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Article

Catalytic Asymmetric Diels–Alder Reaction of 2′-Hydroxychalcone as a Dienophile with a VANOL-Borate Ester Complex

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Cite This: *ACS Omega* 2023, 8, 11588–11595

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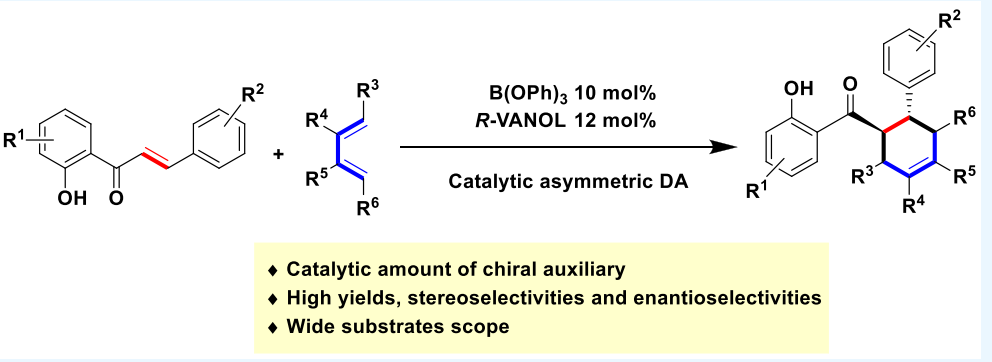


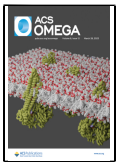
ABSTRACT: Numerous flavonoid Diels–Alder-type natural products have been isolated and received great attention from the synthetic community. Herein, we reported a catalytic strategy for an asymmetric Diels–Alder reaction of 2′-hydroxychalcone with a range of diene substrates using a chiral ligand–boron Lewis acid complex. This method enables the convenient synthesis of a wide range of cyclohexene skeletons in excellent yields with moderate to good enantioselectivities, which is critical to prepare natural product congeners for further biological studies.

INTRODUCTION

A large number of natural products have been isolated from various *Moraceous* and related plants,[1] in which more than 40 classes of prenylflavonoid and related Diels–Alder (DA)-type natural products have been characterized (Figure 1).

Due to their potent biological activities,[2] including anti-oxidant, anti-inflammatory,[3] anti-cancer,[4] anti-HIV,[5] antimicrobial,[6] and so on, the Diels–Alder natural products are intriguing synthetic targets. One of the most effective methods for the synthesis of these DA-type natural products is the Diels–Alder cycloaddition of substituted chalcones and diene substrates. In this context, most methodologies led to the facile synthesis of racemic Diels–Alder products, which fall into three categories: (1) thermal method (Scheme 1a),[7] (2) single-electron transfer-initiated Diels–Alder cycloadditions (Scheme 1b),[8] and (3) a silica-supported silver nanoparticle (AgNPs)-catalyzed Diels–Alder process (Scheme 1c).[9] However, the enantioselective Diels–Alder cyclization is typically more challenging. In 2009, Palomo's group developed the first substrate-controlled asymmetric synthesis of (-)-nicolaiodesin C through Diels–Alder cycloadditions using the chiral dienophiles substrate.[10] Then, our group also synthesized nicolaiodesin C under the promotion of stoichiometric amounts of chiral ligand–boron Lewis acid complex (1.2–2.5 equiv), which is moisture-sensitive and needs to be prebuilt and handled under an inert atmosphere (Scheme 1d).[11] Therefore, developing robust and catalytic Diels–Alder reactions to achieve asymmetric Diels–Alder cycloadditions is highly desirable. In 2016, Porco's group reported the enantioselective Diels–Alder cycloaddition of 2′-hydroxychalcones promoted by a catalytic amount of triphenylborate and (*R*)-3,3′-dibromo-BINOL complex, which facile the optically pure Sanggenons C and O.[12] In 2020, Chang's group developed the (*S*)-2,15-Cl_2-DHTP-boron complex catalyst for the asymmetric Diels–Alder cycloaddition of 2′-hydroxychalcones and dienes.[13] In 2021, Lei's group reported the enzymatic control of endo- and exo-stereoselective Diels–Alder reactions with broad substrate scope.[14] Herein, we reported our synthetic endeavor toward developing an effective catalytic asymmetric Diels–Alder reaction of 2′-hydroxychalcone. This asymmetric Diels–Alder reaction is catalyzed by the chiral ligand–boron Lewis acid complex and featured excellent

