\alpha]_D^{20}$: −7.1 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.05 (dd, *J* = 7.0 Hz, 1.9 Hz, 1H), 4.64 (d, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 3.72 (dd, *J* = 4.9 Hz, 2.7 Hz, 1H), 3.04 (dd, *J* = 19.6 Hz, 3.2 Hz, 1H), 2.89 (dd, *J* = 19.4 Hz, 2.8 Hz, 1H), 2.63 (d, *J* = 17.1 Hz, 1H), 2.68 (d, *J* = 17.1 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.3, 167.0, 166.9, 160.4, 129.8, 125.5, 115.2, 87.8, 86.8, 82.3, 55.5, 50.4, 41.1, 36.5, 35.3, 28.2; IR (KBr): ν = 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2156, 2126, 2055, 1788, 1604, 1551, 1422, 1271, 1156, 986, 896, 696 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): m/z = 428.1316, calcd. for $C_{20}H_{23}NO_8Na$: 428.1316.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(3-Methoxyphenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (17a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.6:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.74 ppm, δ_{endo} = 3.85 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a white solid; yield: 31 mg (51%, 63% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak OD-H column: hexane/*i*-PrOH = 75:25, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 34.30 min, t_{major} = 48.46 min; $[\alpha]_D^{20}$: −8.2 (*c* 0.52 in $CHCl_3$); mp 171–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 1H), 6.90 (m, 1H), 6.61 (m, 1H), 5.10 (dd, 1H, *J* = 7.0 Hz, 2.0 Hz), 4.70 (d, 1H, *J* = 7.0 Hz), 3.80 (s, 3H), 3.74 (m, 1H), 3.05 (dd, 1H, *J* = 19.4 Hz, 3.2 Hz), 2.90 (dd, 1H, *J* = 19.5 Hz, 2.9 Hz), 2.66 (d, 1H, *J* = 17.2 Hz), 2.40 (d, 1H, *J* = 17.2 Hz), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.0, 167.0, 166.9, 160.4, 135.0, 130.9, 120.3, 115.2, 114.2, 87.5, 86.4, 82.4, 55.5, 50.7, 41.0, 36.4, 35.2, 28.2; IR (KBr): ν = 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2156, 2126, 2054, 1788, 1603, 1551, 1422, 1271, 1156, 987, 896, 693 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): m/z = 428.1313, calcd. for $C_{20}H_{23}NO_8Na$: 428.1316.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(4-Hydroxyphenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (19a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.2:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.72 ppm, δ_{endo} = 3.96 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 1:1) as a pale yellow solid; yield: 35 mg (60%, 91% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak AD-H column: hexane/*i*-PrOH = 85:15, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 31.03 min, t_{major} = 45.64 min; $[\alpha]_D^{20}$: −17.3 (*c* 0.55 in $CHCl_3$); mp 101–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.13 (br, 1H), 5.03 (dd, *J* = 7.0 Hz, 1.8 Hz, 1H), 4.64 (d, *J* = 7.1 Hz, 1H), 3.72 (m, 1H), 3.04 (dd, *J* = 19.4 Hz, 3.2 Hz, 1H), 2.88 (dd, *J* = 19.4 Hz, 2.7 Hz, 1H), 2.64 (d, *J* = 17.1 Hz, 1H), 2.38 (d, *J* = 17.1 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.3, 166.9, 166.8, 156.6, 130.1, 125.9, 116.7, 87.8, 86.8, 82.4, 50.3, 41.1, 36.6, 35.3, 28.2; IR (KBr): ν = 3692, 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2155, 2126, 2055, 1788, 1604, 1551, 1422, 1271, 1156, 987, 896, 697 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): m/z = 414.1157, calcd. for $C_{19}H_{21}NO_8Na$: 414.1159.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(3-Hydroxyphenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (20a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.0:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.74 ppm, δ_{endo} = 3.98 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a yellow oil; yield: 34 mg (58%, 89% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak OD-H column: hexane/*i*-PrOH = 75:25, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 22.76 min, t_{major} = 26.83 min; $[\alpha]_D^{20}$: −15.2 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (m, 1H), 6.84 (m, 1H), 6.57 (m, 2H), 5.67 (br, 1H), 5.09 (dd, 1H, *J* = 7.0 Hz, 2.0 Hz), 4.63 (d, 1H, *J* = 7.0 Hz), 3.74 (m, 1H), 3.05 (dd, 1H, *J* = 19.5 Hz, 3.2 Hz), 2.90 (dd, 1H, *J* = 19.4 Hz, 2.9 Hz), 2.67 (d, 1H, *J* = 17.2 Hz), 2.42 (d, 1H, *J* = 17.2 Hz), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1, 167.1, 167.0, 156.7, 135.2, 131.1, 120.6, 116.7, 115.8, 87.4, 86.4, 82.5, 50.7, 41.0, 36.3, 35.2, 28.2; IR (KBr): ν = 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2156, 2126, 2055, 1788, 1603, 1551, 1422, 1259, 1156, 987, 896, 691 cm^{-1}; HR-MS (ESI/[M+Na]$^+$): m/z = 414.1155, calcd. for $C_{19}H_{21}NO_8Na$: 414.1159.

