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Malonate-type bis(oxazoline) ligands with sp^2 hybridized bridge carbon: synthesis and application in Friedel–Crafts alkylation and allylic alkylation

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ABSTRACT

A series of simple and new C_2-symmetric diphenylmethylidene malonate-type bis(oxazoline) ligands were synthesized and applied to the Friedel–Crafts reaction and allylic alkylation. The Cu(II) complex of ligand **4b** bearing the benzyl group afforded good to excellent enantioselectivity for the *F–C* adducts (up to >99% ee) between indole and alkylidene malonate, and the palladium complex of ligand **4c** bearing the phenyl group afforded excellent enantioselectivity (up to 94% ee) for the allylic alkylation product.

1. Introduction

In the past two decades, chiral bis(oxazoline) (BOX) ligands have received a great deal of attention and become one of the most successful and versatile classes of ligands in catalytic asymmetric synthesis. As a result, bis(oxazoline) ligands with diverse skeleton and backbone have been reported.[1] Among them, malonate-type BOX, which is derived from malonate and its analogues, is one of the most typical class.[2] In this class of ligands, the bridge angle, correlating with the bite angle of BOX–metal complex, is considered as an important structural factor influencing the enantioselectivity.[3]

A straightforward strategy to tune the bridge angle has been intentionally or accidentally introduced in alkylidene- and arylidene-linked BOX ligands such as **1**, **2**, and **3** (Fig. 1). The oxazoline rings attached to an sp^2 hybridized bridge carbon can provide a larger bridge angle than those with sp^3 hybridized bridge carbon. In 2005, Burke et al. first reported a family of alkylidene-linked BOX ligands **1** and arylidene-linked BOX **2**,[4] which gave moderate to high ee (up to 89%) in the Cu(I)-catalyzed asymmetric cyclopropanation reaction. Recently, our group showed that ligand **3** with furan and thiophene unit in the backbone provides excellent asymmetric catalytic property in the Cu(II) catalyzed Friedel–Crafts alkylation of indole derivatives with arylidene malonates (99% yield and up to >99% ee).[5] In this type of BOX ligand both the substituents on the oxazoline rings and the heterocycles attached to the other end of the double bond play important roles in asymmetric catalysis owing to their different steric and electronic effects. In our effort to develop highly enantioselective reactions using simple and cheap chiral catalytic systems, the novel C_2-symmetric diphenylmethylidene malonate derived bis(oxazoline) ligands **4** were demonstrated to be efficient in the Cu(II)-catalyzed asymmetric Friedel–Crafts alkylation and the Pd-catalyzed asymmetric allylic alkylation. Herein, we would like to report our preliminary results.

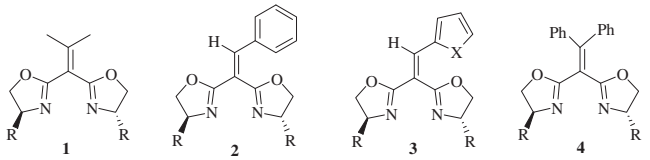

Fig. 1. The alkylidene and arylidene malonate-type bis(oxazoline) ligands.

2. Results and discussion

2.1. Synthesis of new bis(oxazoline) ligands

The novel chiral bis(oxazoline) ligands **4** were conveniently synthesized in four steps, as illustrated in Scheme 1, based on our previous reported procedure.[5] After the saponification of the diester **5**, the dicarboxylic acid was treated with oxalyl chloride in

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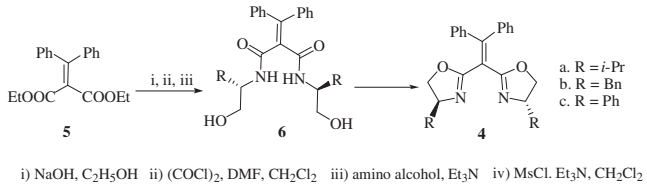
CH_2Cl_2 to yield the diacyl chloride. The catalytic amount of DMF was critical for the smooth conversion. The desired ligands **4** can be obtained through amide bond condensation and methanesulfonyl chloride mediated oxazoline ring formation in good yields (74–81%). The structure of the ligands **4** and bis(β-hydroxylamide) intermediates **6** were finely characterized and confirmed.

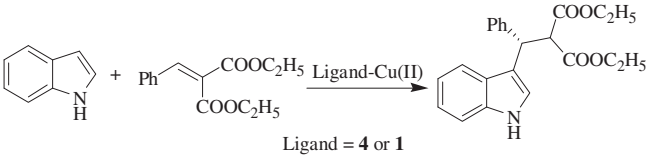


i) NaOH, C_2H_5OH ii) $(COCl)_2$, DMF, CH_2Cl_2 iii) amino alcohol, Et_3N iv) MsCl. Et_3N, CH_2Cl_2

Scheme 1. Synthesis of new bis(oxazoline) ligands. (i) NaOH, C_2H_5OH; (ii) $(COCl)_2$, DMF, CH_2Cl_2; (iii) amino alcohol, Et_3N; (iv) $MsCl{\cdot}Et_3N$, CH_2Cl_2.

2.2. Cu(II)-catalyzed asymmetric Friedel–Crafts alkylation

The Friedel–Crafts reaction is one of the most powerful carbon–carbon bond formation methodology in synthetic organic chemistry.[6] The asymmetric Friedel–Crafts alkylation of indole derivatives and alkylidene malonates has been investigated by Jørgenson et al.,[7] Tang et al.,[8] Reiser et al.,[9] and Feng et al.[10] Based on their pioneering contributions, we recently reported the application of simple heteroarylidene malonate derived bis(oxazoline)(**3**)–Cu(II) complexes in asymmetric Friedel–Crafts alkylation of indole derivatives with alkylidene malonates. Excellent yields and enantioselectivities can be obtained even at room temperature. Considering the structural similarity between ligands **3** and **4**, we first examined the catalytic property of **4** in this model system (Scheme 2).



Scheme 2.