Received: February 6, 2023
Accepted: February 23, 2023
Published: March 17, 2023



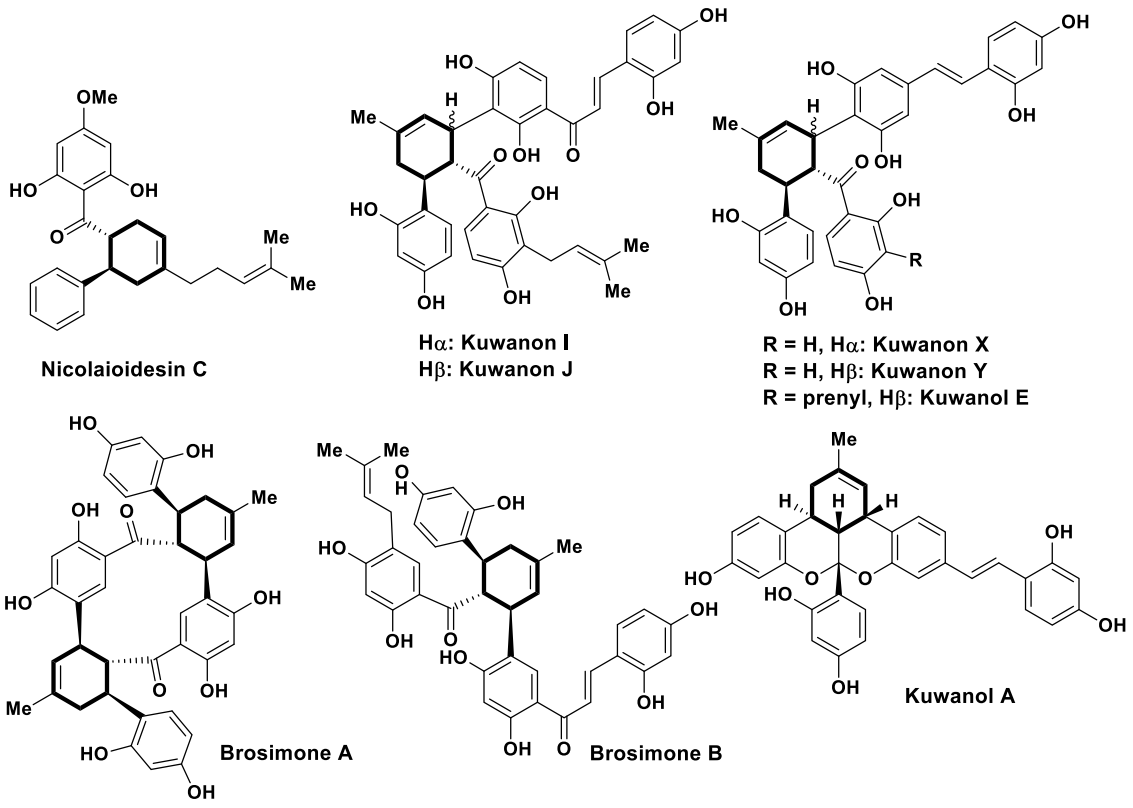
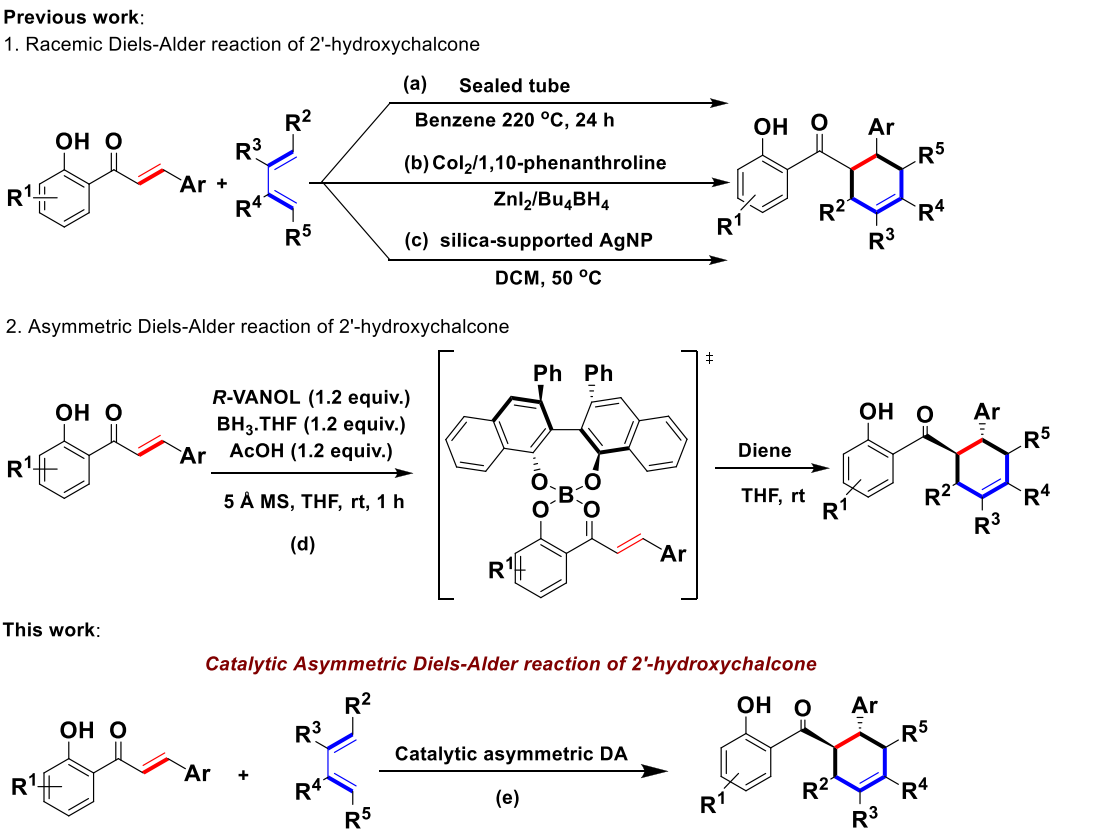


Figure 1. Structures of representative flavonoid Diels–Alder-type natural products derived from 2′-hydroxychalcones.