tert-Butyl 2-{(1*R*,4*R*,7*S*,8*S*)-7-(2-Hydroxyphenyl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (21a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo* = 5.0:1, determined by integration of ^{1}H NMR signal: δ_{exo} = 3.94 ppm, δ_{endo} = 4.18 ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate = 3:1) as a yellow oil; yield: 30 mg (51%, 5% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak AD-H column: hexane/*i*-PrOH = 85:15, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_{minor} = 17.69 min, t_{major} = 22.98 min; $[\alpha]_D^{20}$: −1.3 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.30 (m, 2H), 7.07 (m, 1H), 6.98 (m, 1H), 4.70 (dd, 1H, *J* = 17.4 Hz, 3.7 Hz), 3.94 (d, 1H, *J* = 1.2 Hz), 3.41 (m,

1H), 2.94 (d, 1H, $J=16.1$ Hz), 2.78 (d, 1H, $J=16.1$ Hz), 2.61 (dd, 1H, $J=14.7$ Hz, 4.8 Hz), 2.08 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=171.1$, 166.7, 150.3, 130.7, 129.2, 123.3, 121.5, 118.3, 97.5, 88.8, 84.9, 78.4, 46.2, 40.1, 37.5, 35.7, 28.0; IR (KBr): $\nu=3692$, 3054, 2987, 2831, 2685, 2521, 2411, 2306, 2156, 2126, 2055, 1787, 1604, 1551, 1422, 1263, 1156, 987, 896, 693 cm^{-1}; HR-MS (ESI/$[M+Na]^+$): $m/z=414.1158$, calcd. for $C_{19}H_{21}NO_8Na$: 414.1159.

tert-Butyl 2-{(1*R*,4*R*,7*R*,8*S*)-7-(Furan-2-yl)-8-nitro-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl}acetate (22a)

The reaction was carried out following the general procedure to furnish the crude product (*exo*/*endo*=5.3:1, determined by integration of ^{1}H NMR signal: $\delta_{exo}=3.75$ ppm, $\delta_{endo}=3.98$ ppm). The title compound was isolated by flash column chromatography (silica gel, hexanes/ethyl acetate=3:1) as a yellow oil; yield: 36 mg (65%, 96% *ee*). The *ee* was determined by HPLC analysis (Daicel Chiralpak OD-H column: hexane/*i*-PrOH=75:25, flow rate=0.5 mL min^{-1}, $\lambda=210$ nm): $t_{minor}=29.90$ min, $t_{major}=35.85$ min; $[\alpha]_D^{20}$: −16.8 (*c* 0.55 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.38$ (s, 1H), 6.43 (d, 1H, $J=3.2$ Hz), 6.38 (m, 1H), 5.27 (dd, 1H, $J=5.9$ Hz, 2.2 Hz), 5.11 (d, 1H, $J=5.9$ Hz), 3.75 (m, 1H), 2.95 (d, 2H, $J=1.9$ Hz), 2.74 (d, 1H, $J=16.9$ Hz), 2.45 (d, 1H, $J=16.9$ Hz), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=197.6$, 167.0, 166.6, 146.2, 144.4, 111.7, 111.3, 85.1, 84.7, 82.5, 43.3, 41.0, 35.5, 34.8, 28.2; IR (KBr): $\nu=3056$, 2987, 2831, 2685, 2521, 2411, 2305, 2156, 2126, 2055, 1789, 1602, 1551, 1421, 1267, 1156, 990, 758, 736, 712 cm^{-1}; HR-MS (ESI/$[M+Na]^+$): $m/z=388.1006$, calcd. for $C_{17}H_{19}NO_8Na$: 388.1003.

Synthesis of (1*R*,2*S*,3*S*,4*R*)-Methyl 4-(2-*tert*-Butoxy-2-oxoethyl)-4-hydroxy-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (23)

To a solution of DA cycloadduct **2** (38 mg, 0.10 mmol) in MeOH/CH_2Cl_2 (2 mL, 1:1) at 0 °C was added a 1.0 M solution of sodium methoxide in MeOH (0.2 mL, 0.15 mmol) dropwise under N_2. The resulting mixture was stirred at 0 °C and monitored by TLC until the starting material was consumed. The reaction was then worked up by addition of a saturated aqueous NH_4Cl solution and the aqueous layer was extracted with diethyl ether (×3). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (hexanes/ethyl acetate=3:1) to give **23** as a white solid; yield: 35 mg (86%, 97% *ee*); The *ee* was determined by HPLC analysis (Daicel Chiralpak AD-H column: hexane/*i*-PrOH=90:10, flow rate=0.5 mL min^{-1}, $\lambda=210$ nm): $t_{minor}=22.09$ min, $t_{major}=32.53$ min; $[\alpha]_D^{20}$: −22.8 (*c* 0.50 in $CHCl_3$); mp 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.31$ (m, 3H), 6.89 (m, 2H), 6.27 (s, 1H), 5.98 (dd, 1H, $J=11.7$ Hz, 5.7 Hz), 4.09 (d, 1H, $J=5.4$ Hz), 3.74 (s, 3H), 3.71 (m, 1H), 3.55 (t, 1H, $J=14.1$ Hz), 2.84 (dd, 1H, $J=14.4$ Hz, 5.4 Hz), 2.44 (d, 1H, $J=17.1$ Hz), 2.09 (d, 1H, $J=17.1$ Hz), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.3$, 173.2 171.2, 131.7, 129.5, 129.3, 129.2, 83.1, 82.9, 77.5, 57.1, 53.0, 40.9, 37.8, 36.7, 28.1; IR (KBr): $\nu=3054$, 2987, 2831, 2685, 2521, 2410, 2305, 2156, 2126, 2058, 1602, 1551, 1422, 1271, 1156, 986, 896, 691 cm^{-1}; HR-MS (ESI/$[M+Na]^+$): $m/z=430.1468$, calcd. for $C_{20}H_{25}NO_8Na$: 430.1472.

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