The results of the catalytic Friedel–Crafts reaction using indole and diethyl benzylidene malonate as model substrates are summarized in Table 1. Under the catalysis of 10 mol % ligand–$Cu(OTf)_2$ complexes, quantitative yields can be achieved in *iso*-butanol for ligands **4a**–**c** (entries 1–3), while the highest enantioselectivity (>99% ee) was afforded by **4b** with benzyl substituent on the oxazoline ring (entry 2). This is slightly different from our previous finding, in which both of the ligand **3** with *iso*-propyl or benzyl substituents gave the same highest catalytic enantioselectivity.[5] For comparison, the dimethylmethylidene bis(oxazoline) ligand **1b** was also synthesized and tested in this reaction.[4a] To our surprise, no reaction occurred after being stirred for 6 days under the same condition (entry 4). This result suggested that not only the substituents on the oxazoline rings but also the moiety attached to the other end of the double bond have remarkable impact on the reactivity. When *iso*-propanol and ethanol were used as solvents, similar results (99% yield and >99% ee) can be achieved for the optimized ligand **4b** (entries 5 and 6).

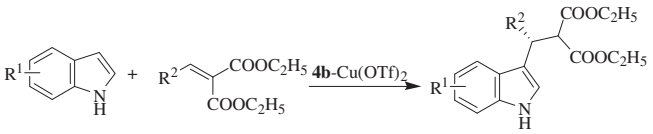
With these encouraging results, we selected ethanol as the solvent in subsequent experiments due to its low cost, non-toxicity, and equal efficiency to *iso*-butanol. The scope of the **4b**–$Cu(OTf)_2$ catalyst in Friedel–Crafts alkylation was further investigated using a variety of structurally different indole derivatives and arylidene malonates (Scheme 3, Table 2). The benzylidene malonates bearing

Table 1
Effect of ligands in the $Cu(OTf)_2$ catalyzed Friedel–Crafts alkylation[a]

Entry	Ligands	Solvent	Yield[b] (%)	ee[c] (%)
1	**4a**	*iso*-Butanol	99	83
2	**4b**	*iso*-Butanol	99	>99
3	**4c**	*iso*-Butanol	99	98
4	**1b**	*iso*-Butanol	—	—
5	**4b**	*iso*-Propanol	99	>99
6	**4b**	Ethanol	99	>99

[a] All the reactions were conducted under nitrogen for 24 h using 10 mol % of catalyst at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC.

both electron-donating and electron-withdrawing substituents at the *para*-position reacted smoothly with indole to yield the alkylation products in excellent yields with high enantioselectivities (entries 1–3). However, for *ortho*-substituted benzylidene malonates, the reaction time has to be prolonged to 72 h to overcome their low reactivity (entries 4–6). The high enantioselectivity can be retained in the case of *fluoro*-substituted benzylidene malonates owing to the smaller size of F than Cl and methyl group (>99% ee, entry 5). The reaction of the less hindered *meta*-substituted substrates can be finished within 48 h, but significant decrease of the enantioselectivities was observed (entries 7 and 8). The effect of substituents on the indole ring was also investigated. The catalytic efficiency varied significantly for differently substituted indoles. Generally, introduction of electron-withdrawing group deactivates indole and leads to lower enantioselectivity (entries 12–14). For indoles with electron-donating group, high reactivity and excellent enantioselectivity can be achieved in 99% yield and more than 98% ee regardless of the position of the substituents (entries 9–11). Interestingly, when 5-MeO indole reacted with *ortho*-Me benzylidene malonate, the alkylation adduct was also obtained in excellent yield and enantioselectivity (99% yield and 91% ee, entry 15).



Scheme 3.

Table 2
Complex **4b**–$Cu(OTf)_2$ catalyzed *F–C* reaction of indole derivatives with alkylidene malonates[a]

Entry	R^1	R^2	Time (h)	Yield[b] (%)	ee[c] (%)
1	H	*p*-MeC_6H_4	24	99	96
2	H	*p*-FC_6H_4	24	99	98
3	H	*p*-BrC_6H_4	48	90	98
4	H	*o*-ClC_6H_4	72	75	87
5	H	*o*-FC_6H_4	72	80	99
6	H	*o*-MeC_6H_4	72	90	79
7	H	*m*-FC_6H_4	48	99	78
8	H	*m*-MeC_6H_4	48	90	79
9	5-MeO	C_6H_5	24	99	>99
10	5-Me	C_6H_5	24	99	>99.9
11	7-Me	C_6H_5	24	99	98
12	5-Cl	C_6H_5	48	90	75
13	6-Cl	C_6H_5	48	90	70
14	6-COOMe	C_6H_5	48	90	82
15	5-MeO	*o*-MeC_6H_4	24	99	91

[a] All reactions were conducted in ethanol under nitrogen using 10 mol % catalyst at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC.

2.3. Palladium-catalyzed asymmetric allylic alkylation

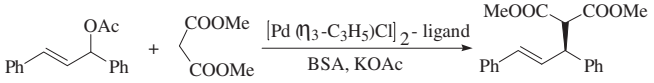
As an important enantioselective C–C bond formation process, the palladium-catalyzed asymmetric allylic alkylation reaction has attracted a great deal of attention from synthetic chemists over the past three decades.[11] A plethora of efficient chiral ligands with P, N, and S as coordinating atoms have been synthesized and applied to this transformation.[12] In general, *N*,*N*-chelating ligands for catalytic allylic alkylation are less common than other types of ligands. Only limited number of BOX ligands have been reported to give high reactivity and enantioselectivity in this reaction.[13]

The novel chiral bis(oxazoline) ligands **4a**–**c** were also applied to the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propen-1-yl acetate with dimethyl malonate, which is commonly used as model substrate in literature for evaluation of chiral catalysts.[14] The reaction was catalyzed by 5 mol % complexes generated in situ from 2.5 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 6 mol % of the chiral ligands, in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 20 mol % of KOAc in dichloromethane. As summarized in Table 3, the reaction proceeded smoothly and the product was obtained in high yields after 48 h (entries 1–3). Highly asymmetric induction was observed for all tested ligands, and the best 90% ee was provided by ligand **4c** with phenyl substituent on the oxazoline ring. The enantioselectivity can be further improved to 94% at 0 °C, though the reaction became slightly sluggish (entry 4). In contrast to our ligands, **1c** and **2c** with similar skeleton gave lower yields and enantioselectivities (entries 5 and 6). Reactions in other solvents than CH_2Cl_2 were also examined, inferior yields and enantioselectivities were obtained (entries 7–10) (Scheme 4).

