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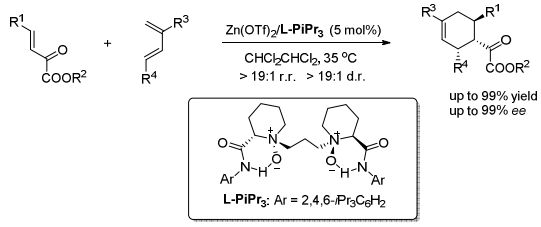
Zinc(II)-Catalyzed Asymmetric Diels-Alder Reaction of (*E*)-1-Phenyldienes with β,γ-Unsaturated α-Ketoesters

Qian Xiong, Lili Lin,* Xiaohu Zhao, Jiawen Lang, Xiaohua Liu, and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu, 610064, People's Republic of China

Fax: (+86) 28-8541-8249; e-mail: lililin@scu.edu.cn; xmfeng@scu.edu.cn



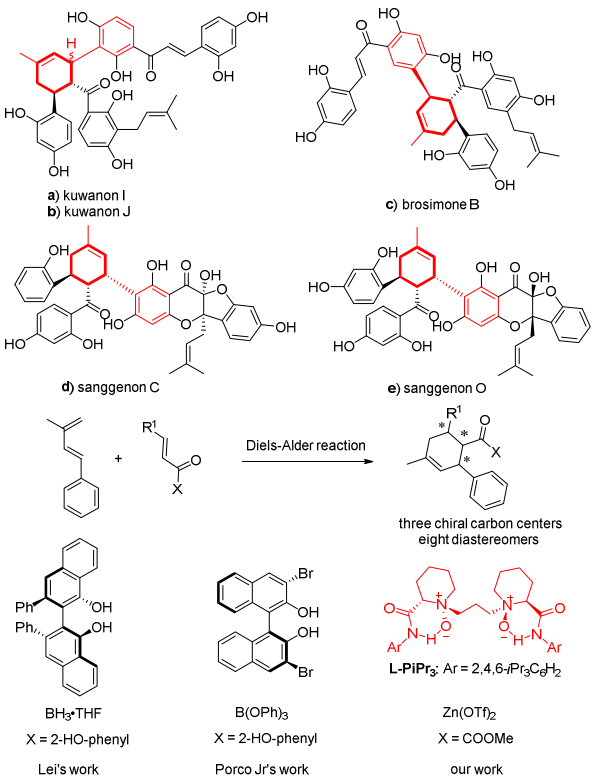
ABSTRACT: A highly regio-, diastereo- and enantioseletive Diels-Alder reaction of β,γ-unsaturated α-ketoesters with (*E*)-1-phenyldienes has been accomplished by using a stable and easily available chiral *N,N′*-dioxide/zinc(II) complex as catalyst. Only one isomer of the corresponding cyclohexenes with three chiral centers were obtained in good to excellent yields with excellent *ee* values under mild reaction conditions. The configurations of the product and chiral *N,N′*-dioxide/zinc(II) catalyst were identified by X-ray diffraction analysis. Besides, a possible catalytic model was proposed to explain the origin of the asymmetric induction.

INTRODUCTION

There is no doubt that Diels-Alder reaction[1] is one of the most efficient methods to construct cyclohexenes. The hypothetical natural Diels-Alder adducts[2] kuwanons I, J, brosimone B and sanggenons C, O (Scheme 1, **a-e**) are isolated from the cultivated mulberry tree and other moraceous plants, which exhibit potential biological activities including anticancer, anti-HIV.[3] Liu's group

developed a cascade strategy via gold-catalyzed isomerization of unactivated allenes into 1,3-dienes and the following cycloaddition with the reactive alkenes to synthesize substituted cyclohexenes.[4a] For the asymmetric synthesis, Lei's group[4c] developed a chiral VANOL/boron complex-catalysed asymmetric Diels-Alder reaction of (*E*)-1-phenyldienes with 2′-hydroxychalcone derivatives, and applied it in the enantioselective synthesis of kuwanons I, J and brosimone B. J. A. Porco Jr's group also used an $B(OPh)_3$/BINOL complex-promoted enantioselective Diels-Alder reaction of (*E*)-1-phenyldiene derivatives with 2′-hydroxychalcones as a key step to synthesize the optically pure natural sanggenons.[4f] Considering the usefulness of Diels-Alder reaction about (*E*)-1-phenyl-3-methyl dienes, developing new catalytic systems to synthesize these cyclohexenes with three chiral centers is still meaningful.

Carbonyl compounds coordinate with Lewis acid catalyst generally in a monodentate manner or a bidentate manner. The monodentate coordination is flexible and can lead to different selectivity under different conditions.[5b] Comparatively, the bidentate coordination is more rigid, which makes it easier to control the reaction selectivity.[5a] Chiral *N,N*′-dioxide[6] developed by our group can coordinate with various metal salts to catalyze asymmetric reactions. Meanwhile, zinc(II) salts feature advantages in economic efficiency, abundance and environment-friendly.[7] Herein, we report our achievements in developing a *N,N*′-dioxide/Zn(II) complex as catalyst to catalyze the asymmetric Diels-Alder reaction of (*E*)-1-phenyldienes with β,γ-unsaturated α-ketoesters[8] under mild reaction conditions.



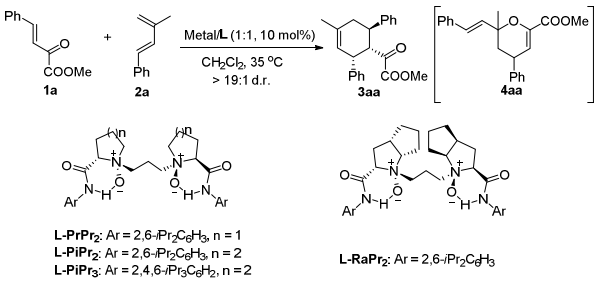
Scheme 1. Natural products and reactions of (*E*)-1-phenyldienes.

RESULTS AND DISCUSSION

Initially, the reaction of β,γ-unsaturated α-ketoester (**1a**) and (*E*)-(3-methylbuta-1,3-dien-1-yl)benzene (**2a**) was employed as the model reaction to optimize the reaction conditions (Table 1). Firstly, no reaction occurred in the absence of metal no matter with or without ligand. Then, various metal salts complexing with chiral *N,N′*-dioxide ligand **L-PrPr$_2$** were investigated in CH_2Cl_2 at 35 °C. Both the Diels-Alder product and hetero-Diels-Alder product were detected (Table 1, entries 3-5).[9,10] When $Mg(OTf)_2$ was applied, a mixture of Diels-Alder product **3aa** and hetero-Diels-Alder product **4aa** was obtained in 37% total yield with poor regioselectivity (Table 1, entry 3). Both of $Ni(OTf)_2$ and $Zn(OTf)_2$ could improve the ratio of **3aa** to **4aa** (entries 4-5), and $Zn(OTf)_2$ showed higher ee value. Subsequently, various *N,N′*-dioxide ligands with different chiral backbones and steric hindrance on aniline were examined (entries 5-8). It was found that L-pipecolic

acid derived **L-PiPr$_2$** was superior to **L-PrPr$_2$** and **L-RaPr$_2$** (entry 7 vs entries 5-6). **L-PiPr$_3$** could increase the yield and keep the enantioselectivity (entry 8). When $CHCl_2CHCl_2$ was used as solvent and adjusting the ratio of **1a** and **2a** to 1:2, only Diels-Alder product was obtained in 97% yield with 98% *ee* (entry 9). The catalyst loading could be decreased to 5 mol%, and still excellent yield and *ee* were obtained (entry 10). So, the optimal reaction condition were established as **1a**/**2a** (1:2), $Zn(OTf)_2$/**L-PiPr$_3$** (1:1, 5 mol%) in $CHCl_2CHCl_2$ at 35 ^oC for 24 h.