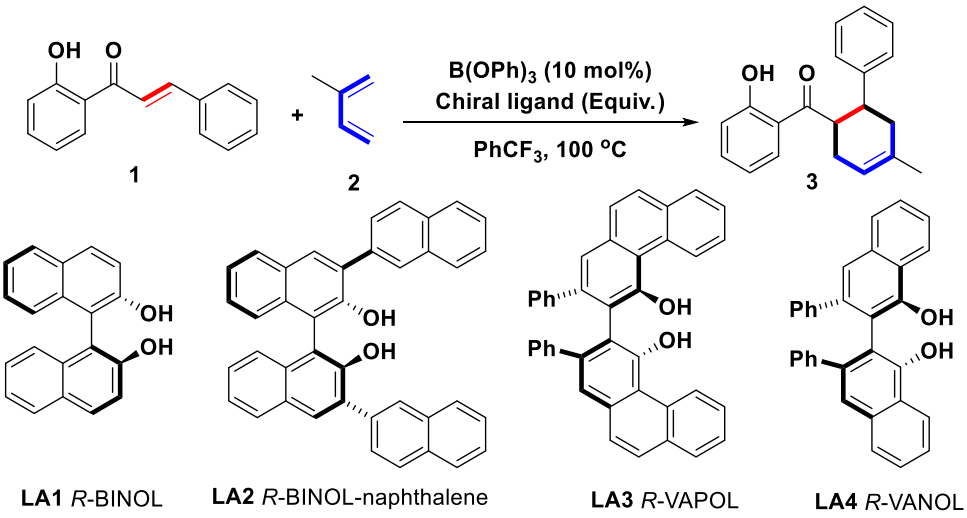
Scheme 1. Diels–Alder Reaction of 2′-Hydroxychalcones



yields and good enantioselectivities. Notably, this transformation avoids the necessity of pre-installing a chiral auxiliary group and provides a one-pot method for the simple preparation of the chiral ligand–boron Lewis acid complex. This chemistry

https://doi.org/10.1021/acsomega.3c00782
ACS Omega 2023, 8, 11588−11595

Table 1. Optimization of Conditions



entry	ligand	equiv	time (h)	yield (%)	ee (%)
1[a]	**LA1**	0.1	4	65	45
2[b]	**LA1**	0.1	>48	trace	
3	**LA2**	0.1	4	60	67
4	**LA3**	0.1	2	88	72
5	**LA4**	0.1	2	98	85
6	**LA4**	1.0	1.3	97	81
7	**LA4**	0.5	1.5	98	83
8	**LA4**	0.2	2	95	84
9	**LA4**	0.05	6	40	77
10	**LA4**	0.01	10	30	44

[a]The ee values of single isomers were determined by chiral HPLC analysis. [b]Reaction conditions: $B(OPh)_3$ 10 mol %, *R*-BINOL 10 mol %, dry $PhCF_3$ (1.0 mL), and 40 °C.

may play a significant role in the total syntheses of the Diels–Alder-type natural products (Scheme 1e).

RESULTS AND DISCUSSION

Enantioselective catalytic Diels–Alder of α,β-unsaturated carbonyl compounds could be activated by chiral Lewis acid.[15] We began by selecting 2′-hydroxychalcone and isoprene as a model substrate to examine the catalytic asymmetric Diels–Alder cycloaddition. As shown in Table 1, we found that the asymmetric [4 + 2] cycloaddition of the model dienophile **1** and diene **2** afforded the cycloadduct **3** in 65% yield and 45% *ee* in the presence of a catalytic amount of $B(OPh)_3$/*R*-BINOL complex (entry 1). Performing the reaction at a lower temperature (40°) led to a significantly diminished yield (entry 2). Other chiral ligands (**LA2**-**LA4**) were also screened to optimize both the yield and enantioselectivity. Among these four ligands, *R*-VANOL exhibited the best performance, producing the D–A product **3** in the highest yield (98%) and enantioselectivity (85% ee) (entries 1–5). In our previous studies,[11] the chiral VANOL/BH_3/AcOH catalyst complex was used in stoichiometric amounts (1.2–2.5 equiv). To probe the effect of catalyst loading on the reaction yield and enantioselectivity, different equivalents of **LA4** were screened under the above optimal conditions ($PhCF_3$, 100 °C). The result suggested that 10 mol % of $B(OPh)_3$/*R*-BINOL complex is sufficient to promote this asymmetric reaction efficiently (entries 6–10, Table 1).

The effect of different solvents on the model reaction was also investigated at the respective boiling points of the reaction solvents (Table 2). Quite unexpectedly, only a trace amount of cycloadduct was detected in THF (entry 3), which was selected as the optimal solvent in our previous research (BH_3/AcOH, THF, rt).[11] Therefore, we chose the reaction conditions in entry 6 as the optimal reaction conditions (A borate ester as catalyst, which was prepared in situ from 10 mol % $B(OPh)_3$ and 12 mol % *R*-VANOL, trifluoromethylbenzene as the solvent, and the reaction temperature of 100 °C).