Table 3
Effect of ligands and solvent in the Pd-catalyzed allylic alkylation[a]

Entry	Ligands	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**4a**	CH_2Cl_2	25	48	90	86
2	**4b**	CH_2Cl_2	25	48	90	78
3	**4c**	CH_2Cl_2	25	48	90	90
4	**4c**	CH_2Cl_2	0	72	85	94
5	**1c**	CH_2Cl_2	25	72	20	75
6	**2c**	CH_2Cl_2	25	48	60	45
7	**4c**	DCE	25	48	90	85
8	**4c**	THF	25	48	60	77
9	**4c**	Toluene	25	48	70	71
10	**4c**	CH_3CN	25	48	65	34

[a] All the reactions were conducted under nitrogen using 2.5 mol % of catalyst.
[b] Isolated yield.
[c] Determined by chiral HPLC.



Scheme 4.

The X-ray structure of the $Cu(OTf)_2$–ligand **4b** or $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$–ligand **4c** complex would be helpful to elucidate the observed asymmetric induction. However, we have not yet obtained such structure after extensive attempts. Two single crystals of the ligands **4b** and **4c** were cultivated from their solution in hexane/ethyl acetate and analyzed by X-ray diffraction.[15] As can be seen from the crystallography diagram of ligand **4b** or **4c** shown in Fig. 2, the four rings (two oxazoline rings and two phenyl rings) attaching to the double bond are clearly not co-planar, but distorted around the double bond due to steric repulsion. The sp^2 hybridized bridging carbon results in 114.13° and 115.46° bridge angles for **4b** and **4c**, respectively, then the geometry of ligand **4**–metal complex should be different from that of the bis(oxazoline) ligand with sp^3 hybridized bridge carbon.[3,16] Besides, the experimental results indicate that the substituents attached to the double bond evidently affected the reactivity and enantioselectivity in asymmetric catalysis. An accurate diagram of the precise coordination sphere around Cu or Pd for this type of ligands is still being pursued.

3. Conclusions

In conclusion, a series of novel chiral bis(oxazoline) ligands **4a**–**c** were conveniently synthesized from diphenyl methylene malonate and chiral amino alcohols. Their application in the asymmetric Friedel–Crafts alkylation of indole derivatives with arylidene malonates was investigated. The $Cu(OTf)_2$ complex of ligands **4b** with the benzyl group afforded excellent enantioselectivity (up to >99% ee). In the palladium-catalyzed allylic alkylation, the palladium complex of ligand **4c** bearing phenyl group afforded the highest 94% ee, which is comparable to the results obtained by other reported BOX ligands.[13] Our results indicate that both the reactivity and the enantioselectivity of asymmetric induction were not only dependent on the substituents on the oxazoline ring, but also the moieties attached to the distal terminus of the double bond in the ligand skeleton. The preliminary evaluation for this type of BOX ligands shows promising application in asymmetric catalysis, and provides a new clue for the development of new chiral ligands. Further study to extend this catalytic system to other asymmetric reactions is now in progress in our group.

4. Experimental section

4.1. General

NMR spectra were recorded with a Bruker Avance DPX300 spectrometer with tetramethylsilane as the internal standard. Infrared spectra were obtained on a Nicolet AVATAR 330 FT-IR spectrometer. Mass spectra were obtained on Bruker APEX II FT-ICRMS mass spectrometer. Optical rotations were measured on a Perkin–Elmer 341 LC polarimeter. The enantiomeric excesses of (*R*)- and (*S*)-enantiomer were determined by HPLC analysis over a chiral column (Daicel Chiralcel OD-H and AD-H; eluted with hexane/*iso*-propyl alcohol; UV detector, 254 nm). The absolute configuration of the major enantiomer was assigned by comparison with literature. Solvents were purified and dried by standard procedures.

4.2. General procedure I: synthesis and characterization of (*S*,*S*)-*N*,*N*-bis(2-hydroxy-1-*iso*-propyl)-2-diphenylmethylidene malonamide 6a

To a solution of diethyl diphenylmethylidene malonate **5** (1.0 g, 3.09 mmol) in CH_3OH (10 mL) was added NaOH solution (10 mL, 2.0 M). The mixture was refluxed for 8 h, then the methanol was removed in vacuo. The residue was cooled to 0 °C and acidified with aqueous HCl (6 M), extracted with ethyl acetate (10 mL×3), dried over Na_2SO_4, and evaporated to give the white solid, which directly reacted with oxalyl chloride (0.98 g, 0.77 mmol) and DMF (0.1 mL) in CH_2Cl_2 (20 mL) at 0 °C for 3 h, after removing the excess oxalyl chloride in vacuo the diacyl dichloride was afforded. Subsequently the diacyl dichloride in CH_2Cl_2 (20 mL) was added dropwise to a solution of L-valinol (0.64 g, 6.20 mmol) and Et_3N (4 mL, 28.9 mmol) in CH_2Cl_2 (20 mL) at 0 °C and stirred at room temperature for 4 h. The reaction mixture was washed with water (5 mL×2), dried over Na_2SO_4, and concentrated to give the crude solid. Purification by silica gel column chromatography (70% ethyl acetate in petroleum ether) afforded the dihydroxy diamide **6a** (1.16 g, 86.0%) as a white solid. Mp 177–178 °C. $[\alpha]_D^{25}$ −15.7 (*c* 0.30, CH_2Cl_2). IR: 3258, 3060, 2961, 1633, 1540, 1449, 1317, 1056, 725. ^1H NMR (300 MHz, DMSO-d_6): δ 7.45 (d, *J*=9.20 Hz, 2H, NH), 7.32–7.21