Table 1 Optimization of the reaction conditions



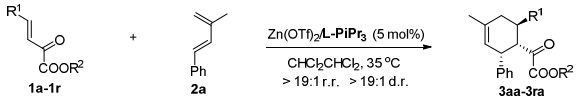
Entry[a]	Ligand	Metal	Yield (%)[b]	**3aa**/**4aa**[c]	*ee* (%)[c]	
					3aa	**4aa**
1	-	-	-	-	-	-
2	**L-PrPr$_2$**	-	-	-	-	-
3	**L-PrPr$_2$**	$Mg(OTf)_2$	37	35:65	50	82
4	**L-PrPr$_2$**	$Ni(OTf)_2$	61	92:8	45	-
5	**L-PrPr$_2$**	$Zn(OTf)_2$	56	82:18	67	15
6	**L-RaPr$_2$**	$Zn(OTf)_2$	49	93:7	55	-
7	**L-PiPr$_2$**	$Zn(OTf)_2$	51	98:2	80	-
8	**L-PiPr$_3$**	$Zn(OTf)_2$	63	98:2	80	-
9[d,e]	**L-PiPr$_3$**	$Zn(OTf)_2$	97	>99:1	98	-

10[d,e,f]	**L-PiPr$_3$**	Zn(OTf)$_2$	94	>99:1	94	-

[a] Unless otherwise noted, all reaction were carried out with **1a** (0.10 mmol), **2a** (0.10 mmol), metal/ligand (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) at 35 °C. [b] total Isolated yield of **3aa** and **4aa**. **4aa** can not be isolated and detected separately. [c] Determined by chiral HPLC analysis. [d] $CHCl_2CHCl_2$ was used. [e] 0.20 mmol **2a** was used. [f] used 5 mol% catalyst.

Under the optimized reaction conditions, the substrate scope was then investigated. Firstly, a wide range of β,γ-unsaturated α-ketoesters were evaluated (Table 2). The different ester groups have little effect on the yields but have some effects on the *ee* values (entries 1-3). The ethyl R^2 improved the *ee* value to 99%, while the benzyl R^2 decreased the *ee* value to 88%. The reason might be that the ester groups are closer to the Zn^{II} center, affecting the face selectivity of the reaction. The β,γ-unsaturated α-ketoesters with either electron-withdrawing or electron-donating substituents on phenyl R^1 group mostly could transformed to the corresponding products in excellent yields and enantioselectivities (entries 4-14). Exceptly, 2-methoxyl product **3ea** was obtained in lower yield, which might be caused by both the electronic nature and steric encumbrance between the catalyst and the substrate (entry 5). To our delight, condensed-ring, cinnamyl and hetero-aromatic β,γ-unsaturated α-ketoesters **1o-q** were also well tolerated in the catalytic system, giving the corresponding products in 78-98% yields with 97-99% *ee* (entries 15-17). Notably, the γ-alkyl-substituted β,γ-unsaturated α-ketoester **1r** also proceeded well, and the desired product **3ra** was obtained in 93% yield with 99% *ee* (entry 18). R^1 group show obvious difference on the yields, which might be caused by it's influence on the LOMO energy.

Table 2 Substrate scope of the β,γ-unsaturated α-ketoesters

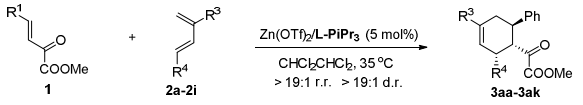


Entry[a]	R^1	R^2	Yield (%)[b]	*ee* (%)[c]
1	Ph	Me	94 **(3aa)**	94 (1*R*, 2*S*, 3*R*)
2	Ph	Et	96 **(3ba)**	99 (1*R*, 2*S*, 3*R*)
3	Ph	Bn	99 **(3ca)**	88 (1*R*, 2*S*, 3*R*)
4	3-MeC_6H_4	Me	98 **(3da)**	99 (1*R*, 2*S*, 3*R*)
5	2-$MeOC_6H_4$	Me	64 **(3ea)**	99 (1*R*, 2*S*, 3*R*)
6	3-$MeOC_6H_4$	Me	90 **(3fa)**	97 (1*R*, 2*S*, 3*R*)
7	4-$MeOC_6H_4$	Me	95 **(3ga)**	99 (1*R*, 2*S*, 3*R*)
8		Me	97 **(3ha)**	99 (1*R*, 2*S*, 3*R*)
9	4-PhC_6H_4	Me	99 **(3ia)**	98 (1*R*, 2*S*, 3*R*)
10	2-FC_6H_4	Me	80 **(3ja)**	99 (1*R*, 2*S*, 3*R*)
11	4-FC_6H_4	Me	81 **(3ka)**	99 (1*R*, 2*S*, 3*R*)
12	3-ClC_6H_4	Me	93 **(3la)**	99 (1*R*, 2*S*, 3*R*)
13	2,6-$Cl_2C_6H_3$	Me	93 **(3ma)**	99 (1*R*, 2*S*, 3*R*)
14	4-BrC_6H_4	Me	95 **(3na)**	99 (1*R*, 2*S*, 3*R*)
15	2-Naphthyl	Me	78 **(3oa)**	99 (1*R*, 2*S*, 3*R*)
16		Me	98 **(3pa)**	98 (1*R*, 2*S*, 3*R*)
17	3-Thienyl	Me	93 **(3qa)**	97 (1*R*, 2*S*, 3*R*)
18	Cyclohexyl	Me	93 **(3ra)**	99

[a] Unless otherwise noted, the reaction was carried out with **1** (0.10 mmol), **2a** (0.20 mmol), $Zn(OTf)_2$/**L-PiPr$_3$** (1:1, 5 mol%) in $CHCl_2CHCl_2$ (1.0 mL) for 24 h. r.r. = regio ratio. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Subsequently, the scope of (*E*)-1-phenyldienes was investigated by reacting with β,γ-unsaturated α-ketoester (**1a**) (Table 2). The substituent R^4 at different positions of the phenyl group had little influence on the yield and selectivity (entries 1-6). The R^3 turned into the ethyl substitution, giving the corresponding compound **3ag** in 99% yield with 93% *ee* (entry 7). However, if R^3 was H or phenyl substituent, the reaction didn't occur (Table 3, entries 8-9). For diene **2h** without the methyl group, the high HOMO energy might prevent the occurrence of the reaction. Meanwhile, the larger steric hindrance between the catalyst might make it difficult for diene **2i** to enter the catalytic active center of the model. So, appropriate steric and electrical properties on the 3-position of diene were critical for the reaction activity. When (*E*)-1-phenyldienes (**2f**) reacted with other β,γ-unsaturated α-ketoesters (**1d** and **1n**), the corresponding compounds were obtained with little influence on the yield and selectivity (entries 10-11). The absolute configuration of **3ad** was determined to be (1*R*, 2*S*, 3*R*) by X-ray crystallographic analysis,[11] and the others were assigned to be the same by comparing the Cotton effect of the CD spectra with that of **3ad** (for details, see the ESI).