Table 2. Effect of Different Solvents on the Reaction[a]

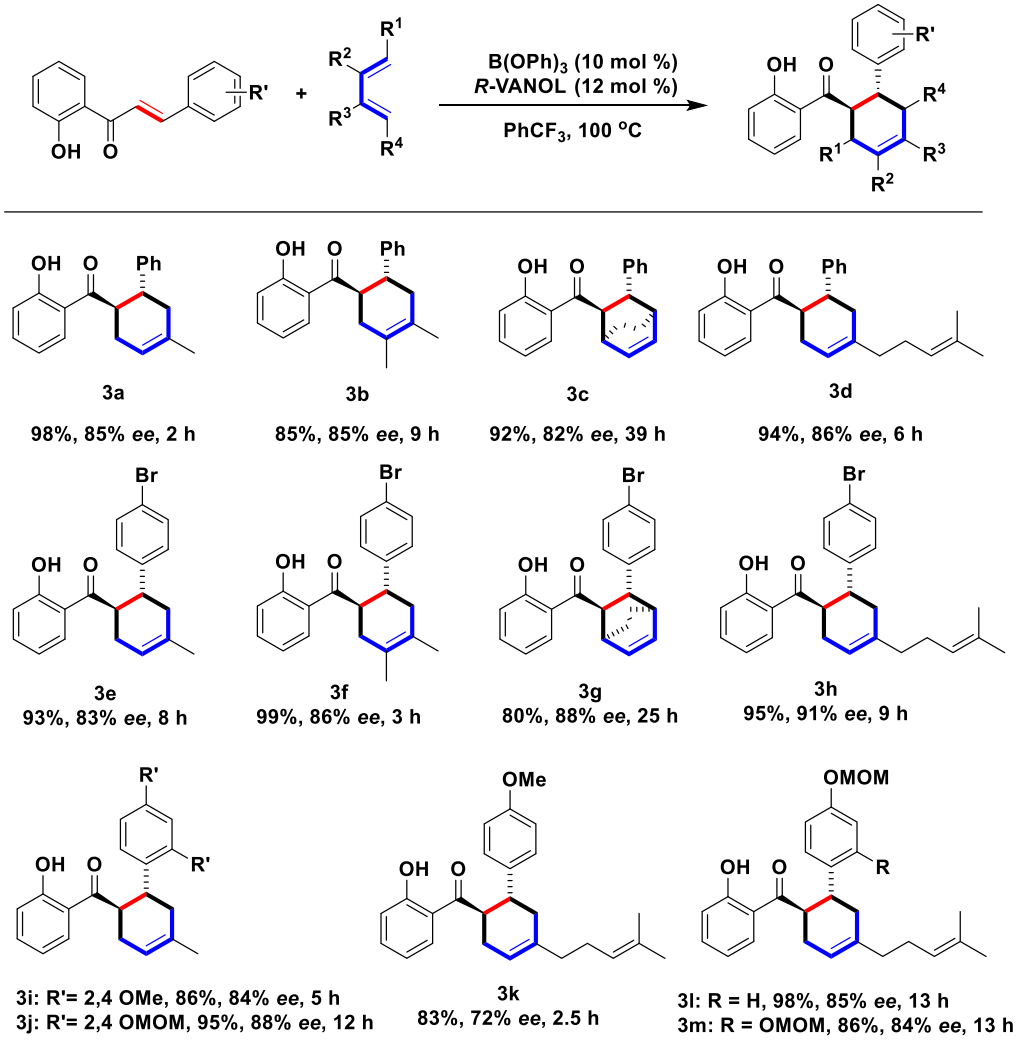
entry	solvent	time (h)	yield (%)
1	MeOH	>16	NR
2	acetone	>16	NR
3	THF	>21	trace
4	DCM	36	80
5	toluene	58	84
6	$PhCF_3$	2	97

[a]Reaction conditions: $B(OPh)_3$ 10 mol %, *R*-VANOL 12 mol %, and dry solvent.

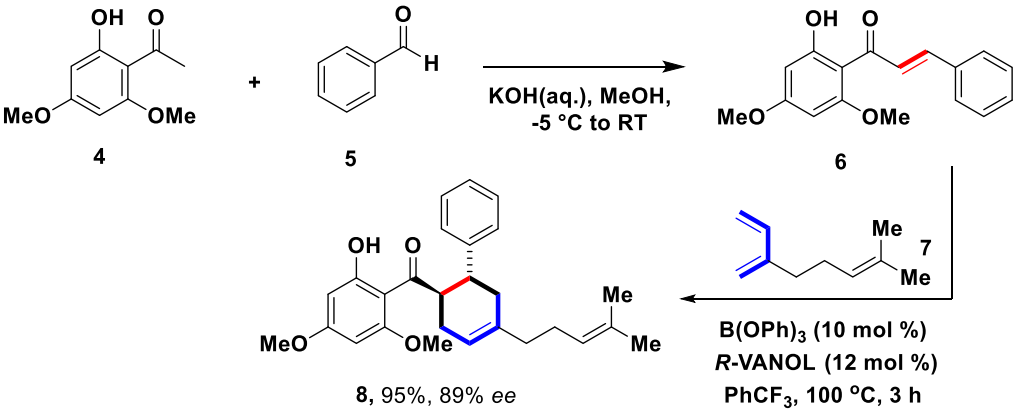
With the optimized conditions in hand, we next examined the scope and limitations of this catalytic strategy. Relatively satisfactory results were obtained when a series of 2′-hydroxychalcones with different substitution groups, such as 4-Br, 4-OMe, 4-OMOM, and 2′,4′-OMOM, were used as the dienophile (Scheme 2). A bright orange color change was observed when the borate catalyst and 2′-hydroxychalcone were combined, indicating the potential generation of an active borate

https://doi.org/10.1021/acsomega.3c00782
ACS Omega 2023, 8, 11588–11595

Scheme 2. Diels–Alder Cycloaddition of Dienophiles and Dienes



Scheme 3. Synthesis of Methylated Nicolaiodesin C



complex that has been previously confirmed by the single X-ray crystal structure analysis and density functional theory calculations.[12,13]