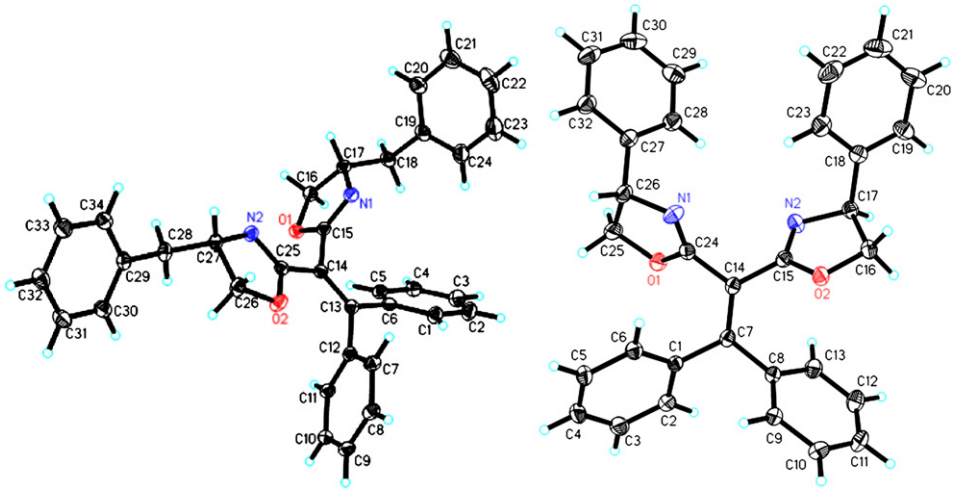


Fig. 2. The X-ray structure of **4b** and **4c**.

(m, 10H, ArH), 4.49 (t, J=5.40 Hz, 2H, OH), 3.50–3.45 (m, 2H, C*H*NH), 3.29–3.18 (m, 4H, CH_2O), 1.73–1.66 (m, 2H, C*H*Me_2), 0.59 (t, J=6.89 Hz, 12H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.86, 140.51, 135.58, 129.07, 128.00, 127.82, 61.06, 55.62, 27.76, 19.56, 17.53. HRMS (ESI): m/z calcd for $C_{26}H_{35}N_2O_4$ ($M+H^+$): 439.25913; found: 439.25837.

4.2.1. (S,S)-N,N-Bis(2-hydroxy-1-benzyl)-2-diphenylmethylidene malonamide ***6b****.* Using the same procedure as described in general procedure I: diethyl diphenylmethylidene malonate **5** (1.0 g, 3.09 mmol), oxalyl chloride (0.98 g, 0.77 mmol), L-phenylalaninol (0.94 g, 6.20 mmol), and Et_3N (4 mL, 28.9 mmol) to afford the dihydroxy diamide **6b** (1.26 g, 76.4%) as a white solid. Mp 187–189 °C. $[\alpha]_D^{25}$ +10.2 (c 0.10, CH_2Cl_2). IR: 3422, 1627, 1537, 1449, 1035, 775, 726, 701. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68 (d, J=8.25 Hz, 2H, NH), 7.27–7.05 (m, 20H, ArH), 4.66 (t, J=5.38 Hz, 2H, OH), 3.83–3.76 (m, 2H, C*H*N), 3.20–3.03 (m, 4H, CH_2O), 2.61–2.42 (m, 4H, CH_2Ph). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.40, 142.98, 140.25, 140.30, 138.86, 134.99, 129.17, 129.08, 128.20, 127.89, 125.95, 79.50, 79.06, 78.62, 61.34, 52.45, 35.91. HRMS (ESI): m/z calcd for $C_{34}H_{35}N_2O_4$ ($M+H^+$): 535.25913; found: 535.25853.

4.2.2. (S,S)-N,N-bis(2-hydroxy-1-phenyl)-2-diphenylmethylidene malonamide ***6c****.* Using the same procedure as described in general procedure I: diethyl diphenylmethylidene malonate **5** (1.0 g, 3.09 mmol), oxalyl chloride (0.98 g, 0.77 mmol), L-phenyl glycinol (0.85 g, 6.20 mmol), and Et_3N (4.0 mL, 28.9 mmol) to afford the dihydroxy diamide **6c** (1.22 g, 78.2%) as a white solid. Mp 211–211.5 °C. $[\alpha]_D^{25}$ +28.9 (c 0.15, CH_2Cl_2). IR: 3436, 1639, 1532, 1449, 1106, 1040, 700. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.23 (d, J=8.13 Hz, 2H), 7.31–7.15 (m, 16H, ArH), 6.97–6.94 (m, 4H, ArH), 4.78–4.69 (m, 4H, C*H*N and OH), 3.41 (t, J=5.70 Hz, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.49, 142.97, 140.59, 140.30, 134.86, 129.17, 128.30, 128.08, 128.03, 127.97, 127.02, 126.67, 64.41, 54.89. HRMS (ESI): m/z calcd for $C_{32}H_{31}N_2O_4$ ($M+H^+$): 507.22783; found: 507.22817.

4.3. General procedure II: bis[(*S*)-4-*iso*-propyloxazoline-2-yl]-2,2′-diphenyethene 4a

To an ice-cooled solution of the dihydroxy diamide **6a** (0.5 g, 1.14 mmol) and Et_3N (4 mL, 28 mmol) in CH_2Cl_2 (20 mL) was added MsCl (0.34 g, 3.0 mmol) slowly. The mixture was allowed to warm to room temperature and was stirred for 12 h. The mixture was washed with water (2×5 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness in vacuo, the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:1, v/v) to afford a white solid **4a** (0.41 g, 73.2%). Mp 111.5–113.0 °C. $[\alpha]_D^{25}$ +26.4 (c 0.25, CH_2Cl_2). IR: 2955, 2875, 1652, 1609, 1448, 1370, 1016, 946, 785, 732. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.21 (m, 10H, ArH), 4.08–4.00 (m, 2H, CHN=), 3.92–3.84 (m, 4H, CH_2O), 1.65–1.59 (m, 2H, C*H*Me_2), 0.80 (d, J=6.75 Hz, 6H), 0.76 (d, J=6.75 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.16, 155.04, 140.92, 129.41, 128.53, 127.75, 117.44, 72.48, 69.82, 32.30, 18.80, 18.16. HRMS (ESI): m/z calcd for $C_{26}H_{35}N_2O_4$ ($M+H^+$): 439.25913; found: 439.25837.