Table 3 Substrate scope of the (*E*)-1-phenyldienes [a]

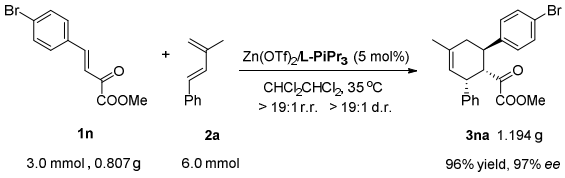


Entry[a]	R^3	R^4	Yield (%)[b]	*ee* (%)[c]
1	Me	Ph	94 (**3aa**)	94 (1*R*, 2*S*, 3*R*)
2	Me	2-ClC_6H_4	87 (**3ab**)	99 (1*R*, 2*S*, 3*R*)
3	Me	3-FC_6H_4	90 (**3ac**)	99 (1*R*, 2*S*, 3*R*)
4	Me	4-FC_6H_4	98 (**3ad**)	91 (1*R*, 2*S*, 3*R*)
5	Me	3-$MeOC_6H_4$	91 (**3ae**)	99 (1*R*, 2*S*, 3*R*)
6	Me	4-$MeOC_6H_4$	94 (**3af**)	97 (1*R*, 2*S*, 3*R*)

7	Et	Ph	99 (**3ag**)	93 (1*R*, 2*S*, 3*R*)
8	H	Ph	NR (**3ah**)	-
9	Ph	Ph	NR (**3ai**)	-
10[d]	Me	4-MeOC$_6$H$_4$	94 (**3aj**)	94 (1*R*, 2*S*, 3*R*)
11[e]	Me	4-MeOC$_6$H$_4$	97 (**3ak**)	94 (1*R*, 2*S*, 3*R*)

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.10 mmol), **2** (0.20 mmol), Zn(OTf)$_2$/**L-PiPr$_3$** (1:1, 5 mol%) in $CHCl_2CHCl_2$ (1.0 mL) for 24 h. r.r. = regio ratio. [b] Isolated yield. [c] Determined by chiral HPLC analysis. NR = no reaction. [d] **1d** was used. [e] **1n** was used.

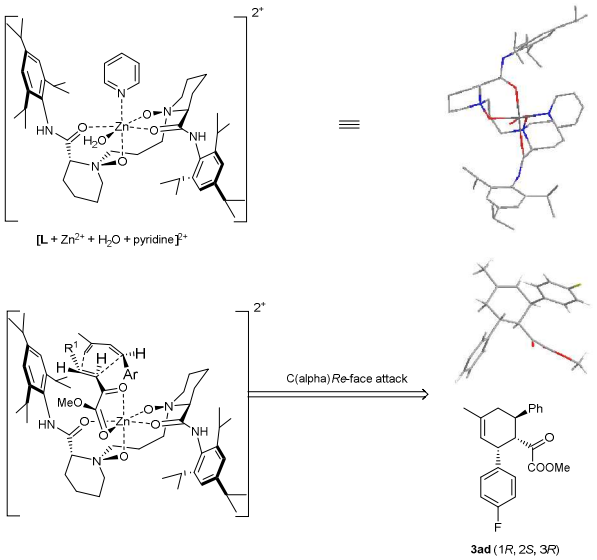
To show the synthetic utility of the current catalytic system, a gram-scale synthesis is of **3na** was carried out under the optimized reaction condition. As shown in the Scheme 2, in the presence of 5 mol% of **L-PiPr$_3$**-Zn(OTf)$_2$ complex, 3.0 mmol of **1n** reacted well with 6.0 mmol of **2a**, and 1.194 g (96% yield) **3na** was obtained with 97% *ee*.



Scheme 2 Scale-up version of the reaction.

To explore the mechanism of the reaction, the single crystal of the catalyst was tried to be prepared. After lots of attempts, the crystal was obtained at the condition of **L-PiPr$_3$**, Zn(BF$_4$)$_2$•6H$_2$O and pyridine in a 1:1:2 ratio in THF and *n*-hexane, which showed four oxygens of the *N*,*N*′-dioxide **L-PiPr$_3$**, one oxygen of H_2O and one nitrogen of pyridine coordinate to the Zn^{II} center to form an octahedral geometry.[12] HRMS analysis was also carried out. The spectrum of a mixture of **L-PiPr$_3$** and Zn(OTf)$_2$ in a 1:1 ratio in $CHCl_2CHCl_2$ displayed an ion at m/z 945.4326 (m/z calcd for [**L-PiPr$_3$** + Zn^{2+} + OTf^-]$^+$:

945.4360), which suggested that the ligand coordinated with the metal in a 1:1 ratio. In the spectrum of a mixture of **L-PiPr$_3$**, Zn(OTf)$_2$ and **1a** in a ratio 1:1:1 in $CHCl_2CHCl_2$, the signal of [**L-PiPr$_3$** + Zn^{2+} + OTf^- + **1a**]$^+$ at m/z 1135.4985 (m/z calcd 1135.4980) was observed, which suggested that the **L-PiPr$_3$**-Zn(OTf)$_2$ complex coordinated with **1a** in a 1:1 ratio. Besides, Operando IR experiments of **1e** and **2a** suggested that the reaction proceeded through a concerted pathway since the amount of product increased with the consumption of starting materials and no intermediates were observed.



Scheme 3 Proposed transition-state model for the reaction.

On the basis of above analysis and the determination of the absolute configuration of the products, a possible transition-state model was proposed. As shown in Scheme 3, four oxygens of the *N*,*N*′-dioxide **L-PiPr$_3$** and the two oxygens of β,γ-unsaturated α-ketoester **1** coordinate to the Zn^{II} center, forming an octahedral complex. At the same time, the coordination could decrease the LUMO energy of β,γ-unsaturated α-ketoester **1** and promote the Diels-Alder reaction. Since the *Si* face of the β,γ-unsaturated α-ketoester **1** is shielded by the neighboring amide group of the ligand, hence, the (*E*)-1-phenyldienes attack from the *Re* face of the β,γ-unsaturated α-ketoester **1** through a concerted pathway to form the (1*R*, 2*S*, 3*R*)-configured product **3**.