To further demonstrate the synthetic power of this new methodology, it was also applied to the asymmetric total synthesis of methylated nicolaiodesin C. Commencing with its selective methylation, the commercially available 2′-hydroxy-4′,6′-dimethoxyacetophenone (**4**) was condensed with benzaldehyde (**5**) to give the required 2′-hydroxy- 4′,6′-dimethoxychalcone (**6**). The Diels–Alder cycloaddition of dienophile (**6**) and diene (**7**) was conducted under the abovementioned optimal reaction conditions to afford the Diels–Alder product (**8**) in excellent yield (95%) with moderate ee value (89%) (Scheme 3).

https://doi.org/10.1021/acsomega.3c00782
ACS Omega 2023, 8, 11588−11595

CONCLUSIONS

We have reported an efficient catalytic asymmetric Diels–Alder cycloaddition of 2′-hydroxychalcone and its derivatives using the catalytic amount of the in situ generated chiral *R*-VANOL-borate complex. In this protocol, the desired chiral cyclohexene skeleton could be afforded with high yields and enantioselectivities, as represented by the asymmetric total synthesis of methylated nicolaiodesin C. Advances in the enantioselective total syntheses of other related complex natural products and their biological evaluation will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. The ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer at ambient temperature (25 °C) with $CDCl_3$ as the solvent unless otherwise stated. The ^{13}C NMR spectra were recorded on a Varian 100 MHz spectrometer (with complete proton decoupling) at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.26; ^{13}C, δ 77.00). The data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet, br = broad), and coupling constants. High-resolution mass spectrometry (HRMS) was obtained on a Q-TOF microspectrometer. Optical rotations were recorded on a Rudolph AUTOPOL III automatic polarimeter at 589 nm, and are recorded as $[\alpha]_D^{25}$ in CH_2Cl_2 unless otherwise noted. The chiral HPLC analysis was performed on an Agilent 1200 series (Chiralcel OD-H, column no. ODH0CE-MJ037; Chiralcel AD-H, column no. ADH0CE-MK114). The enantiomers were separated by Chiralcel OD-H using isopropanol and *n*-hexane as the mobile phase (1:99, 1 mL/min) unless otherwise noted. The TLC plates (0.25 mm silica gel 60-F plates) were visualized by exposure to ultraviolet light. Flash column chromatography was performed over silica gel (200–300 m) using a mixture of ethyl acetate (EtOAc) and petroleum ether (PE). Yields refer to chromatographically and spectroscopically pure materials unless otherwise stated. The reagents and solvents purchased were of reagent grade and used without further purification. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

Dienes, chirals, and ligands were either purchased from commercial suppliers or synthesized according to the literature procedure. Chalcones were synthesized via the Claisen–Schmidt condensation between the corresponding 2′-hydroxyacetophenones and the appropriate aldehydes under basic conditions.[11a,b]

Enantioselective Model Diels–Alder Cycloaddition. To a solution of 2′-hydroxychalcone **1** (22 mg, 0.1 mmol, 1.0 equiv) in $PhCF_3$ (1 mL) in a flame-dried round-bottom flask were consecutively added $B(OPh)_3$ (2.9 mg, 0.01 mmol, 0.1 equiv) and *R*-VANOL (**LA4**, 5.3 mg, 0.012 mmol, 0.12 equiv). The reaction mixture was stirred at 100 °C for 1 h before being cooled down to room temperature. Then, diene **2** (isoprene, 12 μL, 0.12 mmol, 1.2 equiv) was added with the aid of 0.5 mL of $PhCF_3$. The mixture was stirred at 100 °C for 2 h before being cooled to room temperature. The reaction mixture was diluted with distilled water, extracted with EtOAc (50 mL × 2), washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was further purified by silica gel chromatography, eluting with a gradient of ethyl acetate–petroleum ether to afford the desired Diels–Alder cycloadduct **3** and recovered chiral ligand, unless otherwise stated. Further separation was accomplished using preparative TLC (hexanes/EtOAc = 10:1). The racemate Diels–Alder cycloadduct was prepared using the general procedure, employing the racemate BINOL or VANOL as the ligand. The Diels–Alder products **3a–3d** exhibited spectral properties consistent with previous literature reports.[16]

*Preparation of Cycloadduct **3a**.* Two hours, 98% yield, light yellow solid. 85% ee (isopropanol/hexane = 1:99), retention time 6.5 and 7.8 min; $[\alpha]_D^{25}$ = +10.78° (*c* 0.9, CH_2Cl_2).