4.3.1. Bis[(S)-4-benzyloxazoline-2-yl]-2,2′-diphenyethene ***4b****.* Using the same procedure as described in general procedure II: from dihydroxy diamide **6b** (0.50 g, 0.94 mmol), MsCl (0.25 g, 2.20 mmol), and Et_3N (4 mL, 28 mmol) to afford **4b** (0.38 g, 81.2%) as a white solid. Mp 120.0–121.0 °C. $[\alpha]_D^{25}$ +19.0 (c 0.20, CH_2Cl_2). IR: 3035, 1648, 1614, 1496, 1474, 1449, 1309, 1228, 1147, 1018, 976, 960, 932, 783, 728, 700. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.19 (m, 16H, ArH), 7.08–7.05 (m, 4H, ArH), 4.44–4.34 (m, 2H, CHN=), 4.06 (t, J=8.65 Hz, 2H, CH_2O), 3.85 (dd, J=6.96, 8.42 Hz, 2H, CH_2O), 2.92 (dd, J=5.63, 13.66 Hz, 2H, CH_2Ph), 2.50 (dd, J=8.62, 13.65 Hz, 2H, CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.78, 155.79, 140.84, 137.93, 129.48, 129.17, 128.78, 128.37, 127.79, 126.30, 116.94, 71.60, 67.79, 40.82. HRMS (ESI): m/z calcd for $C_{34}H_{35}N_2O_4$ ($M+H^+$): 535.25913; found: 535.25853.

4.3.2. Bis[(S)-4-phenyloxazoline-2-yl]-2,2′-diphenyethene ***4c****.* Using the same procedure as described in general procedure II: from dihydroxy diamide **6c** (0.50 g, 0.99 mmol), MsCl (0.26 g, 2.28 mmol), and Et_3N (4 mL, 28 mmol) to afford **4c** (0.44 g, 76.2%) as a white solid. Mp 173.0–174.5 °C. $[\alpha]_D^{25}$ +37.7 (c 0.30, CH_2Cl_2). IR: 3015, 2346, 1653, 1448, 1357, 1269, 1204, 1145, 1017, 957, 938, 786, 735, 701. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.31 (m, 10H, ArH), 7.24–7.20 (m, 6H, ArH), 7.08–7.05 (m, 4H, ArH), 5.24 (dd, J=8.10, 9.90 Hz, 2H, CHN=), 4.47 (dd, J=8.36, 10.20 Hz, 2H, CH_2O), 3.96 (t, J=8.25 Hz, 2H, CH_2O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.82, 156.13, 142.02, 140.83, 129.47, 128.82, 128.44, 128.04, 127.25, 126.73, 116.84, 74.60, 69.84. HRMS (ESI): m/z calcd for $C_{32}H_{31}N_2O_4$ ($M+H^+$): 507.22783; found: 507.22817.

4.4. General procedure for asymmetric *F–C* alkylation of indoles with alkylidene malonates

To a Schlenk tube $Cu(OTf)_2$ (0.025 mmol) was added, followed by ligand **4b** (0.0275 mmol) in the solvent ethanol (1.0 mL) under

N_2, the solution was stirred for 1.5 h at room temperature, a mixture of diethyl arylidenemalonate (0.25 mmol) in the above solvent (1.0 mL) was added. After stirring for 30 min, indole (0.25 mmol) was added. After stirring for 24–72 h at room temperature, the solution was concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel [eluted with ethyl acetate/petroleum ether (1:5, v/v)] to afford the (*S*)-ethyl 2-ethoxycarbonyl 3-(3-indolyl)-3-arylpropanoate as a white solid. The enantiomeric excesses were determined by HPLC with a chiral column (Daicel Chiralcel OD-H; hexane/*iso*-propanol 90:10; flow rate 0.8 mL/min; 254 nm).

4.4.1. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-phenyl propanoate. White solid. Mp: 179–180 °C. $[\alpha]_D^{25}$ +42.2 (*c* 0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.54 (d, *J*=8.0 Hz, 1H), 7.09–7.37 (m, 8H), 7.02 (t, *J*=7.50 Hz, 1H), 5.07 (d, *J*=11.82 Hz, 1H), 4.28 (d, *J*=11.82 Hz, 1H), 3.94–4.03 (m, 4H), 0.95–1.02 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.02, 167.83, 141.41, 136.20, 128.30, 128.17, 126.8, 126.70, 122.21, 120.88, 119.49, 119.38, 116.99, 110.96, 61.43, 61.37, 58.39, 42.86, 13.75, 13.71; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{23}KNO_4$ ($M+K^+$): 404.12587; found: 404.12590. HPLC analysis (Chiralcel OD-H, *n*-hexane/2-PrOH, 90:10, 0.8 mL/min, 254 nm): t_R (minor)=13.71 min, t_R (major)=15.65 min; >99% ee.

4.4.2. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-methylphenyl) propanoate. White solid. Mp 147–149 °C. $[\alpha]_D^{25}$ +22.6 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, NH), 7.54 (d, *J*=7.80 Hz, 1H, ArH), 7.26–7.22 (m, 3H, ArH), 7.13–7.08 (m, 2H, ArH), 7.04–6.99 (m, 2H, ArH), 5.03 (d, *J*=11.85 Hz, 1H, CH), 4.27 (d, *J*=11.80 Hz, 1H, CH), 2.23 (s, 3H, CH_3), 1.03 (t, *J*=7.11 Hz, 3H, CH_3), 0.96 (t, *J*=7.11 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.10, 167.88, 138.42, 136.20, 136.12, 128.97, 127.96, 126.68, 122.11, 120.84, 119.40, 119.36, 117.12, 110.94, 61.36, 61.33, 58.43, 42.43, 20.92, 13.75, 13.67. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{25}KNO_4$ ($M+K^+$): 418.14152; found: 418.14176. HPLC analysis t_R (minor)=15.01 min, t_R (major)=13.78 min, 96% ee.