In summary, a highly regioselective, diastereoseletive and enantioseletive Diels-Alder reaction of (*E*)-1-phenyldienes with β,γ-unsaturated α-ketoesters is realized in the presence of a chiral *N*,*N*′-dioxide-Zn^{II} complex. A wide range of cyclohexenes were obtained in excellent yields with excellent ee values. Furthermore, a possible transition model was proposed to explain the origin of chirality.

EXPERIMENTAL SECTION

General remarks:

Reactions were carried out using commercial available reagents in oven-dried apparatus. CH_2Cl_2 was dried over powdered K_2CO_3 and distilled over CaH_2 just before use. $CHCl_2CHCl_2$ was dried and distilled over CaH_2. ^1H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. Metal catalysts obtained from commercial sources were used without further purification. Enantiomeric excesses were determined by chiral HPLC analysis on Daicel Chiralcel IA/IB/IC/ID/IE/OX-H in comparison with the authentic racemates. Optical rotations were reported as follows: $[\alpha]^T_\lambda$ = (c: g/100 mL, in CH_2Cl_2, D: 589 nm). HRMS was recorded on a commercial apparatus (ESI Source, TOF).

General procedure for the synthesises of dienes

General procedure: To a solution of methyltriphenylphosphonium bromide (8.0 g, 22.0 mmol) in THF (50 mL), was added NaH (1.0 g, 22.0 mmol). The mixture was stirred for 1 hour at 60 °C. The ketone (20.0 mmol) was then added and the solution was stirred at 60 °C until the reaction is completed by GC analysis or by TLC. The solvent was removed under reduced pressure and the crude diene was purified by flash chromatography (petroleum ether: 100%) on silica gel or by distillation.

General procedure for the synthesis of racemic products

General procedure: To an oven-dried tube was added $Zn(OTf)_2$ (0.005 mmol, 5 mol%), racemic $PiPr_2$ (0.005 mmol, 5 mol %), β,γ-unsaturated α-ketoester **1a** (0.10 mmol), (*E*)-(3-methylbuta-1,3-dien-1-yl)benzene **2a** (0.20 mmol) and CH_2Cl_2 (1.0 mL). The

reaction was stirred at 0 or 35 ºC, and then crude product was directly purified by flash chromatography on silica gel column (eluent: petroleum ether/ethyl acetate = 9/1) to afford the racemic mixture.

Typical procedure for the asymmetric reaction

General procedure: To an oven-dried tube was added $Zn(OTf)_2$ (0.005 mmol, 5 mol%), L-$PiPr_3$ (0.005 mmol, 5 mol %). After nitrogen replacement, β,γ-unsaturated α-ketoester **1a** (0.10 mmol) and $Cl_2CHCHCl_2$ (1.0 mL) were added under nitrogen atmosphere. The mixture was stirred in $Cl_2CHCHCl_2$ (1.0 mL) at 35 °C for 0.5 h. Subsequently, (*E*)-(3-methylbuta-1,3-dien-1-yl)benzene **2a** (0.20 mmol) was added. The reaction was stirred at the same temperature for 24 h, and then crude product was directly purified by flash chromatography on silica gel column (eluent: petroleum ether/ethyl acetate = 9/1) to afford the desired product 3aa (94% yield, 94% *ee* and >19:1 d.r.).

Methyl 2-((1'*R*,2'*S*,3'*R*)-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-yl)-2-oxoacetate **(3aa)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 31.4 mg, 94% yield, 94% *ee*; $[\alpha]^{21}_D$ = -215.2 (*c* = 0.62 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 7.37 min, t_R (major) = 7.74 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 – 7.12 (m, 8H), 7.09 – 7.02 (m, 2H), 5.62 – 5.49 (m, 1H), 4.23 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.68 (s, 3H), 3.36 (td, *J* = 10.6, 6.0 Hz, 1H), 2.46 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.28 – 2.15 (m, 1H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.1, 161.3, 144.6, 140.1, 134.9, 129.5, 128.6, 128.4, 127.5, 127.4, 126.5, 122.1, 52.9, 52.5, 43.7, 38.9, 37.0, 23.4. HRMS (ESI-TOF) calcd for $C_{22}H_{22}O_3Na^+$ ([M+Na^+]) = 357.1461, Found 357.1466.

Ethyl 2-((1'*R*,2'*S*,3'*R*)-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-yl)-2-oxoacetate （**3ba**）

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 33.4 mg, 96% yield, 99% *ee*; $[\alpha]^{21}_D$ = -181.1 (*c* = 0.58 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 7.02 min, t_R (major) = 7.66 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 – 7.12 (m, 8H), 7.10 – 7.03 (m, 2H), 5.60 – 5.50 (m, 1H), 4.22 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.18 – 4.04 (m, 3H), 3.36 (td, *J* = 10.6, 6.0 Hz, 1H), 2.46 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.21 (dd, *J* = 17.6, 9.6 Hz, 1H), 1.83 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.4, 160.9, 144.7, 140.2, 134.7, 129.5, 128.6, 128.4, 127.6, 127.3, 126.5, 122.2, 62.3, 52.4, 43.7, 38.9, 37.0, 23.4, 14.0. HRMS (ESI-TOF) calcd for $C_{23}H_{24}O_3Na^+$ ([M+Na^+]) = 371.1618, Found 371.1621.

Benzyl 2-((1'*R*,2'*S*,3'*R*)-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-yl)-2-oxoacetate **(3ca)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 40.1 mg, 99% yield, 88% *ee*; $[\alpha]^{21}_D$ = -181.1 (*c* = 0.76 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 11.04 min, t_R (major) = 11.56 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.28 (m, 5H), 7.23 – 7.11 (m, 8H), 7.00 – 6.92 (m, 2H), 5.57 – 5.47 (m, 1H), 5.20 – 5.12 (m, 1H), 5.09 – 4.99 (m, 1H), 4.22 (dd, *J* = 11.2, 6.0 Hz,

1H), 4.11 – 4.03 (m, 1H), 3.34 (td, *J* = 10.8, 6.0 Hz, 1H), 2.44 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.19 (dd, *J* = 18.0, 10.4 Hz, 1H), 1.81 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.0, 160.6, 144.6, 140.1, 134.7, 129.4, 128.8, 128.7, 128.6, 128.4, 127.5, 127.3, 126.5, 122.1, 67.7, 52.5, 43.7, 38.9, 36.9, 23.4. HRMS (ESI-TOF) calcd for $C_{28}H_{26}O_3Na^+$ ([M+Na^+]) = 433.1774, Found 433.1776.

Methyl 2-((1'*R*,2'*S*,3'*R*)-3'',5'-dimethyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3da)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 34.1 mg, 98% yield, 99% *ee*; $[\alpha]^{21}_D$ = -201.9 (*c* = 0.59 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.64 min, t_R (major) = 7.13 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.19 (m, 3H), 7.13 – 7.04 (m, 3H), 7.01 – 6.91 (m, 3H), 5.61 – 5.49 (m, 1H), 4.23 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.10 – 4.05(4.14, 1H), 3.69 (s, 3H), 3.36 – 3.28 (m, 1H), 2.45 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.29 – 2.15 (m, 4H), 1.82 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.1, 161.3, 144.5, 140.2, 138.1, 134.8, 129.5, 128.6, 128.5, 128.4, 127.3, 124.3, 122.1, 52.9, 52.5, 43.8, 39.1, 36.9, 23.4, 21.5. HRMS (ESI-TOF) calcd for $C_{23}H_{24}O_3Na^+$ ([M+Na^+]) = 371.1618, Found 371.1620.