*Preparation of Cycloadduct **3b**.* Nine hours, 85% yield, light yellow oil. 85% ee (isopropanol/hexane = 1:99), retention time 6.0 and 7.9 min; $[\alpha]_D^{25}$ = +41.15 (*c* 1.0, CH_2Cl_2).

*Preparation of Cycloadduct **3c**.* Thirty-nine hours, 92% yield, light yellow solid. 82% ee (isopropanol/hexane = 0.5:99.5, 0.8 mL/min), retention time 9.7 and 9.8 min; $[\alpha]_D^{25}$ = +123.24 (*c* 1.0, CH_2Cl_2).

*Preparation of Cycloadduct **3d**.* Six hours, 94% yield, light yellow solid. 86% ee (isopropanol/hexane = 1:99), retention time 5.2 and 6.7 min; $[\alpha]_D^{25}$ = +29.65 (*c* 01.0, CH_2Cl_2).

*Preparation of Cycloadduct **3e**.* Eight hours, 93% yield, light yellow solid. 83% ee (isopropanol/hexane = 1:99), retention time 5.6 and 7.7 min; $[\alpha]_D^{25}$ = +34.40 (*c* 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (s, 1H, −OH), 7.71 (dd, 1H, *J* = 1.6, 8.4 Hz), 7.34 (m, 1H), 7.22 (m, 2H), 6.99 (m, 2H), 6.79 (m, 2H), 5.42 (m, 1H), 3.84 (m, 1H), 3.22 (m, 1H), 2.35 (m, 1H), 2.25 (m, 1H), 2.18 (d, 1H, *J* = 6.8 Hz), 1.96 (m, 1H), 1.65 (s,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.07, 161.92, 142.45, 135.45, 132.93, 132.93, 130.52, 130.52, 128.55, 128.00, 119.02, 118.14, 118.03, 117.82, 117.67, 44.65, 40.79, 37.92, 30.32, 22.05. HRMS (ESI) calcd for $C_{20}H_{20}BrO_2$ $(M + H)^+$: 371.0641, found: 371.0486.

*Preparation of Cycloadduct **3f**.* Three hours, 99% yield, light yellow solid. 86% ee (isopropanol/hexane = 1:99), retention time 5.5 and 8.3 min; $[\alpha]_D^{25}$ = +51.39 (*c* 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.25 (s, 1H, −OH), 7.70 (d, 1H, *J* = 8.0 Hz), 7.37 (m, 1H), 7.22 (d, 2H, *J* = 8.0 Hz), 6.98 (d, 2H, *J* = 8.4 Hz), 6.80 (dd, 2H, *J* = 8.0, 8.0 Hz), 3.91 (m, 1H), 3.20 (m, 1H), 2.20 (m, 4H), 1.59 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.89, 161.92, 142.44, 135.45, 130.47, 130.47, 128.57, 128.57, 127.94, 124.63, 122.97, 118.92, 118.12, 117.84, 117.66, 45.45, 40.98, 39.63, 36.36,17.66, 17.57. HRMS (ESI) calcd for $C_{21}H_{22}{}^{79}BrO_2^+$ $(M + H)^+$ 385.0798, found 385.0623.

*Preparation of Cycloadduct **3g**.* Twenty-five hours, 80% yield, light yellow solid. 88% ee (isopropanol/hexane = 1:99), retention time 6.5 and 7.0 min; $[\alpha]_D^{25}$ = +127.67 (*c* 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H, −OH), 7.63(dd, 1H, *J* = 1.2, 8.0 Hz), 7.36 (m, 3H), 7.08 (s, 1H), 7.06 (s, 1H), 6.90 (dd, 1H, *J* = 0.8, 8.4 Hz), 6.77 (t, 1H, *J* = 7.6, 7.2 Hz), 6.52 (t, 1H, *J* = 7.6, 7.2 Hz), 6.05 (t, 1H, *J* = 7.2, 7.2 Hz), 3.71 (d, 1H, *J* = 6.4 Hz), 3.40 (d, 1H, *J* = 6.8 Hz), 2.91 (t, 1H, *J* = 1.2, 3.2 Hz), 2.62 (dd, 1H, *J* = 2.8, 6.0 Hz), 1.82 (m, 1H), 1.70 (m, 1H), 1.43 (m, 1H), 1.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.37, 162.14, 140.46, 135.23, 135.16, 130.59, 130.53, 129.45, 128.71, 128.58, 128.38, 119.13, 117.88, 117.82, 117.35, 49.34, 42.95, 35.14, 34.56, 25.65, 17.14. HRMS (ESI) calcd for $C_{21}H_{20}{}^{79}BrO_2^+$ $(M + H)^+$ 383.0641, found 383.0465.