4.4.3. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-fluorophenyl) propanoate. White solid. Mp 130–132 °C. $[\alpha]_D^{25}$ +14.2 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, NH), 7.48 (d, *J*=7.80 Hz, 1H, ArH), 7.35–7.29 (m, 3H, ArH), 7.19–7.12 (m, 2H, ArH), 7.11–7.10 (m, 1H, ArH), 6.91 (d, *J*=8.70 Hz, 1H, ArH), 6.84 (dd, *J*=3.90, 5.10 Hz, 1H), 5.06 (d, *J*=12.0 Hz, 1H, CH), 4.23 (d, *J*=12.0 Hz, 1H, CH), 4.03 (q, *J*=4.80 Hz, 2H, CH_2), 3.97 (q, *J*=4.80 Hz, 2H, CH_2), 1.03 (t, *J*=7.20 Hz, 3H, CH_3), 0.99 (t, *J*=7.20 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.86, 167.74, 163.26, 160.01, 137.20, 137.16, 136.27, 129.82, 129.71, 126.55, 122.36, 120.79, 119.59, 119.27, 116.83, 115.24, 114.96, 111.04, 61.51, 61.47, 58.43, 42.12, 13.80, 13.72. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}FKNO_4$ ($M+K^+$): 422.11644; found: 422.11655. HPLC analysis t_R (minor)=13.78 min, t_R (major)=15.61 min, 98% ee.

4.4.4. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-bromophenyl) propanoate. White solid. Mp 141–142 °C. $[\alpha]_D^{25}$ +28.5 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H, NH), 7.48 (d, *J*=7.50 Hz, 1H, ArH), 7.36–7.23 (m, 5H, ArH), 7.18–7.12 (m, 2H, ArH), 7.06–7.01 (m, 1H, ArH), 5.04 (d, *J*=11.70 Hz, 1H, CH), 4.23 (d, *J*=11.70 Hz, 1H, CH), 4.03 (q, *J*=7.20 Hz, 2H, CH_2), 3.98 (q, *J*=6.90 Hz, 2H, CH_2), 1.07 (t, *J*=7.20 Hz, 3H, CH_3), 0.99 (t, *J*=7.20 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.75, 167.64, 140.55, 136.23, 131.41, 129.96, 126.47, 122.42, 120.89, 120.58, 119.65, 119.20, 116.43, 111.06, 61.55, 61.7, 58.07, 42.23, 13.80, 13.71; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}BrKNO_4$ ($M+K^+$): 422.11644; found: 422.11655. HPLC analysis t_R (minor)=14.73 min, t_R (major)=16.04 min, 98% ee.

4.4.5. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(o-chlorophenyl) propanoate. White solid. Mp 123–125 °C. $[\alpha]_D^{25}$ +24.8 (*c* 0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H, NH), 7.68 (d, *J*=7.50 Hz, 1H, ArH), 7.39–7.19 (m, 3H, ArH), 7.14–7.00 (m, 5H, ArH), 5.67 (d, *J*=11.70 Hz, 1H, CH), 4.46 (d, *J*=11.70 Hz, 1H, CH), 4.02 (q, *J*=7.20 Hz, 2H, CH_2), 3.93 (q, *J*=7.20 Hz, CH_2), 1.01 (t, *J*=7.20 Hz, 3H, CH_3), 0.90 (t, *J*=7.20 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.90, 167.55, 139.05, 135.97, 133.91, 129.73, 128.87, 127.73, 126.77, 126.55, 122.01, 121.97, 119.40, 119.31, 115.41, 111.05, 61.46, 57.60, 38.53, 13.61, 13.56. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}ClKNO_4$ ($M+K^+$): 482.03638; found: 482.03650. HPLC analysis t_R (minor)=16.84 min, t_R (major)=27.56 min, 87% ee.

4.4.6. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(o-fluorophenyl) propanoate. White solid. Mp 154–156 °C. $[\alpha]_D^{25}$ +10.6 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, NH), 7.50 (d, *J*=7.50 Hz, 1H, ArH), 7.37 (d, *J*=1.80 Hz, 1H, ArH), 7.29–7.22 (m, 2H, ArH), 7.16–6.96 (m, 5H, ArH), 5.35 (d, *J*=12.0 Hz, 1H, CH), 4.46 (d, *J*=12.0 Hz, 1H, CH), 4.03 (q, *J*=7.20 Hz, 2H, CH_2), 3.97 (q, *J*=7.08 Hz, CH_2), 1.03 (t, *J*=10.10 Hz, 3H, CH_3), 0.97 (t, *J*=7.11 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.84, 167.67, 162.28, 159.01, 135.89, 129.75, 129.70, 129.0, 128.68, 128.50, 128.40, 128.29, 126.64, 124.06, 124.01, 122.17, 121.40, 119.54, 118.97, 115.82, 115.61, 110.98, 61.47, 56.9, 56.89, 36.30, 36.27, 13.68. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}FKNO_4$ ($M+K^+$): 422.11644; found: 422.11670. HPLC analysis t_R (minor)=15.74 min, t_R (major)=21.09 min, 99.5% ee.

4.4.7. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(o-methylphenyl) propanoate. Colorless oil. $[\alpha]_D^{25}$ +15.2 (*c* 0.30, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H, NH), 8.05 (d, *J*=0.81 Hz, 1H, ArH), 7.74–7.71 (m, 1H, ArH), 7.58 (d, *J*=8.40 Hz, 1H, ArH), 7.37–7.34 (m, 3H, ArH), 7.26–7.21 (m, 1H, ArH), 7.18–7.13 (m, 2H, ArH), 5.08 (d, *J*=12.0 Hz, 1H, CH), 4.28 (d, *J*=12.0 Hz, 1H, CH), 4.02–3.93 (m, 4H, CH_2), 3.90 (s, 3H, CH_3), 1.01 (t, *J*=6.90 Hz, 3H, CH_3), 0.96 (t, *J*=7.11 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.39, 167.88, 140.08, 136.29, 135.99, 130.68, 126.75, 126.42, 126.30, 125.96, 122.27, 122.03, 119.46, 119.28, 116.47, 110.97, 61.40, 61.28, 58.48, 38.05, 19.89, 13.68, 13.57. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{25}KNO_4$ ($M+K^+$): 418.14152; found: 418.14178. HPLC analysis t_R (minor)=11.02 min, t_R (major)=13.21 min, 79% ee.