Methyl 2-((1'*R*,2'*S*,3'*R*)-2''-methoxy-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3ea)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 23.3 mg, 64% yield, 99% *ee*; $[\alpha]^{21}_D$ = -163.4 (*c* = 0.41 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), ,t_R (minor) = 8.94 min, t_R (major) = 10.67 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.27 – 7.17 (m, 3H), 7.14 – 7.03 (m, 4H), 6.87 – 6.76 (m, 2H), 5.58 – 5.50 (m, 1H), 4.42 (dd, *J* = 10.4, 6.0 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.78 (s, 3H), 3.73 – 3.64 (m, 4H), 2.49 – 2.42 (m, 1H), 2.21 (dd, *J* = 17.6, 9.6 Hz, 1H), 1.83 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.5, 161.5, 157.1, 140.4, 135.3, 132.4, 129.5, 128.3, 128.2, 127.4, 127.2, 122.1, 120.9, 111.1, 55.6, 52.7, 51.2, 43.7, 36.8, 23.4. HRMS (ESI-TOF) calcd for $C_{23}H_{24}O_4Na^+$ ([M+Na^+]) = 387.1567, Found 387.1570.

Methyl 2-((1'*R*,2'*S*,3'*R*)-3''-methoxy-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3fa)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 32.4 mg, 90% yield, 97% *ee*; $[\alpha]^{21}_D$ = -197.6 (*c* = 0.50 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =20/80, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.09 min, t_R (major) = 7.06 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.24 (m, 3H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.09 – 7.03 (m, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.74 – 6.70 (m, 1H), 6.70 – 6.64 (m, 1H), 5.59 – 5.50 (m, 1H), 4.23 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.14 – 4.05 (m, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.33 (td, *J* = 10.6, 6.0 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.62 – 2.16 (m, 1H), 1.83 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.0, 161.3, 159.8, 146.3, 140.1, 134.8, 129.6, 129.5,

128.4, 127.4, 122.1, 119.8, 113.4, 111.8, 55.2, 52.9, 52.4, 43.7, 38.9, 37.0, 23.4. HRMS (ESI-TOF) calcd for $C_{23}H_{24}O_4Na^+$ ([M+Na^+]) = 387.1567, Found 387.1574.

Methyl 2-((1'*R*,2'*S*,3'*R*)-4''-methoxy-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3ga)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 34.6 mg, 95% yield, 99% *ee*; $[\alpha]^{21}_D$ = -198.0 (*c* = 0.51 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =20/80, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.41 min, t_R (major) = 7.26 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.17 (m, 3H), 7.13 – 7.02 (m, 4H), 6.81 – 6.71(m, 2H), 5.61 – 5.48 (m, 1H), 4.17 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.11 – 4.03 (m, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.31 (td, *J* = 10.6, 6.0 Hz, 1H), 2.44 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.19 (dd, *J* = 18.4, 10.4 Hz, 1H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.3, 161.3, 158.1, 140.2, 136.6, 134.9, 129.5, 128.5, 128.4, 127.3, 122.1, 114.0, 55.3, 52.9, 43.8, 39.0, 36.1, 23.4. HRMS (ESI-TOF) calcd for $C_{23}H_{24}O_4Na^+$ ([M+Na^+]) = 387.1567, Found 387.1564.

Methyl 2-((1*R*,2*S*,3*R*)-3-(benzo[d][1,3]dioxol-5-yl)-5-methyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)-2-oxoacetate **(3ha)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 36.7 mg, 97% yield, 99% *ee*; $[\alpha]^{21}_D$ = -176.7 (*c* = 0.63 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =20/80, 1.0 mL/min, λ = 254 nm), t_R (minor) = 7.44 min, t_R (major) = 8.53 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (m, 2H), 7.21 (m, 1H), 7.09 – 7.00 (m, 2H), 6.72 – 6.59 (m, 3H), 5.87 (s, 2H), 5.59 – 5.48 (m, 1H), 4.15 (dd, *J* = 11.2, 6.0 Hz, 1H), 5.59 – 5.48 (m, 1H), 3.71 (s, 3H), 3.27 (td, *J* = 10.6, 6.0 Hz, 1H), 2.44 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.17 (dd, *J* = 18.4, 10.4 Hz, 1H), 1.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.1, 161.2, 147.7, 146.0, 140.1, 138.5, 134.7, 129.5, 128.4, 127.4, 122.1, 120.6, 108.4, 107.9, 100.9, 52.9, 52.8, 43.8, 39.1, 36.7, 23.3. HRMS (ESI-TOF) calcd for $C_{23}H_{22}O_5Na^+$ ([M+Na^+]) = 401.1359, Found 401.1369.

Methyl 2-((1'*R*,2'*S*,3'*R*)-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-yl)-2-oxoacetate **(3ia)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford white solid; m.p. 48-52 ºC; 40.6 mg, 99% yield, 98% *ee*; $[\alpha]^{21}_D$ = -193.9 (*c* = 0.62 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 11.03 min, t_R (major) = 12.67 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 – 7.50 (m, 2H), 7.47 – 7.43 (m, 2H), 7.42 – 7.37 (m, 2H), 7.32 – 7.21 (m, 6H), 7.11 – 7.01 (m, 2H), 5.63 – 5.49 (m, 1H), 4.28 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.18 – 4.09 (m, 1H), 3.70 (s, 3H), 3.40 (td, *J* = 10.4, 6.0 Hz, 1H), 2.50 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.25 (dd, *J* = 18.4, 10.4 Hz, 1H), 1.84 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.1, 161.2, 143.7, 141.0, 140.1, 139.4, 134.8, 129.5, 128.8, 128.4, 128.0, 127.4, 127.2, 127.1, 122.1, 52.9, 52.5, 43.8, 38.9, 36.6, 23.4. HRMS (ESI-TOF) calcd for $C_{28}H_{26}O_3Na^+$ ([M+Na^+]) = 433.1774, Found 433.1778.

Methyl 2-((1'*R*,2'*S*,3'*R*)-2''-fluoro-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3ja)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 34.8 mg, 80% yield, 99% *ee*; $[\alpha]^{21}_{D}$ = -179.8 (*c* = 0.50 in CH_2Cl_2); the ee was determined by UPC^2 Phenomenex analysis using a chiral OJH column (methanol/ CO_2 =10/90, 1.0 mL/min, λ = 254 nm) t_R (minor) = 5.92 min, t_R (major) = 7.17 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.19 (m, 3H), 7.15 – 7.03 (m, 4H), 7.02 – 6.90 (m, 2H), 5.62 – 5.47 (m, 1H), 4.34 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.21 – 4.11 (m, 1H), 3.72 (s, 3H), 3.65 (td, *J* = 10.8, 6.0 Hz, 1H), 2.47 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.24 (dd, *J* = 18.0, 10.4 Hz, 1H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 193.9, 161.2, 160.8 (d, *J* = 246.1), 139.9, 134.7, 131.1 (d, *J* = 13.9), 129.4, 128.8 (d, *J* = 4.9), 128.5, 128.0 (d, *J* = 8.5), 127.5, 124.4 (d, *J* = 3.3), 122.2, 115.8 (d, *J* = 22.8), 52.9, 51.4, 43.8, 37.3, 31.1, 23.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -117.86. HRMS (ESI-TOF) calcd for $C_{22}H_{21}FO_3Na^+$ ([M+Na^+]) = 375.1367, Found 375.1365.