*Preparation of Cycloadduct **3h**.* Nine hours, 95% yield, light yellow solid. 91% ee (isopropanol/hexane = 1:99), retention time 4.7 and 6.3 min; $[\alpha]_D^{25}$ = +22.70 (*c* 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (s, 1H, −OH), 7.72 (dd, 1H, *J* = 1.2, 8.0 Hz), 7.35 (m, 1H), 7.23 (m, 2H), 7.00 (d, 2H, *J* = 8.8 Hz), 6.80 (m, 2H), 5.44 (s, 1H), 5.04 (m, 1H), 3.85 (m, 1H), 3.23 (m,1H), 2.37 (m, 1H), 2.22 (m, 3H), 2.04 (m, 2H), 1.97 (m,

https://doi.org/10.1021/acsomega.3c00782
ACS Omega 2023, 8, 11588−11595

2H), 1.63 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.05, 161.93, 142.52, 136.67, 135.46, 130.79, 130.79, 130.54, 130.54, 128.57, 128.00, 122.89, 119.03, 118.14, 117.82, 117.68, 117.62, 44.83, 40.83, 36.41, 36.17, 30.34, 25.32, 24.69, 16.72; HRMS (ESI) calcd for $C_{25}H_{28}{}^{79}BrO_2^+$ $(M + H)^+$ 439.1267, found 439.1090.

Preparation of Cycloadduct ***3i***. Five hours, 92% yield, light yellow solid. 82% ee (isopropanol/hexane = 1:99), retention time 7.4 and 9.9 min; $[\alpha]_D^{25}$ = +5.92(*c* 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{22}H_{25}O_4^+$ $(M + H)^+$ 353.1747, found 353.1742. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.37 (s, 1H, −OH), 7.86 (d, 1H, *J* = 8.0 Hz), 7.32 (m, 1H), 6.89 (d, 1H, *J* = 8.0 Hz), 6.78 (m, 2H), 6.23 (m, 2H), 5.43 (s, 1H), 4.07 (m, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.48 (m, 1H), 2.23 (m, 3H), 2.41 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.14, 161.78, 158.10, 158.10, 156.97, 135.06, 133.33, 128.94, 127.76, 123.44, 118.31, 118.01, 117.53, 117.40, 103.19, 97.80, 54.19, 54.19, 43.16, 35.73, 29.75, 22.17.

Preparation of Cycloadduct ***3j***. Twelve hours, 95% yield, light yellow solid. 88% ee (isopropanol/hexane = 1:99), retention time 7.0 and 7.8 min; $[\alpha]_D^{25}$ = +10.43 (*c* 0.9, CH_2Cl_2). HRMS (ESI) calcd for $C_{24}H_{29}O_6^+$ $(M + H)^+$ 413.1959.1747, found 413.1946. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (s, 1H, −OH), 7.85 (dd, 1H, *J* = 1.2, 8.0 Hz), 7.30 (t, 1H, *J* = 8.4, 15.6 Hz), 6.90 (d, 1H, *J* = 8.4 Hz), 6.80 (t, 2H, *J* = 8.4, 8.4 Hz), 6.60 (d, 1H, *J* = 2.4 Hz), 6.40 (dd, 1H, *J* = 2.4, 8.4 Hz), 5.41 (s, 1H), 5.09 (d, 2H, *J* = 1.2 Hz), 4.99 (d, 2H, *J* = 1.2 Hz), 4.00 (m, 1H), 3.60 (m, 1H), 3.41 (s, 3H), 3.35 (s, 3H), 2.20 (m, 4H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.71, 161.86, 155.56, 154.54, 135.12, 133.31, 128.85, 127.25, 125.56, 118.23, 118.02, 117.61, 117.52, 107.96, 102.77, 93.74, 93.55, 55.10, 54.99, 43.55, 36.28, 35.34, 29.99, 22.14.

Preparation of Cycloadduct ***3k***. 2.5 h, 83% yield, light yellow solid. 72% ee (isopropanol/hexane = 1:99), retention time 6.8 and 8.8 min; $[\alpha]_D^{25}$ = +31.81 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 1H, −OH), 7.74 (d, 1H, *J* = 8.0 Hz), 7.32 (t, 1H, *J* = 8.0, 8.0 Hz), 7.02 (d, 2H, *J* = 8.4 Hz), 6.79 (m, 2H), 6.64 (d, 2H, *J* = 8.4 Hz), 5.05 (m, 2H), 3.85 (m, 1H), 3.62 (s, 3H), 3.18 (m, 1H), 2.30 (m, 2H), 2.20 (m, 2H), 2.04 (m, 2H), 1.96 (m, 2H), 1.62 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.63, 161.84, 156.95, 136.93, 135.44, 135.22, 130.72, 128.74, 127.15, 127.15, 122.96, 118.34, 117.70, 117.58, 117.51, 112.84, 112.84, 54.10, 45.09, 40.61, 36.65, 36.17, 30.32, 25.36, 24.70, 16.67; HRMS (ESI) calcd for $C_{26}H_{31}O_3^+$ $(M + H)^+$ 391.2268, found 391.2100.

Preparation of Cycloadduct ***3l***. Nine hours, 95% yield, light yellow solid. 91% ee (isopropanol/hexane = 1:99), retention time 7.8 and 9.2 min; $[\alpha]_D^{25}$ = +24.64 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 1H, −OH), 7.74 (d, 1H, *J* = 8.0 Hz), 7.33 (t, 1H, *J* = 7.6, 7.6 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 6.79 (m, 4H), 5.43 (s, 1H), 5.02 (m, 3H), 3.86 (m, 1H), 3.34 (s, 3H), 3.19 (m, 1H), 2.33 (m, 2H), 2.20 (m, 2H), 2.05 (m, 2H), 1.96 (m, 2H), 1.62 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.52, 161.88, 154.67, 136.90, 136.79, 135.23, 130.69, 128.74, 128.74, 127.16, 127.16, 123.00, 118.31, 117.72, 117.53, 115.20, 115.20, 93.45, 54.88, 45.01, 40.60, 36.66, 36.24, 30.33, 25.35, 24.70, 16.67; HRMS (ESI) calcd for $C_{27}H_{32}NaO_4^+$ $(M + Na)^+$ 443.2193, found 443.2179.