4.4.8. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-fluorophenyl) propanoate. White solid. Mp 144–146 °C. $[\alpha]_D^{25}$ +8.4 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, NH), 7.55 (d, *J*=8.40 Hz, 1H, ArH), 7.32–7.29 (m,1H, ArH), 7.21–7.17 (m, 4H, ArH), 7.07–7.02 (m, 2H, ArH), 6.82 (t, *J*=6.30 Hz, 1H, ArH), 5.08 (d, *J*=11.76 Hz, 1H, CH), 4.25 (d, *J*=11.70 Hz, 1H, CH), 4.03 (q, *J*=2.40 Hz, 2H, CH_2), 3.98 (q, *J*=2.40 Hz, 2H, CH_2), 1.04 (t, *J*=7.24 Hz, 3H, CH_3), 0.99 (t, *J*=7.24 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.72, 167.62, 164.37, 161.12, 144.14, 144.11, 136.19, 134.2, 129.79, 129.69, 126.53, 123.95, 123.92, 122.3, 122.42, 120.92, 119.67, 119.23, 116.42, 116.39, 115.29, 115.01, 113.82, 113.56, 111.04, 61.53, 58.13, 42.48, 13.79, 13.72. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}FKNO_4$ ($M+K^+$): 422.11644; found: 422.11649. HPLC analysis t_R (minor)=12.52 min, t_R (major)=16.22 min, 78% ee.

4.4.9. (S)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-methylphenyl) propanoate. White solid. Mp 106–108 °C. $[\alpha]_D^{25}$ +11.2 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, NH), 7.57 (d, *J*=8.10 Hz, 1H, ArH), 7.30–7.26 (m,1H, ArH), 7.18–7.05 (m, 5H, ArH), 7.03–7.00 (m, 1H, ArH), 6.94 (d, *J*=7.24 Hz, 1H, ArH), 5.03 (d, *J*=12.00 Hz, 1H, CH), 4.27 (d, *J*=12.00 Hz, 1H, CH), 4.01 (q, *J*=4.32 Hz, 2H, CH_2), 3.96 (q, *J*=1.26 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.01 (t, *J*=5.67 Hz, 3H, CH_3), 0.97 (t, *J*=7.20 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.04, 167.83, 141.32, 137.75, 136.20, 128.95, 128.17, 127.48, 126.79, 125.11, 122.22, 120.87, 119.51, 119.47, 117.22, 110.90, 61.37, 61.32, 58.44, 42.75, 21.42, 13.77, 13.72. HRMS (ESI): *m*/*z* calcd

for $C_{23}H_{25}KNO_4$ ($M+K^+$): 418.14152; found: 418.14184. HPLC analysis t_R (minor)=13.60 min, t_R (major)=15.67 min, 78% ee.

4.4.10. (S)-Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-phenylpropanoate. White solid. Mp 147–148.5 °C. $[\alpha]_D^{25}$ +17.5 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H, NH), 7.37–7.35 (m, 2H, ArH), 7.25–7.12 (m, 4H, ArH), 6.96 (s, 1H, ArH), 6.78 (dd, *J*=2.40 Hz, 9.00 Hz, ArH), 5.01 (d, *J*=11.76 Hz, CH), 4.25 (d, *J*=11.76 Hz, CH), 4.05–3.94 (m, 4H, 2×CH_2), 3.77 (s, 3H, OCH_3), 0.99 (t, *J*=6.00 Hz, 6H, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.05, 167.85, 153.94, 141.37, 131.36, 128.31, 128.16, 127.16, 126.72, 121.59, 116.76, 112.46, 111.62, 101.28, 61.45, 61.38, 58.38, 55.82, 42.86, 13.75. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{25}KNO_5$ ($M+K^+$): 434.13643; found: 434.13697. HPLC analysis t_R (minor)=17.39 min, t_R (major)=22.18 min, >99% ee.

4.4.11. (S)-Ethyl 2-ethoxycarbonyl-3-[3-(5-methylindolyl)]-3-phenylpropanoate. White solid. Mp 181–182 °C. $[\alpha]_D^{25}$ +18.2 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 1H, NH), 7.38–7.33 (m, 3H, ArH), 7.26–7.13 (m, 5H, ArH), 6.94 (d, *J*=8.40 Hz, 1H, ArH), 5.04 (d, *J*=11.70 Hz, 1H, CH), 4.26 (d, *J*=11.70 Hz, 1H, CH), 4.03–3.93 (m, 4H, 2×CH_2), 2.38 (s, 3H, CH_3), 1.02–0.97 (m, 6H, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.99, 167.86, 141.51, 134.52, 128.68, 128.29, 128.17, 126.97, 126.65, 123.88, 120.97, 118.95, 116.53, 110.58, 61.39, 61.34, 58.50, 42.80, 21.49, 13.76, 13.71. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{25}KNO_4$ ($M+K^+$): 418.14152; found: 418.14193. HPLC analysis t_R (minor)=11.93 min, t_R (major)=15.39 min, >99.9% ee.

4.4.12. (S)-Ethyl 2-ethoxycarbonyl-3-[3-(7-methylindolyl)]-3-phenylpropanoate. White solid. Mp 125–126 °C. $[\alpha]_D^{25}$ +23.5 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H, NH), 7.41–7.34 (m, 3H, ArH), 7.25–7.09 (m, 4H, ArH), 6.97–6.91 (m, 2H, ArH), 5.05 (d, *J*=11.70 Hz, 1H, CH), 4.28 (d, *J*=11.70 Hz, 1H, CH), 4.04–3.93 (m, 4H, 2×CH_2), 2.42 (s, 3H, CH_3), 1.04–0.97 (m, 6H, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.01, 167.83, 141.43, 135.78, 128.26, 128.16, 126.64, 126.21, 123.7, 122.70, 120.53, 120.06, 119.57, 117.46, 117.10, 61.41, 61.33, 58.37, 42.97, 16.43, 13.72. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{25}KNO_4$ ($M+K^+$): 418.14152; found: 418.14172. HPLC analysis t_R (minor)=12.64 min, t_R (major)=15.32 min, 99% ee.