Methyl 2-((1'*R*,2'*S*,3'*R*)-4''-fluoro-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3ka)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 28.5 mg, 81% yield, 99% *ee*; $[\alpha]^{21}_{D}$ = -186.0 (*c* = 0.48 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.85 min, t_R (major) = 7.43 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.24 (m, 2H), 7.22 (m, 1H), 7.13 (m, 2H), 7.07 – 7.01 (m, 2H), 6.90 (m, 2H), 5.59 – 5.51 (m, 1H), 4.19 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.14 – 4.07 (m, 1H), 3.71 (s, 3H), 3.38 – 3.30 (m, 1H), 2.44 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.24 – 2.13 (m, 1H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.0, 161.5 (d, *J* = 245.2), 161.2, 140.2 (d, *J* = 3.1), 140.0, 134.7, 129.5, 129.0 (d, *J* = 7.9), 128.5, 127.4, 122.2, 115.4 (d, *J* = 21.2), 53.0, 52.7, 43.8, 39.0, 36.3, 23.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -116.73. HRMS (ESI-TOF) calcd for $C_{22}H_{21}FO_3Na^+$ ([M+Na^+]) = 375.1367, Found 375.1367.

Methyl 2-((1'*R*,2'*S*,3'*R*)-3''-chloro-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3la)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 34.2 mg, 93% yield, 99% *ee*; $[\alpha]^{21}_{D}$ = -194.8 (*c* = 0.50 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 7.00 min, t_R (major) = 7.23 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.21 (m, 3H), 7.18 – 7.16 (m, 1H), 7.15 – 7.08 (m, 2H), 7.08 – 7.01 (m, 3H), 5.59 – 5.51 (m, 1H), 4.21 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.73 (s, 3H), 3.62 – 3.29 (m, 1H), 2.45 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.19 (dd, *J* = 18.0, 10.4 Hz, 1H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 193.8, 161.2, 146.8, 139.8, 134.5, 134.4, 129.9, 129.4, 128.5, 127.8, 127.5, 126.8, 125.7, 122.2, 53.0, 52.4, 43.7, 38.8, 36.8, 23.3. HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClO_3Na^+$ ([M+Na^+]) = 391.1071, Found 391.1074. HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{37}ClO_3Na^+$ ([M+Na^+]) = 393.1042, Found 393.1065.

Methyl 2-((1'*R*,2'*S*,3'*R*)-2",6"-dichloro-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-yl)-2-oxoacetate **(3ma)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 37.5 mg, 93% yield, 99% *ee*; $[\alpha]^{21}_{D}$ = -111.4 (*c* = 0.68 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.79 min, t_R (major) = 7.00 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 –7.19 (m, 4H), 7.13 – 7.03 (m, 3H), 6.97 (t, J = 8.0 Hz, 1H), 5.64 – 5.52 (m, 1H), 5.09 (dd, J = 11.6, 5.2 Hz, 1H), 4.42 – 4.26 (m, 2H), 3.83 (s, 3H), 2.72 – 2.56 (m, 1H), 2.24 (dd, J = 17.6, 5.6 Hz, 1H), 1.85 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 193.0, 160.9, 139.4, 137.9, 137.4, 134.9, 133.5, 129.9, 129.5, 128.7, 128.4, 127.9, 127.5, 122.6, 53.0, 51.1, 44.7, 34.1, 33.6, 23.3. HRMS (ESI-TOF) calcd for $C_{22}H_{20}{}^{35}Cl_2O_3Na^+$ ([M+Na$^+$]) = 425.0682, Found 425.0690. HRMS (ESI-TOF) calcd for $C_{22}H_{20}{}^{35}Cl^{37}ClO_3Na^+$ ([M+Na$^+$]) = 427.0652, Found 427.0669.

Methyl 2-((1'*R*,2'*S*,3'*R*)-4"-bromo-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-yl)-2-oxoacetate **(3na)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford white solid; m.p. 38-42 ºC; 39.2 mg, 95% yield, 99% *ee*; $[\alpha]^{21}_{D}$ = -181.5 (*c* = 0.69 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm) t_R (minor) = 7.17 min, t_R (major) = 7.90 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.31 (m, 2H), 7.24 (m, 3H), 7.11 – 7.00 (m, 4H), 5.63 – 5.47 (m, 1H), 4.19 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.16 – 4.06 (m, 1H), 3.71 (s, 1H), 3.35 – 3.27 (m, 1H), 2.43 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 193.9, 161.2, 143.7, 139.9, 134.5, 131.7, 129.4, 128.5, 127.5, 122.2, 120.2, 53.0, 52.5, 43.7, 38.8, 36.5, 23.3. HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{79}BrO_3Na^+$ ([M+Na$^+$]) = 435.0566, Found 435.0575. HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{81}BrO_3Na^+$ ([M+Na$^+$]) = 437.0546, Found 437.0562.

Methyl 2-((1*R*,2*S*,3*R*)-5-methyl-3-(naphthalen-2-yl)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)-2-oxoacetate **(3oa)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford white solid; m.p. 44-46 ºC; 30.0 mg, 78% yield, 99% *ee*; $[\alpha]^{21}_{D}$ = -176.7 (*c* = 0.58 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =10/90, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.84 min, t_R (major) = 8.02 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 – 7.69 (m, 3H), 7.62 (s, 1H), 7.44 – 7.37 (m, 2H), 7.33 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.30 – 7.20 (m, 3H), 7.13 – 7.05 (m, 2H), 5.64 – 5.52 (m, 1H), 4.36 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.20 – 4.08 (m, 1H), 3.65 (s, 3H), 3.53 (td, *J* = 10.4, 6.0 Hz, 1H), 2.53 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.32 (dd, *J* = 17.2, 9.6 Hz, 1H), 1.85 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.0, 161.2, 142.0, 140.1, 134.8, 133.6, 132.4, 129.5, 128.5, 128.3, 127.8, 127.7, 127.4, 126.2, 126.1, 126.0, 125.5, 122.2, 52.9, 52.6, 43.8, 38.9, 37.1, 23.4. HRMS (ESI-TOF) calcd for $C_{26}H_{24}O_3Na^+$ ([M+Na$^+$]) = 407.1618, Found 407.1624.