Preparation of Cycloadduct ***3m***. Thirteen hours, 86% yield, light yellow solid. 84% ee (isopropanol/hexane = 1:99), retention time 8.5 and 11.2 min; $[\alpha]_D^{25}$ = +22.70 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (s, 1H, −OH), 7.72 (dd, 1H, *J* = 1.2, 8.0 Hz), 7.35 (m, 1H), 7.23 (m, 2H), 7.00 (d, 2H, *J* = 8.8 Hz), 6.80 (m, 2H), 5.44 (s, 1H), 5.04 (m, 1H), 3.85 (m, 1H), 3.23 (m,1H), 2.37 (m, 1H), 2.22 (m, 3H), 2.04 (m, 2H), 1.97 (m, 2H), 1.63 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.05, 161.93, 142.52, 136.67, 135.46, 130.79, 130.79, 130.54, 130.54, 128.57, 128.00, 122.89, 119.03, 118.14, 117.82, 117.68, 117.62, 44.83, 40.83, 36.41, 36.17, 30.34, 25.32, 24.69, 16.72; HRMS (ESI) calcd for $C_{29}H_{36}O_6^+$ $(M + H)^+$ 481.2585, found 481.2582.

General Procedure for the Synthesis of Methylated Nicolaiodesin C (8). To the solution of 2′-hydroxy-4′,6′-dimethoxyacetophenone (**4**) (0.45 g, 2.3 mmol, 1.0 equiv) in EtOH (10 mL) was added KOH aqueous solution (20 mmol/mL, 5.3 mL) slowly at −5 °C. Then, the mixture was continued to be stirred for another 30 min at this temperature. After that, benzaldehyde (**5**) (0.37 g, 3.5 mmol, 1.5 equiv) was added dropwise at this temperature. Then, the mixture was slowly warmed to room temperature for 3 days. Subsequently, cold water (200 mL) was added to the solution, adjusted to pH 3−4 by adding 1 M HCl, and extracted with EtOAc (100 mL × 2). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether = 1:5) to afford 2′-hydroxy-4′,6′-dimethoxychalcone (**6**) (0.62 g, 95%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.29 (s, 1H, −OH), 7.85 (m, 2H), 7.61 (m, 2H), 7.41 (m, 3H), 6.12 (d, 1H, *J* = 4.0 Hz), 5.97 (d, 1H, *J* = 2.0 Hz), 3.93 (s, 3H), 3.84 (s, 3H).

Methylated nicolaiodesin C (**8**) was prepared using the general procedure for enantioselective model Diels−Alder cycloaddition. *R*-VANOL (10 mg, 0.0024 mmol, 0.12 equiv), dienophile chalcone **6** (60 mg, 0.2 mmol, 1.0 equiv), and diene **7** (42 μL, 0.24 mmol, 1.2 equiv) were employed. The desired Diels−Alder adduct **8** (70 mg, 85%) was isolated as a light yellow solid. Eighty-nine percent ee (isopropanol/hexane = 1:99), retention time 8.1 and 10.8 min; $[\alpha]_D^{25}$ = −11.99 (*c* 0.90, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.62 (s, 1H, −OH), 7.11 (m, 4H), 7.00 (m, 1H), 5.87 (d, 1H, *J* = 2.4 Hz), 5.82 (d, 1H, *J* = 2.4 Hz), 5.43 (d, 1H, *J* = 4.0 Hz), 5.05 (m, 1H), 4.20 (m, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 3.20 (m, 1H), 2.17 (m, 2H), 2.05 (m, 3H), 1.95 (m, 3H), 1.63 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.58, 166.46, 164.63, 161.21, 144.45, 136.29, 130.50, 127.21, 127.21, 126.23, 126.23, 124.91, 123.15, 118.38, 105.43, 92.54, 89.90, 54.72, 54.43, 49.30, 41.88, 37.04, 36.25, 29.51, 25.35, 24.72, 16.72; HRMS (ESI) calcd for $C_{27}H_{32}NaO_4^+$ $(M + Na)^+$ 443.2193, found 443.2179.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00782.

^{1}H, ^{13}C NMR spectra, and chiral HPLC chromatography of the compounds synthesized in the present study (PDF)

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https://doi.org/10.1021/acsomega.3c00782
ACS Omega 2023, 8, 11588−11595

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 81471823), the Innovative Research Project of People's Armed Police Forces (No. ZZKY20222419), the Basic Research Project of Armed Police Logistics College (No. WHJ202010), and the Innovative Research Team Program for Science and Technology in Logistics University of People's Armed Police Forces. The authors thank M.S. Qingcui Wu (National Institute of Biological Sciences) for the chiral HPLC analysis and Dr. Lei Gao (Peking University) and Wenying Ai (Zhongyuan University of Technology) for editing the draft of this manuscript.

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https://doi.org/10.1021/acsomega.3c00782
ACS Omega 2023, 8, 11588−11595