4.4.13. (S)-Ethyl 2-ethoxycarbonyl-3-[3-(5-chloroindolyl)]-3-phenylpropanoate. White solid. Mp 196–198 °C. $[\alpha]_D^{25}$ −4.4 (*c* 0.20, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (s, 1H, NH), 7.51 (d, *J*=1.98 Hz, 1H, ArH), 7.35–7.05 (m, 8H, ArH), 5.00 (d, *J*=12.00 Hz, 1H, CH), 4.25 (d, *J*=12.00 Hz, 1H), 4.03–3.94 (m, 4H, CH_2), 1.03–0.97 (m, 6H, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.92, 167.65, 140.99, 134.50, 128.45, 128.04, 127.74, 126.91, 125.32, 122.62, 122.39, 118.77, 116.76, 112.04, 61.52, 61.47, 58.36, 42.60, 13.74, 13.71. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}ClKNO_4$ ($M+K^+$): 438.08689; found: 438.08762. HPLC analysis t_R(minor)=12.79 min, t_R(major)=16.45 min, 75% ee.

4.4.14. (S)-Ethyl 2-ethoxycarbonyl-3-[3-(6-chloroindolyl)]-3-phenylpropanoate. White solid. Mp 208–210 °C. $[\alpha]_D^{25}$ +42.2 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H, NH), 7.44–7.14 (m, 8H, ArH), 7.01–6.97 (m, 1H, ArH), 5.03 (d, *J*=11.70 Hz, 1H, CH), 4.25 (d, *J*=11.70 Hz, 1H, CH), 4.04–3.94 (m, 4H, 2×CH_2), 1.00 (t, *J*=7.14 Hz, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.95, 167.69, 141.09, 136.53, 128.41, 128.09, 126.89, 125.31, 121.54, 120.34, 120.24, 117.28, 110.95, 77.20, 61.51, 61.46, 58.30, 42.70, 13.76. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}ClKNO_4$ ($M+K^+$): 438.08689; found: 438.08746. HPLC analysis t_R(minor)=13.13 min, t_R (major)=15.79 min, 70% ee.

4.4.15. (S)-Ethyl 2-ethoxycarbonyl-3-[3-(6-methoxycarbonylindolyl)]-3-phenylpropanoate. White solid. Mp 146–147 °C. $[\alpha]_D^{25}$ +8.2 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 1H, ArH), 8.26 (s, 1H, NH), 7.84 (dd, *J*=2.40, 8.70 Hz, 1H, ArH), 7.41 (dd, *J*=1.92, 7.85 Hz, 2H, ArH), 7.34–7.22 (m, 4H, ArH), 7.27 (dd, *J*=1.80, 7.24 Hz, 1H, ArH), 5.10 (d, *J*=12.0 Hz, 1H, CH), 4.29 (d, *J*=12.0 Hz, 1H, CH), 4.04–3.93 (m, 4H, 2×CH_2), 3.91 (s, 3H, CH_3), 1.02 (t, *J*=7.20 Hz, 3H, CH_3), 0.96 (t, *J*=7.20 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.02, 167.83, 167.62, 141.04, 138.65, 128.46, 128.02, 126.90, 126.32, 123.74, 122.30, 122.24, 121.77, 118.47, 110.74, 61.49, 58.45, 51.83, 51.80, 42.44, 13.76, 13.70. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{25}KNO_6$ ($M+K^+$): 462.13135; found: 462.13253. HPLC analysis t_R(minor)=23.92 min, t_R (major)=28.11 min, 82% ee.

4.4.16. (S)-Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-(p-methylphenyl)propanoate. White solid. Mp 105–107 °C. $[\alpha]_D^{25}$ +13.5 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 1H, NH), 7.36 (d, *J*=7.50 Hz, 1H, ArH), 7.16–6.97 (m, 6H, ArH), 6.77 (dd, *J*=2.37, 8.70 Hz, 1H, ArH), 5.26 (d, *J*=11.80 Hz, 1H, CH), 4.31 (d, *J*=11.80 Hz, 1H, CH), 3.99 (q, *J*=7.08 Hz, 2H, CH_2), 3.91 (q, *J*=7.11 Hz, 2H, CH_2), 3.80 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 0.99 (t, *J*=7.11 Hz, 3H, CH_3), 0.91 (t, *J*=7.14 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.45, 167.89, 153.92, 140.03, 136.31, 131.15, 130.70, 127.17, 126.44, 126.29, 125.93, 122.98, 116.25, 112.31, 111.61, 101.16, 61.42, 61.29, 58.34, 55.77, 38.17, 19.89, 13.70, 13.62. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{27}KNO_5$ ($M+K^+$): 448.152085; found: 448.15218. HPLC analysis t_R(minor)=12.70 min, t_R (major)=15.63 min, 91% ee.

4.5. General procedure for catalytic asymmetric allylic alkylation

To a flame dried Schlenk tube, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4.6 mg, 0.0125 mmol), anhydrous KOAc (10 mg, 0.10 mmol), and ligand **4c** (13.1 mg, 0.03 mmol) were added under nitrogen, followed by addition of CH_2Cl_2 (2.0 mL). The solution was stirred at room temperature for 0.5 h. then a solution of (*E*)-1,3-diphenylprop-2-en-1-yl acetate (126 mg, 0.50 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was stirred for 10 min before the addition of dimethyl malonate (0.17 mL, 1.5 mmol) and BSA (0.37 mL, 1.5 mmol). After being stirred for 48–72 h at room temperature or 0 °C, water was added and the mixture was extracted with EtOAc (2×10 mL), and the combined organic phase was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash chromatography to afford a colorless oil. This is a known compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.17 (m, 10H, ArH), 6.47 (d, *J*=15.75 Hz, 1H, −CH=), 6.32 (dd, *J*=8.43, 15.90 Hz, 1H, CH=), 4.26 (dd, *J*=8.43, 10.80 Hz, 1H, CH), 3.95 (d, *J*=10.80 Hz, 1H, CH), 3.71 (s, 3H, CH_3O), 3.52 (s, 3H, CH_3O). HPLC analysis (Chiralcel AD-H, *n*-hexane/2-PrOH, 90:10, 1.0 mL/min, 254 nm): t_R (minor)=14.43 min, t_R (major)=19.77 min; 94% ee.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.09.106.

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