Methyl 2-((1*R*,2*S*,3*S*)-5-methyl-3-((*E*)-styryl)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)-2-

oxoacetate **(3pa)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 35.3 mg, 98% yield, 98% *ee*; $[\alpha]^{21}_{D}$ = -247.1 (*c* = 0.61 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 8.15 min, t_R (major) = 8.92 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.15 (m, 8H), 7.09 – 7.00 (m, 2H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.01 (dd, *J* = 16.0, 8.0 Hz, 1H), 5.57 – 5.44 (m, 1H), 4.10 – 4.00 (m, 1H), 3.83 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.71 (s, 3H), 3.09 – 2.95 (m, 1H), 2.38 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.09 (dd, *J* = 17.2, 9.6 Hz, 1H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.3, 161.4, 140.3, 137.3, 134.0, 131.9, 131.3, 129.4, 128.6, 128.4, 127.3, 126.2, 122.0, 52.9, 52.3, 43.2, 35.5, 34.1, 23.6. HRMS (ESI-TOF) calcd for $C_{24}H_{24}O_3Na^+$ ([M+Na^+]) = 383.1618, Found 383.1627.

Methyl 2-((1*R*,2*S*,3*S*)-5-methyl-3-(thiophen-3-yl)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)-2-oxoacetate **(3qa)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 32.0 mg, 94% yield, 97% *ee*; $[\alpha]^{21}_{D}$ = -237.1 (*c* = 0.46 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 8.74 min, t_R (major) = 9.32 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.23 (m, 2H), 7.23 – 7.16 (m, 2H), 7.08 – 7.02 (m, 2H), 6.99 – 6.90 (m, 2H), 5.58 – 5.48 (m, 1H), 4.12 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.08 – 3.99 (m, 1H), 3.68 (s, 3H), 3.53 (td, *J* = 10.0, 6.0 Hz, 1H), 2.50 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.22 (dd, *J* = 18.0, 10.0 Hz, 1H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.2, 161.3, 145.2, 140.2, 134.5, 129.5, 128.4, 127.3, 127.0, 125.7, 122.0, 120.8, 53.0, 43.6, 38.1, 32.5, 23.4. HRMS (ESI-TOF) calcd for $C_{20}H_{20}SO_3Na^+$ ([M+Na^+]) = 363.1025, Found 363.1024.

Methyl 2-(3-cyclohexyl-5-methyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)-2-oxoacetate **(3ra)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 32.0 mg, 94% yield, 99% *ee*; $[\alpha]^{21}_{D}$ = -214.9 (*c* = 0.45 in CH_2Cl_2).; the ee was determined by UPC^2 Phenomenex analysis using a chiral OJH column (methanol/ CO_2 =10/90, 1.0 mL/min, λ = 254 nm), t_R (major) = 4.41 min, t_R (minor) = 5.42 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.16 (m, 3H), 7.11 – 6.91 (m, 2H), 5.58 – 5.40 (m, 1H), 3.95 – 3.85 (m, 2H), 3.80 (s, 3H), 2.16 – 2.05 (m, 2H), 1.94 (dd, *J* = 18.8, 11.2 Hz, 1H), 1.80 (s, 3H), 1.75 – 1.66 (m, 2H), 1.66 – 1.57 (m, 2H), 1.48 – 1.35 (m, 2H), 1.22 – 0.97 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 194.9, 161.9, 140.4, 134.9, 129.6, 128.2, 127.1, 121.7, 53.0, 49.7, 43.2, 37.5, 34.9, 31.4, 29.6, 27.0, 26.9, 26.8, 26.5, 23.8. HRMS (ESI-TOF) calcd for $C_{22}H_{28}O_3Na^+$ ([M+Na^+]) = 363.1931, Found 363.1931.

Methyl 2-((1'*R*,2'*S*,3'*R*)-2-chloro-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3ab)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 32.1 mg, 87% yield, 99% *ee*; $[\alpha]^{21}_{D}$ = -115.1 (*c* = 0.61 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 7.91 min, t_R (major) = 8.74 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.34 (m, 1H), 7.27 – 7.12 (m, 8H), 5.53 – 5.43 (m, 1H), 4.57 (dd, *J* = 10.8, 5.6 Hz, 1H), 4.46 – 4.36 (m, 1H), 3.69 (s, 3H), 3.29 (td, *J* = 10.2, 6.0 Hz,

1H), 2.49 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.32 – 2.21 (m, 1H), 1.85 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 193.2, 160.9, 143.9, 137.5, 135.5, 134.4, 131.7, 129.5, 128.7, 128.5, 127.6, 126.7, 121.6, 53.0, 50.0, 39.3, 38.5, 37.9, 23.4. HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClO_3Na^+$ ([M+Na^+]) = 391.1071, Found 391.1070. HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{37}ClO_3Na^+$ ([M+Na^+]) = 393.1042, Found 393.1050.

Methyl 2-((1'*R*,2'*S*,3'*R*)-3-fluoro-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-yl)-2-oxoacetate **(3ac)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 31.7 mg, 90% yield, 98% *ee*; $[\alpha]^{21}_D$ = -221.9 (*c* = 0.60 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.93 min, t_R (major) = 7.54 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25 – 7.12 (m, 6H), 6.93 – 6.86 (m, 1H), 6.85 – 6.75 (m, 2H), 5.58 – 5.45 (m, 1H), 4.22 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.14 – 4.06 (m, 1H), 3.70 (s, 3H), 3.32 (td, *J* = 10.8, 6.0 Hz, 1H), 2.46 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.28 – 2.17 (m, 1H), 1.83 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 193.9, 162.8 (d, *J* = 246.9), 161.3, 144.3, 142.9 (d, *J* = 6.7), 135.4, 129.8 (d, *J* = 8.4), 128.7, 127.5, 126.6, 125.2 (d, *J* = 2.8), 121.5, 116.5 (d, *J* = 21.6), 114.3 (d, *J* = 21.2), 53.0, 52.4, 43.4, 38.8, 36.9, 23.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -112.86. HRMS (ESI-TOF) calcd for $C_{22}H_{21}FO_3Na^+$ ([M+Na^+]) = 375.1367, Found 375.1366.

Methyl 2-((1'*R*,2'*S*,3'*R*)-4-fluoro-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-yl)-2-oxoacetate **(3ad)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford white solid; m.p. 86-90 °C; 34.5 mg, 98% yield, 91% *ee*; $[\alpha]^{21}_D$ = -182.6 (*c* = 0.62 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.99 min, t_R (major) = 7.46 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25 – 7.20 (m, 2H), 7.16 (m, 3H), 7.03 (m, 2H), 6.94 (m, 2H), 5.58 – 5.46 (m, 1H), 4.21 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.70 (m, 3H), 3.34 – 3.26 (m, 1H), 2.45 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.27 – 2.15 (m, 1H), 1.83 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.2, 162.1 (d, *J* = 246.7), 161.3, 144.3, 135.8 (d, *J* = 3.2), 135.0, 131.0 (d, *J* = 8.1), 128.7, 127.5, 126.6, 122.0, 115.2 (d, *J* = 21.4), 52.9, 52.5, 43.0, 38.9, 37.0, 23.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -115.53. HRMS (ESI-TOF) calcd for $C_{22}H_{21}FO_3Na^+$ ([M+Na^+]) = 375.1367, Found 375.1363.

Methyl 2-((1'*R*,2'*S*,3'*R*)-3-methoxy-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-yl)-2-oxoacetate **(3ae)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 33.1 mg, 91% yield, 99% *ee*; $[\alpha]^{21}_D$ = -230.0 (*c* = 0.56 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 9.65 min, t_R (major) = 12.16 min. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25 – 7.10 (m, 6H), 6.77 – 6.70 (m, 1H), 6.67 – 6.58 (m, 2H), 5.59 – 5.48 (m, 1H), 4.22 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.12 – 4.05 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.36 (td, *J* = 10.8, 6.0 Hz, 1H), 2.45 (dd, *J* = 18.4, 6.0 Hz, 1H), 2.20 (dd, *J* = 18.0, 10.4 Hz, 1H), 1.82 (s, 3H). $^{13}C\{^1H\}$

NMR (101 MHz, $CDCl_3$) δ = 193.9, 161.3, 159.5, 144.6, 141.8, 134.8, 129.4, 128.6, 127.5, 126.5, 122.0, 121.9, 115.8, 112.1, 55.2, 52.8, 52.4, 43.7, 38.9, 37.0, 23.4. HRMS (ESI-TOF) calcd for $C_{23}H_{24}O_4Na^+$ ([M+Na^+]) = 387.1567, Found 387.1568.

Methyl 2-((1'*R*,2'*S*,3'*R*)-4-methoxy-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3af)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford colorless oil; 34.2 mg, 94% yield, 97% *ee*; $[\alpha]^{21}_D$ = -235.9 (*c* = 0.57 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.63 min, t_R (major) = 7.25 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 – 7.10 (m, 5H), 7.01 – 6.93 (m, 2H), 6.84 – 6.73 (m, 2H), 5.62 – 5.44 (m, 1H), 4.22 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.33 (td, *J* = 10.8, 6.0 Hz, 1H), 2.44 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.20 (dd, *J* = 18.0, 10.4 Hz, 1H), 1.82 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.2, 161.3, 158.8, 144.7, 134.4, 132.0, 130.5, 128.6, 127.5, 126.5, 122.5, 113.8, 55.3, 52.9, 52.6, 43.0, 39.1, 36.9, 23.3. HRMS (ESI-TOF) calcd for $C_{23}H_{24}O_4Na^+$ ([M+Na^+]) = 387.1567, Found 387.1566.

Methyl 2-((1'*R*,2'*S*,3'*R*)-5'-ethyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3ag)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford olorless oil; 34.5 mg, 99% yield, 94% *ee*; $[\alpha]^{21}_D$ = -174.0 (*c* = 0.39 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =5/95, 1.0 mL/min, λ = 254 nm), t_R (minor) = 11.27 min, t_R (major) = 8.10 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 – 7.11 (m, 8H), 7.09 – 7.02 (m, 2H), 5.63 – 5.48 (m, 1H), 4.25 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.69 (s, 3H), 3.38 – 3.29 (m, 1H), 2.48 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.23 (dd, *J* = 18.0, 10.4 Hz, 1H), 2.17 – 2.08 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.2, 161.3, 158.8, 144.7, 134.4, 132.0, 130.5, 128.6, 127.5, 126.5, 122.5, 113.8, 55.3, 52.9, 52.6, 43.0, 39.1, 36.9, 23.3. HRMS (ESI-TOF) calcd for $C_{23}H_{24}O_3Na^+$ ([M+Na^+]) = 371.1618, Found 371.1621.

Methyl 2-((1'*R*,2'*S*,3'*R*)-4-methoxy-3'',5'-dimethyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3aj)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford olorless oil; 35.4 mg, 94% yield, 94% *ee*; $[\alpha]^{25}_D$ = -209.3 (*c* = 0.52 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =20/80, 1.0 mL/min, λ = 254 nm), t_R (minor) = 5.95 min, t_R (major) = 6.59 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.08 – 6.94 (m, 6H), 6.81– 6.78 (m, 2H), 5.54 – 5.50 (m, 1H), 4.18 (dd, *J* = 11.2, 5.6 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.34 – 3.25 (m, 1H), 2.46 – 2.35 (m, 1H), 2.25 (s, 3H), 2.12 –2.13 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.2, 161.3, 158.8, 141.6, 135.9, 134.5, 132.1, 130.5, 129.3, 127.4, 122.5, 113.8, 55.3, 52.8, 43.0, 39.2, 36.5, 23.3, 21.1. HRMS (ESI-TOF) calcd for $C_{24}H_{26}O_4Na^+$ ([M+Na^+]) = 401.1723, Found 401.1715.

Methyl 2-((1'*R*,2'*S*,3'*R*)-4''-bromo-4-methoxy-5'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-yl)-2-oxoacetate **(3ak)**

Purified by flash chromatography (petroleum ether: EtOAc = 9:1) to afford olorless oil; 42.7 mg, 97% yield, 94% *ee*; $[\alpha]^{21}_{D}$ = -189.2 (*c* = 0.65 in CH_2Cl_2); the ee was determined by HPLC analysis using a chiral IE column (2-propanol/ *n*-hexane =20/80, 1.0 mL/min, λ = 254 nm), t_R (minor) = 6.15 min, t_R (major) = 6.86 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.30 (m, 2H), 7.09 – 7.03 (m, 2H), 7.00 – 6.92 (m, 2H), 6.83 – 6.74 (m, 2H), 5.57 – 5.48 (m, 1H), 4.18 (dd, *J* = 11.2, 5.6 Hz, 1H), 4.13 – 4.06 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.34 – 3.23 (m, 1H), 2.47 – 2.37 (m, 1H), 2.20 – 2.11 (m, 1H), 1.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 193.9, 161.2, 158.9, 143.7, 134.2, 131.8, 131.7, 130.4, 129.4, 122.6, 120.2, 113.8, 55.3, 53.0, 52.6, 42.9, 38.9, 36.5, 23.3. HRMS (ESI-TOF) calcd for $C_{23}H_{23}{}^{79}BrO_4Na^+$ ([M+Na$^+$]) = 465.0672, Found 465.0678. $C_{23}H_{23}{}^{81}BrO_4Na^+$ ([M+Na$^+$]) = 467.0651, Found 467.0659.

Supporting Information

ESI-MS analysis, operando IR experiments, X-ray crystallography data for compound **3ad** and compound [L-PiPr$_3$ + Zn^{2+} + H_2O + Pyridine]$^{2+}$, full optimization details, ^{1}H and ^{13}C NMR spectra, HPLC and CD spectra are available. This material is available free of charge via the Internet at http://pubs.acs.org

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(10) See the ESI of ^{1}H NMR spectra of DA and HDA product and HPLC.

(11) CCDC 1581047 (**3ad**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

(12) CCDC 1839343 ([**L-PiPr$_3$** + Zn^{2+} + H_2O + Pyridine]$^{2+}$) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.